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Viewpoint

One Year of Pandemic Learning Response: Benefits of Massive Online Delivery of the World Health Organization's Technical Guidance

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Abstract

The World Health Organization (WHO) launched the first web-based learning course on COVID-19 on January 26, 2020, four days before the director general of the WHO declared a public health emergency of international concern. The WHO is expanding access to web-based learning for COVID-19 through its open-learning platform for health emergencies, OpenWHO. Throughout the pandemic, OpenWHO has continued to publish learning offerings based on the WHO's emerging evidence-based knowledge for managing the COVID-19 pandemic. This study presents the various findings derived from the analysis of the performance of the OpenWHO platform during the pandemic, along with the core benefits of massive web-based learning formats.

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KEYWORDS

COVID-19; e-learning; massive open web-based courses; OpenWHO; pandemic; public health; web-based learning; World Health Organization

Introduction

The World Health Organization (WHO) launched the first web-based learning course on COVID-19 on January 26, 2020, four days before the director general of the WHO declared a public health emergency of international concern. The WHO is expanding access to web-based learning for COVID-19 through its open-learning platform for health emergencies, OpenWHO. Throughout the pandemic, OpenWHO has continued to publish learning offerings based on the WHO's emerging evidence-based knowledge for managing the pandemic.

Several findings derived from the analysis of the performance of the OpenWHO platform during the pandemic are presented herein, with regards to the global reach of the courses [1], growth in the uptake of OpenWHO's web-based learning resources [2], and trends in platform usage and the incidence of COVID-19 [3].

The course "Introduction to COVID-19" is hosted on the WHO Health Emergencies learning platform OpenWHO.org and the Pan American Health Organization's Virtual Campus platform and has registered more than 1.15 million enrollments with versions in 40 languages, and versions in several more languages are in current production. As new evidence emerges, the course content is continuously updated to include the latest scientific knowledge and align with the WHO's latest technical guidelines. The course has been revised 11 times since its' launch. The "Introduction to COVID-19" course is currently available in Arabic, Chinese, English, French, Russian, Spanish, Amharic, Bengali, Dari, Esperanto, Fula, German, Hausa, Hindi, Hungarian, Igbo, Indian sign language, Indonesian, Kurdish, Latvian, Macedonian, Marathi, Oriya, Oromo, Pashto, Persian, Portuguese, Punjabi, Serbian, Somali, Swahili, Tetum, Telugu, Thai, Turkish, Vietnamese, Urdu, Yoruba, and Zulu.

As shown in Figure 1, by March 2021, the OpenWHO platform has encompassed 50 languages and 5 million course enrollments,

of which more than 80% are related to COVID-19. OpenWHO has issued a total of 2.8 million certificates, half for completion and half for achievement, thus achieving an average course completion rate of 50% on the platform.

Free training is available on 30 different COVID-19–related topics to support the COVID-19 response. These COVID-19–related courses cover the following topics: an introduction to COVID-19, clinical care, infection prevention and control, COVID-19 vaccination training, national deployment and vaccination planning, vaccine-specific knowledge resources, guidance on mask use, long-term care, clinical management, rehabilitation of patients with COVID-19, leadership in infection prevention and control, staying healthy and safe at work, country capacitation, treatment facility design, the Go.Data tool, personal protective equipment, hand hygiene, waste management, risk assessment for mass gatherings, occupational health and safety, eProtect predeployment training, country intra-action reviews, neglected tropical diseases in the pandemic context, COVID-19 risk communication, public health emergency operations centers, and other related topics (Figure 2).

Figure 1. OpenWHO key figures as of March 2021.

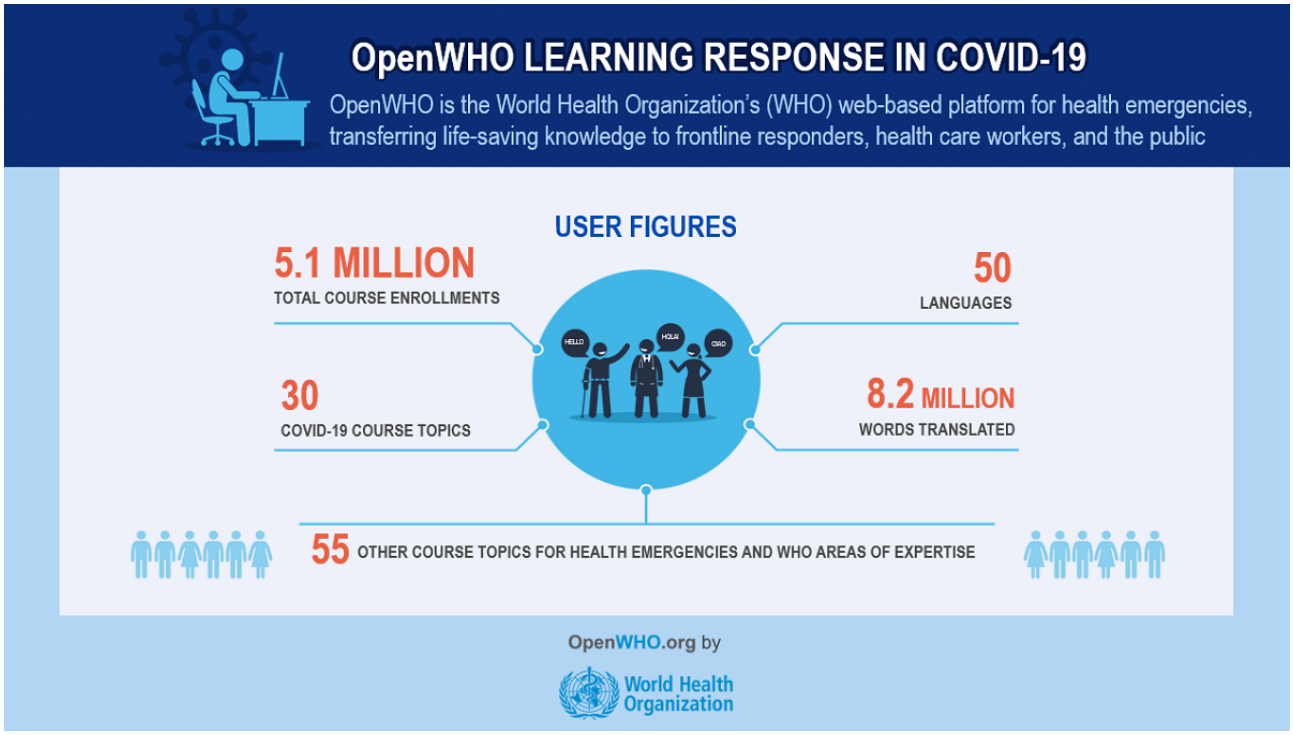


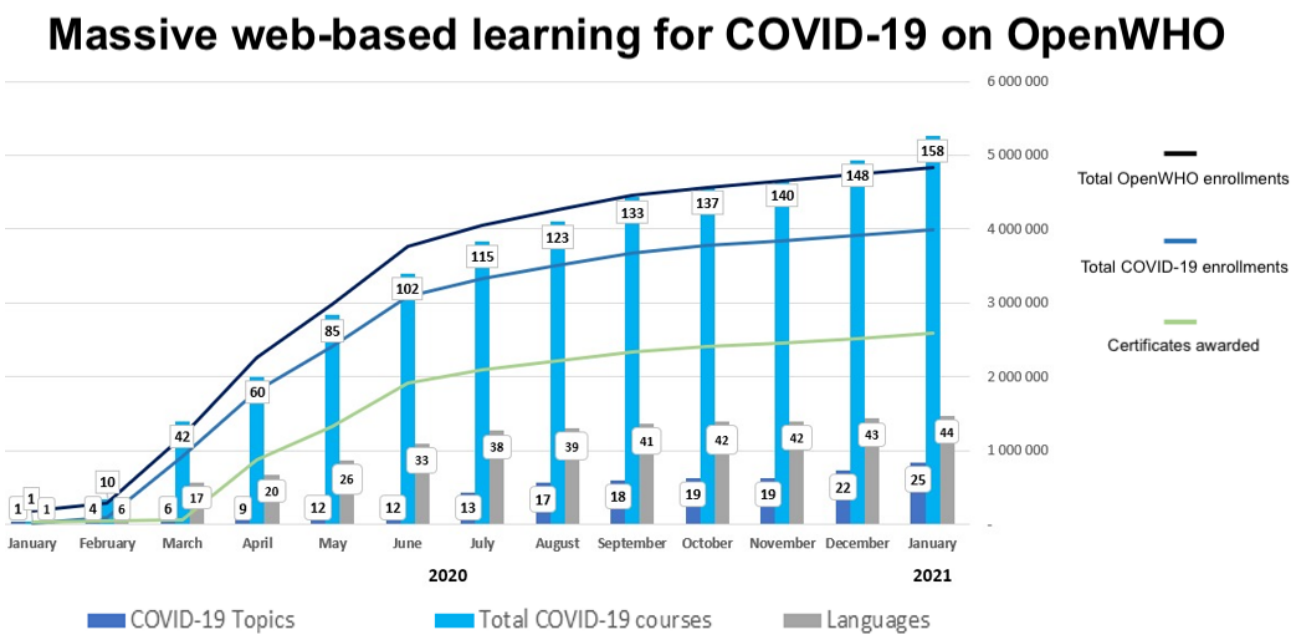
Figure 2. OpenWHO courses span all the intervention areas of the COVID-19 special preparedness and response plan.

Core Benefits of the Massive Web-Based Learning Formats

The COVID-19 pandemic has led to a significant and rapid increase in all forms of digital and web-based learning. The application of an equity lens to the web-based learnings offered by the OpenWHO platform (Figure 3) has yielded unprecedented access to the WHO's knowledge and know-how during the current crisis. The following factors have led to the success of this unprecedented training and learning response in response to the current pandemic:

1. Equity: the design of learning activities is based on the principles of equity to health, supported by equity in access to education, and learning for health. Cost and digital barriers often inhibit those who most need knowledge from accessing it. The elimination of these barriers has been the fundamental premise of the WHO's health emergency training response. Equitable access to critical health emergency knowledge helps provide core learning in the native languages of the most vulnerable populations and includes sign language.
2. Accessibility: web-based learning enables participants with even basic technology to access learning from almost anywhere in the world. OpenWHO courses are globally successful because they are free, self-paced, low-bandwidth adjusted, downloadable and portable, and available on any device. Offline options increase access even further.
3. Flexibility: self-paced mass web-based learning delivery enables individuals to learn at their own speed, at their preferred time, and in their preferred place. It builds on and provides for the learners' preferences and availability.
4. Learner-centricity: user-friendly options allow individuals to choose formats specific to their learning needs and provide the basis for more customized "just-in-time" learning experiences and continuous, lifelong learning.
5. Quality: courses that are based on the latest scientific evidence and on WHO technical guidance and the use of adult learning techniques assure the quality of content and enhance learning.

Figure 3. OpenWHO COVID-19 topics, languages, enrollments, and certificates from January 26, 2020 to January 26, 2021.



Literature Review and Discussion

Even though embedding impactful digital and web-based learning remains a challenge for all areas of knowledge [4-6], its effectiveness has already been demonstrated in medical education and beyond in times of distress [4-9].

The current COVID-19 crisis could be seen as a so-called "black swan moment" with regard to the training of health professionals and the need to examine the role of e-learning in particular [10-12]. The experience of OpenWHO in responding at scale and pace to the urgent need for high-quality and accessible web-based learning for COVID-19 has clearly and consistently demonstrated that the positive effects of digital learning are diverse and multiple and are relevant to many other spheres of a learners' life and work. This includes not only the direct and short-term results in response to learners´ immediate learning needs (eg, improved levels of technical knowledge) but also, as previously reported, it potentially includes additional beneficial long-term contributions suited to the broader needs of learners; for example, the development of more advanced information technology literacy skills, which improves overall work performance, organizational capacity development, and contributes to an individual learner's continuous professional development and ultimately to the goal of lifelong learning, which is essential to navigate life and work in the 21st century.

A more systematic and nuanced understanding of digital approaches to learning and its impact on a learner's life is therefore needed [4,6,7]. Thus, OpenWHO's massive open web-based courses may be considered a paradigm breaker, bringing continuous innovation to pedagogy and learning, in order to provide a truly blended, learner-centered, flexible approach to teaching and learning, which is at the heart of the learning landscape and ecosystem. Other platforms that provide large-scale open-source web-based learning include, for instance, the Indira Gandhi National Open University, which provides a wide range of courses including those related to agriculture, education, and law and has a current total active enrollment of over 4 million students. Moreover, Khan Academy provides web-based courses in mathematics, science, computing, history, economics, and other topics, with more than 10 million users globally subscribing each year.

Conclusions

This is the first time in the WHO's history that a learning resource has been launched this rapidly in high-quality, globally accessible learning formats, which are widely and freely available on a massive scale to manage a health threat. The pandemic has shown that web-based learning is no longer a temporary replacement for direct training, but rather a new way for more efficient and equitable learning. The experience and findings reported herein provide guidance for any individual to be better prepared for subsequent instances where a major and fast learning response is required.

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Authors' Contributions

HU conceived the study and drafted the manuscript. MVK, AT, GOC, and GG contributed to writing of the manuscript. GOC critically revised the manuscript. HU, MVK, AT, GOC, GG, and ISF approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

WHO: World Health Organization

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Viewpoint

Collect Once, Use Many Times: Attaining Unified Metrics for Tuberculosis Preventive Treatment for People Living With HIV

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Abstract

The World Health Organization (WHO) recommends providing tuberculosis preventive treatment (TPT) to all persons living with HIV and to all household contacts of persons with bacteriologically confirmed pulmonary tuberculosis disease. Regrettably, the absence of a harmonized data collection and management approach to TPT indicators has contributed to programmatic challenges at local, national, and global levels. However, in April 2020, the WHO launched the Consolidated HIV Strategic Information Guidelines, with an updated set of priority indicators. These guidelines recommend that Ministries of Health collect, report, and use data on TPT completion in addition to TPT initiation. Both indicators are reflected in the WHO's list of 15 core indicators for program management and are also required by the US President's Emergency Plan for AIDS Relief's Monitoring, Evaluation, and Reporting (MER) guidance. Although not perfectly harmonized, both frameworks now share essential indicator characteristics. Aligned indicators are necessary for robust strategic and operational planning, resource allocation, and data communication. "Collect once, use many times" is a best practice for strategic information management. Building harmonized and sustainable health systems will enable countries to successfully maintain essential HIV, tuberculosis, and other health services while combatting new health threats.

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KEYWORDS

tuberculosis preventive treatment; monitoring and evaluation; people living with HIV; HIV; TB; infectious disease; preventative treatment

Commentary

Tuberculosis (TB) is the leading cause of death from a single infectious disease, with 1.2 million annual deaths worldwide and 10 million persons with incident TB estimated in 2019 [1]. To prevent TB disease in persons infected with HIV and at high risk for disease progression, the World Health Organization (WHO) recommends providing tuberculosis preventive treatment (TPT) to all persons living with HIV (PLHIV) and to all household contacts of persons with bacteriologically confirmed pulmonary TB disease [2].

At the 2018 United Nations High-Level Meeting on TB, member states committed to ambitious targets for TPT scale-up, supporting the long-term goal of ending the global TB epidemic

by 2030. This pledge aims to provide TPT to at least 30 million people by 2022 (including 6 million PLHIV, 4 million children <5 years, and 20 million other household contacts of people affected by TB) [3,4]. Concomitantly, the US President's Emergency Plan for AIDS Relief (PEPFAR) committed to providing a course of TPT to all 13.6 million PLHIV on antiretroviral therapy (ART) supported by PEPFAR by 2021 [5]. The WHO's multisectoral TB accountability framework and HIV strategy also hold governments and stakeholders responsible for accelerating progress to end the TB epidemic and reduce TB-associated mortality among PLHIV including meeting the TPT targets [6]. In concert with these commitments, the Global Fund urges high TB/HIV burden countries to incorporate TPT into their funding requests and matches funds to incentivize country allocations for TPT scale-up among PLHIV [7].

Global reporting for 2019 showed gains in TPT scale-up among PLHIV, with 75 countries reporting initiation of TPT for 3.5 million individuals, up from 1.8 million in 2018 [1]. Examples of successful TPT expansion [8] demonstrate how resource-limited countries can overcome barriers, including modifying national and subnational health information systems (HIS) and monitoring and evaluation (M&E) processes to accommodate TPT data collection and reporting [9]. However, these modifications remain more of an exception than the rule, as the absence of a harmonized data collection and management approach to TPT indicators has contributed to programmatic challenges at local, national, and global levels. This includes challenges in identifying impactful global health trends (a consequence commonly seen with data silos), in ensuring timely communication between programmatic stakeholders, and in enhancing the usability of the data in programmatically meaningful ways. Data reported to the WHO and PEPFAR entail parallel and varying reporting periods, indicator definitions, and partner engagement; harmonizing these efforts could help to decrease reporting burden and unify data metrics for programmatic decision making.

In April 2020, the WHO launched the Consolidated HIV Strategic Information Guidelines, with an updated set of priority indicators [10]. These guidelines recommend that Ministries of Health collect, report, and use data on TPT completion in addition to TPT initiation. Both TPT indicators are reflected in the WHO's list of 15 core, or highest priority, indicators for program management and monitoring and are also required by PEPFAR's Monitoring, Evaluation, and Reporting (MER) guidance [11]. Although not perfectly harmonized, both frameworks now share essential indicator characteristics (Table 1). Global Fund's modular performance framework uses the TPT initiation indicator to assess grant performance; while this alignment is only partial, it encourages countries to report TPT data as recommended by the WHO.

The ability to strengthen program management through improved data cannot be overstated. Robust data allow programs to identify geographic and sociodemographic differences in service coverage and quality and help ensure that no one is left behind. Aligned indicators are also necessary for robust strategic and operational planning, resource allocation, and data communication. Eliminating redundancies in the TPT data collection and management process will allow health care workers, data clerks, and TB and HIV program managers to reallocate their time toward optimizing service delivery and scale-up efforts, thereby becoming more efficient and effective. Simplified data collection methods may also reduce data entry errors and delays in reporting, although these benefits will not accrue immediately. National HIV and TB programs, which typically operate independently and use separate data systems, can strengthen their contributions by harmonizing metadata, M&E tools, and digital data systems, making HIS interoperable across health sector programs, training staff on new data collection requirements, and capitalizing on movements toward primary and universal health care.

"Collect once, use many times" is a best practice for strategic information at local, national, and global levels. Application of this principle includes standards-based indicator alignment and coordinated resource allocation for national M&E tools and HIS, along with concomitant coordination at the global level. It will eliminate parallel reporting systems and allow for the creation of a harmonized data set for use by partners at all levels. Such resilient, harmonized, and sustainable health systems will enable countries to successfully maintain essential HIV, TB, and other health services while combatting new health threats.

Table 1. A comparison of the World Health Organization and US President's Emergency Plan for AIDS Relief's global tuberculosis/HIV indicators[a].

Indicators	World Health Organization (and Global Fund)	US President's Emergency Plan for AIDS Relief (PEPFAR)
Document name (version)	Consolidated HIV Strategic Information Guidelines: Driving Impact Through Programme Monitoring and Management (April 2020)	Monitoring, Evaluation, and Reporting Indicator Reference Guide – MER 2.5 (September 2020)
Description	Proportion of patients receiving ART who started on a standard course of TPT in the previous reporting period who completed therapy	Proportion of patients receiving ART who started on a standard course of TPT in the previous reporting period who completed therapy
Numerator (TPT completion)	Number of PLHIV on ART who completed a course of TPT among those who initiated TPT	Among those who started a course of TPT in the previous reporting period, the number that completed a full course of therapy. For continuous IPT programs, this includes the patients who have completed the first 6 months of IPT, or any other standard course of TPT, such as 3 months of weekly isoniazid and rifapentine, or 3-HP.
Denominator (TPT initiation)	Number of eligible PLHIV on ART who initiated TPT	Number of patients on ART who were initiated on any course of TPT during the previous reporting period
Data elements (disaggregates)	Descriptions: • Sex: male, female, transgender • Age bands: <15 years, ≥15 years • Type of TPT regimen • ART initiation: <12 months on ART, ≥12 months on ART	Age/sex by ART start descriptions: • Newly enrolled on ART: these individuals initiated TPT within 6 months of being enrolled on ART • Previously enrolled on ART: these individuals initiated TPT at least 6 months (or longer) after being enrolled on ART • Age/sex bands: <15 years female/male, ≥15 years female/male, unknown age female/male
Reporting level	Facility	Facility
Reporting frequency	Quarterly, semiannually, and/or annually	Semiannually, with results encompassing achievements from October 1-March 31 and April 1-September 30
Most recent changes	New indicator in 2020.	No changes between MER v2.4 to v2.5.

[a]ART: antiretroviral therapy; IPT: isoniazid preventive therapy; MER: monitoring, evaluation, and reporting guidance; PLHIV: persons living with HIV; TPT: tuberculosis preventive treatment.

Disclaimer

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
HIS: health information system
MER: Monitoring, Evaluation, and Reporting
M&E: monitoring and evaluation
PEPFAR: US President's Emergency Plan for AIDS Relief
PLHIV: persons living with HIV
TB: tuberculosis
TPT: tuberculosis preventive treatment
WHO: World Health Organization

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Review

Web-Based Apps for Responding to Acute Infectious Disease Outbreaks in the Community: Systematic Review

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Abstract

Background: Web-based technology has dramatically improved our ability to detect communicable disease outbreaks, with the potential to reduce morbidity and mortality because of swift public health action. Apps accessible through the internet and on mobile devices create an opportunity to enhance our traditional indicator-based surveillance systems, which have high specificity but issues with timeliness.

Objective: The aim of this study is to describe the literature on web-based apps for *indicator-based surveillance and response to acute communicable disease outbreaks* in the community with regard to their design, implementation, and evaluation.

Methods: We conducted a systematic search of the published literature across four databases (MEDLINE via OVID, Web of Science Core Collection, ProQuest Science, and Google Scholar) for peer-reviewed journal papers from January 1998 to October 2019 using a keyword search. Papers with the full text available were extracted for review, and exclusion criteria were applied to identify eligible papers.

Results: Of the 6649 retrieved papers, 23 remained, describing 15 web-based apps. Apps were primarily designed to improve the early detection of disease outbreaks, targeted government settings, and comprised either complex algorithmic or statistical outbreak detection mechanisms or both. We identified a need for these apps to have more features to support secure information exchange and outbreak response actions, with a focus on outbreak verification processes and staff and resources to support app operations. Evaluation studies (6 out of 15 apps) were mostly cross-sectional, with some evidence of reduction in time to notification of outbreak; however, studies lacked user-based needs assessments and evaluation of implementation.

Conclusions: Public health officials designing new or improving existing disease outbreak web-based apps should ensure that outbreak detection is automatic and signals are verified by users, the app is easy to use, and staff and resources are available to support the operations of the app and conduct rigorous and holistic evaluations.

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KEYWORDS

software; mHealth; infectious diseases; outbreaks; mobile apps; mobile phone; eHealth

Introduction

Background

Despite global progress in improving environmental health, household living conditions, vaccination coverage, and medical treatments, communicable diseases remain a significant threat to public health and emergency preparedness and are among the biggest contributors to disease and disability worldwide [1]. Factors such as climate change, population growth, global travel and trade, and persistent social inequalities further contribute to the potential risks and impacts of emergent or re-emergent communicable disease outbreaks [2-5].

It is well recognized that the earlier outbreak containment and response actions are initiated, the greater the potential for these measures to reduce attack rates, disease spread, and overall morbidity and mortality. The outbreak of severe acute respiratory syndrome in China in early 2003 provides a good example of the effectiveness of detection and outbreak containment measures, that is, isolation and quarantine, in reducing the spread of a disease [6,7]. A more contemporary example is the early implementation of enhanced surveillance and proactive case finding for COVID-19 in Taiwan, where, to date, case numbers remain comparatively low despite Taiwan's proximity to China, high inter-Strait trade and travel, and early entry into the pandemic [8,9]. A rapid and effective response to a communicable disease outbreak is a complex process reliant on early recognition of an aberrant disease pattern (compared with some baseline or *normal* activity), with notification and verification of the cluster or outbreak important before containment is initiated.

Historically, country-level indicator-based surveillance systems have involved paper-based or phone notifications of communicable diseases under respective local public health legislation and International Health Regulations [10-13]. Although electronic laboratory reporting has improved the timeliness of this type of surveillance system, inherent delays in case notification result in time delays in the detection of aberrant patterns and subsequent outbreak containment [14,15]. From the early 1980s, there has been investment in *early warning systems* such as syndromic surveillance systems that collect, analyze, and detect unusual signals related to a syndrome (ie, a group of symptoms) or *event-based systems* that capture and analyze internet-based or *rumor surveillance* data to detect public health risks [16-21]. These systems have complemented, rather than replaced, traditional indicator-based systems. Although event-based or early warning systems can detect unusual patterns of communicable diseases earlier than traditional indicator-based systems, the mathematical algorithms used to support accurate and valid signal detection are still controversial, and the filtering of statistical signals into truly meaningful public health risk alerts requires significant input or moderation [16,17].

The field of communicable disease surveillance has evolved markedly over the past few decades in terms of digital systems, software, and accessibility, particularly with the rapid evolution of the internet [22]. Apps accessible through the internet and on mobile devices are increasingly being used to monitor the health and well-being of individual clients or users and by public health staff to track and monitor population epidemiology [23-25]. These technological developments present an opportunity to modernize traditional paper- and indicator-based surveillance systems using functions such as digitized data entry and storage; automated outbreak detection; and real-time case reporting, analysis, and alert notifications [17]. In addition, the wider accessibility (in terms of both physical access and ease of use) of web-based, or mobile-based apps in particular, can improve the awareness and ability of users to participate in surveillance activities [24].

Although improving the timeliness and sensitivity of surveillance activity is a worthwhile goal in outbreak management, there is a growing opportunity to use web-based apps to help deliver response actions. Examples include automated alerts to key responders about actions needed, links to guidelines and resources, and checklists to guide field staff action on the ground. The Integrated Disease Surveillance and Response strategy from the World Health Organization (WHO) recognizes the importance of scaling up electronic surveillance systems to respond to infectious disease outbreaks [26]. An example of the real-time use of a web-based surveillance system to facilitate an outbreak response during a public health emergency is the Chinese system Decision Support System for Response to Infectious Disease Emergencies tested during the H1N1 pandemic [27]. Although examples of these systems appear increasingly in the published literature, the reporting on their design, implementation, and evaluation of these systems is highly variable. In contrast to previous systematic reviews [16,17,28,29], we aimed to systematically review the literature describing web-based apps for *indicator-based surveillance and response to acute communicable disease outbreaks* in the community with regard to their design, implementation, and evaluation.

Objectives

The three key objectives of this review were to:

1. Identify and describe the mobile and web-based apps that use surveillance data to respond to acute communicable disease outbreaks in the community.
2. Identify key lessons learned for the design and implementation of these apps.
3. Identify any methods used to evaluate the effectiveness of these apps.

We hope that our review will inform the effective development and use of these apps from a health system perspective [30].

Methods

Scope of This Review

The scope of this review is defined here, as the evidence in this area is rapidly emerging and technically focused; therefore, we felt the need to clarify the terms and definitions used throughout this review. This review focuses on software apps that collate and analyze communicable disease outbreak data. We defined *software apps* as sequential operating programs that instruct the functioning of a digital computer. These software apps may be web based or mobile based and are accessible via devices such

as mobile phones and other smart devices (also known as mobile health [mHealth] or mobile apps) and desktop or laptop computers [23].

We defined an *outbreak* as the occurrence of cases of disease in excess of *normal pattern*, with cases linked in place and time as demonstrated by epidemiological or laboratory data. The number of cases defining an outbreak varies according to the disease-causing agent and context. We targeted acute (epidemic not endemic) outbreaks in a community setting (ie, not nosocomial outbreaks). Importantly, we specifically considered confirmed outbreaks using indicator-based surveillance data. Indicator-based surveillance data require defined counts of cases and contacts (as per national case definitions) using clinical, laboratory, and epidemiological information to define and monitor an outbreak. Thus, papers describing apps used for early warning, syndromic, or event-based (rumor or internet) surveillance were outside the scope of this study. We used *response* in this study to specifically refer to the detection and notification of the outbreak to the appropriate public health authority and initiation of interventions to help control the spread and impact of the outbreak, for example, outbreak investigation, cohorting, isolation and quarantine, infection control, treatment, and prophylaxis and vaccination. Papers were excluded if the app collected data without the explicit capacity to trigger a specific outbreak notification to a public health authority for further investigation. Finally, we considered app effectiveness in this context to comprise 2 things: (1) end users' measured or self-reported ease, comfort, and ability to use the technology for its intended purpose and (2) measured ability of the app to meet its intended goals/objectives, for example, increased sensitivity, specificity, or timeliness in outbreak detection.

Search Methodology

A systematic review of the literature was conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework [31] (Multimedia Appendix 1) to identify eligible papers for review. A search of 3 web-based databases was conducted: (1) MEDLINE via OVID, (2) Web of Science Core Collection, and (3) ProQuest Science for peer-reviewed journal papers (ie, case studies, case reports, original papers, and reviews) from January 1998 to October 2019 using the following search terms as *keywords* where databases allowed or selected as *anywhere in the paper*:

- (((smartphone OR android OR software OR system OR computer OR website OR web OR application OR app) AND
- (infectious disease OR communicable diseases) AND
- (outbreak)))

Limits to the search were also applied, including only papers published in English, human subjects (if appropriate), and full text available. Google Scholar was also searched using a multifield keyword search using the terms listed earlier for the years between 1998 and 2019 [32]. As Google provides search results listed by relevance, only papers listed in the first 10 pages of the Google search were retrieved for review.

Papers obtained via our database and Google search were excluded if they:

1. Did not describe a web-based, mobile-based, or phone-based app or software associated with managing an acute human infectious disease outbreak in the community
2. Described apps or software used solely for management during an outbreak after it had already begun (ie, without function of disease surveillance and/or outbreak detection), including monitoring drug or vaccine therapy and/or effectiveness and mapping of cases
3. Described apps or software used for modeling, estimating, or simulating infectious disease outbreak responses only (eg, not used to monitor real-time events) or using geographic information systems to model spatial distributions and patterns
4. Described apps or software for surveillance and detection (both retrospective and prospective) of infectious disease outbreaks but did not report directly to a public health organization or workforce or trigger any explicitly stated public health outbreak control action in response
5. Described apps or software exclusively focused on early warning, syndromic, or event-based surveillance.

Citation searches were also performed by checking the reference lists of the included papers to identify any new relevant papers not captured by our original searches [33,34].

Data Extraction and Synthesis

Paper titles and abstracts were independently screened by 3 of the authors (EQ, IS, and KH), using the exclusion criteria to identify a list of papers for full-text review. The same 3 authors independently screened the full-text papers against the exclusion criteria. Two authors (EQ and IS) extracted the following information from each paper: (1) overview of the purpose of the app, (2) setting (location where the app was mainly used, eg, national to local public health offices or in field-based locations), (3) mechanisms for detecting outbreaks (eg, algorithmic and/or statistical models), (4) features to support outbreak response (eg, notification to key responders, advice on outbreak investigation, information on how to conduct contact tracing, implement infection control, or targeted education resources), (5) lessons learned from app development or implementation (as described by each paper's authors and extracted by EQ and IS for the entire paper), and (6) evaluation methods and effectiveness of apps. Data extracted from all included papers were discussed and agreed upon by the authors (EQ and IS) before reporting. Lessons learned from the development or implementation of the apps were further classified into 3 categories: (1) technical (factors related to app features and functions), (2) personal or social (factors related to the users of the app), and (3) organizational (factors related to the owning organization of the app). These categories are consistent with those used by Cresswell et al [35] and Gagnon et al [36] to classify themes in relation to health care technology adoption.

Results

Search Results

The search (Figure 1) generated 6649 papers, with 5676 papers remaining after removal of duplicates and application of limits, as described earlier. Of these, 5545 were excluded based on

title and abstract and 131 remained for full-text review (Figure 1). After full-text review, 111 papers were excluded and 20 were included (Figure 1). An additional 3 papers were identified via our citation search (Figure 1). In total, 23 papers describing 15 apps were included in this study (Table 1). The majority (20/23, 87%) were descriptive in nature, including 1 review paper [37] describing several apps. Only 3 papers were empirical studies that provided comparative outcomes before and after implementation [38-40], with 1 of these studies also using an adjacent district as a control [38] (Table 1). Of the 23 papers, 19 described web-based apps that were implemented [27,37,39-55], 3 described apps that were being piloted [38,56,57], and 1 described a web-based app in development [58]. The unit of analysis for reporting the results in this review is the number of web-based apps (n=15), as some papers described multiple apps.

Figure 1. Systematic search strategy results. ID: infectious diseases.

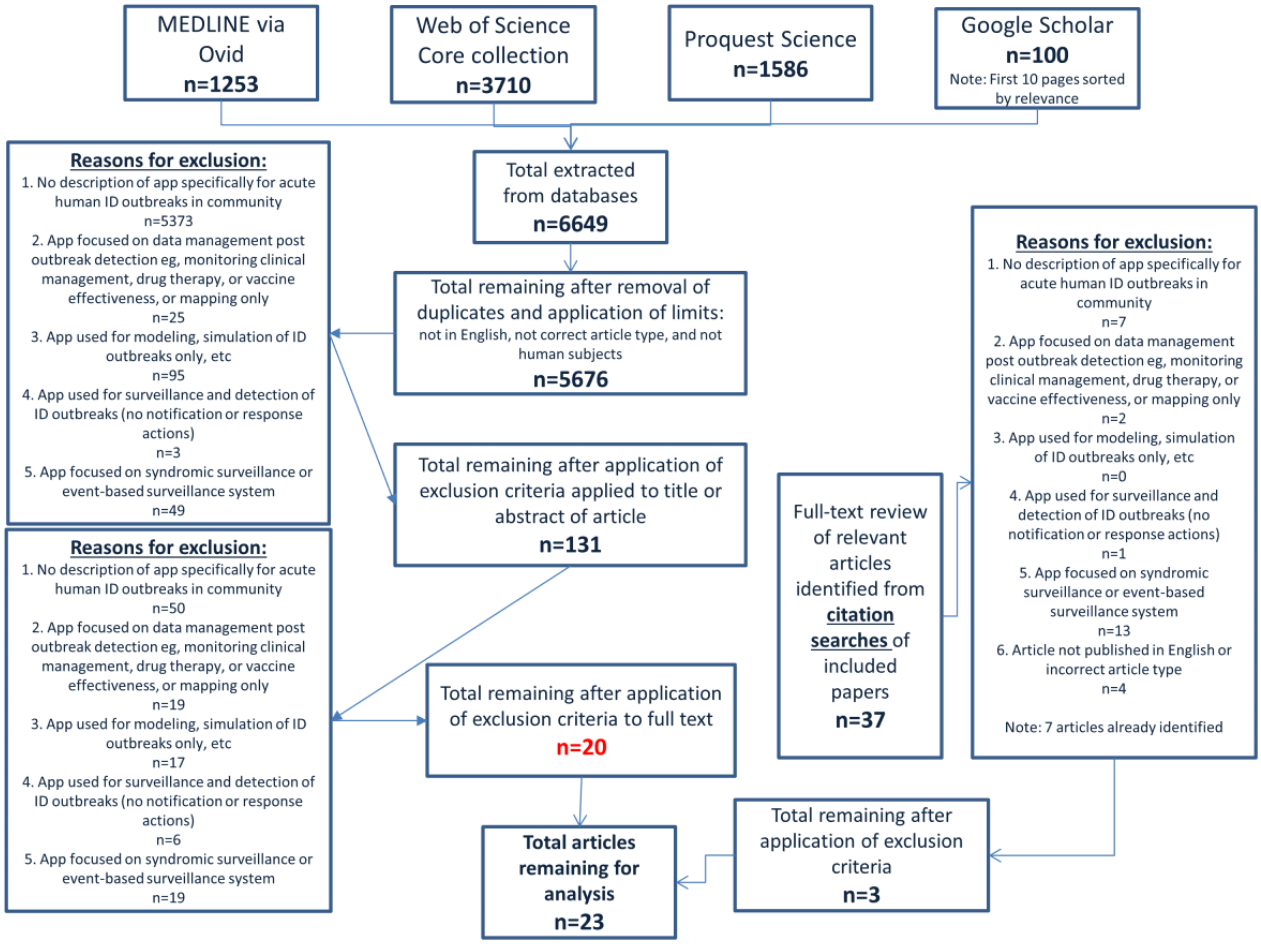

Table 1. Summary of included papers.

App name and reference	Study type	Stage of app development or implementation (as described in paper)
Computer-Assisted Outbreak Detection — SmiNET		
Cakici et al (2010) [41]	Descriptive	Implemented (currently in routine use at Swedish Institute for Infectious Disease Control)
Kling et al (2012) [42]	Descriptive	Implemented
Rolfhamre et al (2006) [43]	Descriptive	Implemented
Argus		
El-Khatib et al (2018) [38]	Empirical (before and after+adjacent district control)	Piloted (15 weeks)
SurvNet @Robert Koch Institute		
Faensen et al (2006) [44]	Descriptive	Implemented (used at local, state, and national levels)
Hulth et al (2010) [37]	Review - descriptive	Implemented
Krause et al (2007) [45]	Descriptive	Implemented
Salmon et al (2016) [46]	Descriptive	Implemented
Straetemans et al (2008) [47]	Descriptive	Implemented
Integrated Crisis Alert and Response System		
Groeneveld et al (2017) [56]	Descriptive	Piloted (using 3 syndromes)
Vesuv		
Guzman-Herrador et al (2016) [48]	Descriptive	Implemented
Statens Serum Institut automated outbreak detection system		
Hulth et al (2010) [37]	Review - descriptive	Implemented
National Institute for Public Health and Environment (RIVM[a]) automated surveillance		
Hulth et al (2010) [37]	Review - descriptive	Implemented
Early Warning and Response System		
Karo et al (2018) [49]	Descriptive	Implemented
Sheel et al (2019) [50]	Descriptive	Implemented
Decision Support System for Response to Infectious Disease Emergencies		
Li et al (2013) [27]	Descriptive	Implemented
China Infectious Diseases Automated Alert and Response System		
Li et al (2014) [39]	Empirical (before and after)	Implemented
Yang et al (2011) [51]	Descriptive	Implemented
Zhang et al (2014) [52]	Descriptive	Implemented
Public Health Emergency Response Information System		
Liang et al (2004) [58]	Descriptive	In development
WHONET — SaTScan		
Stelling et al (2010) [53]	Descriptive	Implemented
Vinas et al (2013) [57]	Descriptive	Piloted (participating laboratories in select provinces)
French Institute for Public Health Surveillance app		
Vaux et al (2009) [54]	Descriptive	Implemented
Infectious Disease Surveillance System		
Widdowson et al (2003) [55]	Descriptive	Implemented
Adjustable Epidemiologic Information System		
Wu et al (2011) [40]	Empirical (before and after)	Implemented

[a]RIVM: Rijksinstituut voor Volksgezondheid en Milieu; English name or translation is National Institute for Public Health and Environment.

Overview of App Purpose

As shown in Multimedia Appendix 2 [27,37-64], the most commonly stated purpose of the 15 web-based apps described in the 23 included papers was to improve the early detection of infectious disease outbreaks (8/15 apps) [38,39,41-43,48,51,52,54-57], predominantly by improving the timeliness of reporting, thereby enabling a rapid response. Other app purposes include automatic outbreak detection, usually involving complex statistical modeling on routinely collected notifiable disease data to determine if thresholds for an outbreak were met (4/15 apps) [37,53,55] and enhanced surveillance for infectious disease outbreaks during emergencies (3/15 apps) [49,50,58].

Setting and Location of Web-Based App Use

As shown in Multimedia Appendix 2, most of the 15 web-based apps were targeted at multiple users from across public health authorities or government departments (12/15 apps) [27,37-48,51-53,55,57,58]. A total of 8 apps were designed for users from national, regional, and local public health authorities [27,38,40-43,48,53,55,57,58], and 4 apps focused on surveillance and reporting at the national level only [37,39,44-47,51,52]. A total of 3 apps were designed for use at the community level [49,50,54,56], either in general practice clinics and hospitals, sentinel facilities, field-based locations, or nursing homes. Of the 15 web-based apps, 8 were used in the European Union [37,41-48,54-56]; 3 in China [27,39,51,52,58]; and the remainder in the Central African Republic [38], Fiji and Myanmar [49,50], Argentina [53,57], and Taiwan [40].

Mechanisms for Detecting and Responding to Outbreaks

Outbreak detection functionality [37,39-48,51-57] was specifically described for 11 web-based apps, with all of these using some form of algorithmic detection of outbreaks, usually based on historical data (Multimedia Appendix 2).

A total of 8 other apps [37,39,41-47,51-53,55-57] also had in-built statistical capability to model and detect outbreaks based on whether the disease activity had exceeded *normal levels* (Multimedia Appendix 2). The most common model used was by Farrington et al [59], followed by SaTScan [60] and Stroup et al [61]. For all 15 web-based apps, the outbreak response functionality was limited to email or SMS notifications of outbreak detection to public health authorities for further follow-up and investigation (Multimedia Appendix 2).

Lessons Learned From the Development and Implementation of the Apps

Technical

The 2 most common lessons learned (Table 2) relating to a technical aspect of apps, as reported by the authors of the papers [37,39,41-48,51,52,55,56], were the need to ensure outbreak detection was automatic (ie, real-time and proactive without human involvement) and that signals were verified by users (ie, to ensure action was initiated). This was central to the *early outbreak detection* function of the apps [37,56]. Associated with this, however, is the issue of false-positive outbreak signals, which were mentioned across 6 web-based apps [37,39,41-47,49,51,52,55,56]. Outbreak detection methods that yield a low positive predictive value increase the number of outbreak signals, which, in turn, increases the workload for public health staff in reviewing and responding to these signals. Authors suggested that having standard operating procedures to detail how users or staff should respond to outbreak signals would not only potentially reduce workload but also ensure no signal is missed [37,44-47] (Table 2). *Flexibility and ease of use of the app* were also frequently mentioned (10 times across 5 apps) [37,38,41-47,49,50,53,55,57], and this specifically included using open-source or off-the-shelf software to promote web-based collaborative development of the app, simple data entry forms that could be tailored to disease groups, and flexible detection algorithms that were configurable to the epidemiology of the disease, for example, low- versus high-incidence condition (Table 2). Ensuring the *confidentiality and security of information within the app* [27,56] and *integration with other existing software* [37,41-43] (Table 2) were also mentioned as important in maintaining appropriate use of the app.

Table 2. Summary of technical, personal, and organizational lessons learned from development and implementation of web-based apps for infectious disease outbreak response.

Lessons learned	Number of mentions and number of apps	References
Technical		
Ensure detection methods are automatic and signals are verified by users	12 mentions; 8 apps	Hulth et al (2010) [37]; Li et al (2014) [39]; Cakici et al (2010) [41]; Kling et al (2012) [42]; Rolfhamre et al (2006) [43]; Faensen et al (2006) [44]; Krause et al (2007) [45]; Salmon et al (2016) [46]; Straetemans et al (2008) [47]; Guzman-Herrador et al (2016) [48]; Yang et al (2011) [51]; Zhang et al (2014) [52]; Widdowson et al (2003) [55]; Groeneveld et al (2017) [56]
Ensure flexibility and ease of use	10 mentions; 5 apps	Hulth et al (2010) [37]; El-Khatib et al (2018) [38]; Cakici et al (2010) [41]; Kling et al (2012) [42]; Rolfhamre et al (2006) [43]; Faensen et al (2006) [44]; Krause et al (2007) [45]; Salmon et al (2016) [46]; Straetemans et al (2008) [47]; Karo et al (2018) [49]; Sheel et al (2019) [50]; Stelling et al (2010) [53]; Widdowson et al (2003) [55]; Vinas et al (2013) [57]
Maintain security	2 mentions; 2 apps	Li et al (2013) [27]; Groeneveld et al (2017) [56]
Ensure the app integrates with other software	2 mentions; 2 apps	Hulth et al (2010) [37]; Cakici et al (2010) [41]; Kling et al (2012) [42]; Rolfhamre et al (2006) [43]
Personal		
Increase user awareness and engagement with the app	2 mentions; 2 apps	Hulth et al (2010) [37]; Faensen et al (2006) [44]; Krause et al (2007) [45]; Salmon et al (2016) [46]; Straetemans et al (2008) [47]; Guzman-Herrador et al (2016) [48]
Organizational		
Develop and maintain resources for operational support of the app	13 mentions; 6 apps	Li et al (2013) [27]; Hulth et al (2010) [37]; El-Khatib et al (2018) [38]; Li et al (2014) [39]; Faensen et al (2006) [44]; Krause et al (2007) [45]; Salmon et al (2016) [46]; Straetemans et al (2008) [47]; Guzman-Herrador et al (2016) [48]; Karo et al (2018) [49]; Sheel et al (2019) [50]; Yang et al (2011) [51]; Zhang et al (2014) [52]
Conduct rigorous evaluations of the app	7 mentions; 5 apps	Hulth et al (2010) [37]; Wu et al (2011) [40]; Cakici et al (2010) [41]; Kling et al (2012) [42]; Rolfhamre et al (2006) [43]; Faensen et al (2006) [44]; Krause et al (2007) [45]; Salmon et al (2016) [46]; Straetemans et al (2008) [47]; Vaux et al (2009) [54]; Groeneveld et al (2017) [56]
Education and training	4 mentions; 2 apps	Hulth et al (2010) [37]; El-Khatib et al (2018) [38]; Faensen et al (2006) [44]; Krause et al (2007) [45]; Salmon et al (2016) [46]; Straetemans et al (2008) [47]
Coverage of uptake of the app	3 mentions; 3 apps	Hulth et al (2010) [37]; Widdowson et al (2003) [55]; Groeneveld et al (2017) [56]

Personal

The main lesson learned relating to users of apps was the need to *maintain user awareness or engagement with the app* (2 mentions across 2 apps) [37,44-48] (Table 2). There was a distinct lack of themes related to the environment of the user, for example, culture or governance of the organization that the user works in, which can impact technology adoption [36].

Organizational

At the organizational level, the most frequently reported lesson learned was the need to *develop and maintain operational resources to support the use of the app* (13 mentions across 6 apps) [27,37-39,44-52] (Table 2). This included having not only staff with the necessary skills to ensure adequate governance of the app from an information technology (IT) perspective but also staff to train users and assist with implementation of the app within field or sentinel sites, for example, user profile management [27,38,48]. In addition, organizations that implement the app need to ensure there is adequate IT infrastructure and potentially Wi-Fi or mobile reception to support use [49]. There were also 7 mentions across 5 apps [37,40-47,54,56] (Table 2) of the need to *conduct comprehensive and rigorous evaluations of the use and effectiveness of these apps*, both from a user-based design perspective and to ensure the app was meeting its goals and objectives, that is, detect and respond to outbreaks.

Evaluation Methods and Reported Effectiveness of Web-Based Apps

Papers on 6 out of 15 apps reported evaluation data [37-39,44-47,50-52]. Most evaluations were cross-sectional studies reporting effectiveness of the apps for detecting outbreaks, compared with paper-based or routine methods, that is, sensitivity of detection or time from detection of an outbreak to notification of public health staff.

Other than the evaluation conducted by Sheel et al [50], which used the surveillance system evaluation criteria of the Centers for Disease Control and Prevention [63], there were no user-based evaluations, for example, measuring user satisfaction. The evaluation by El-Khatib et al [38] was the only empirical study comparing 15 weeks of pilot data from the app before (2015) and after (2016) the study in a pilot district, that is, Mambere-Kadei, compared with a control district, that is, Nana-Mambere in the Central African Republic. They found that the median completeness of weekly reports significantly improved in the pilot district over time and in comparison with the control district (81% in 2016 vs 29% in 2015 for Mambere-Kadei and 52% for Nana-Mambere in 2016; $P<.01$). An overall significant reduction in time to reporting was observed in the Mambere-Kadei district over the pilot period (Kaplan-Meier survival analysis; $P<.01$). However, no evaluation study measured the effectiveness of implementation of the apps (for future scale-up and use) or more proximal health outcomes related to decreased response time, for example, attack rates, hospitalization rates, and death rates from outbreaks captured by the apps.

Discussion

Principal Findings

This systematic review summarizes the features of indicator-based surveillance web-based apps for acute infectious disease outbreak detection and response and uniquely reports on lessons learned from their development and implementation and evaluation of these apps. Our review identified 23 papers describing 15 web-based apps [27,37-58], the majority of which were developed to improve the early detection of infectious disease outbreaks, targeting government settings and experienced public health staff, and comprising complex algorithmic and/or statistical outbreak detection mechanisms.

Most web-based apps identified in this study were designed for government public health staff (usually at the national or regional level) who, in their capacity to collect surveillance data under relevant public health legislation, use these web-based apps to better coordinate outbreak detection and notification. This is not surprising, as there has been an impetus over recent decades toward harnessing web-based apps and, more recently, cloud computing to better facilitate surveillance of infectious diseases to improve upon the capacity and timeliness of paper-based systems [65].

In addition to improving outbreak detection, our review identified the need for web-based apps to have features that support secure information exchange and analysis [37-49,51,52,54,56,58]. For example, this included dashboard functionality (ie, visual display of outbreak data), capability to distribute bulletins, or integration with other statistical software for analysis. However, as identified in this study and other studies, web-based app features that directly support response activities to outbreaks on the ground (eg, outbreak action checklists and notifications of remaining response actions) are lacking [66]. A systematic review of 58 mHealth apps used in Africa to aid the response to the 2014-2015 Ebola outbreak revealed that very few had functionality to support surveillance, case management and contact tracing, or reporting on infection control measures and few were designed with both medical and public health users in mind [67].

Another common theme is the need for web-based apps to be user-centric in their design to enhance adoption, uptake, and use [36]. The authors have recommended mixed methods research be used in user-based design to elucidate the scenario, tasks, workflows, and user characteristics that can influence the success of an app [66]. There are a growing number of validated evaluation tools and frameworks to help assess user engagement and usability [68] with web-based apps, for example, user version of the Mobile Application Rating Scale tool [69]. However, this study identified no current evidence of the use of these user-based evaluation frameworks in the development of web-based apps for acute infectious disease responses. It must be noted that there was a distinct lack of analysis of the environment of the user (eg, culture or governance of their organization), which can be important to understand in terms of technology adoption [36].

Our review identified evaluation studies showing that some of these web-based apps can reduce the time to detection and notification of infectious disease outbreaks [38-40]. Improvements in the timeliness of outbreak detection are likely because of app features that support automated outbreak detection and notification, that is, statistical models that analyze complex data quickly to determine if a disease activity is above *normal* and then automatically notify the right public health staff at the right time. Authors publishing other reviews on the evaluation of prospective statistical methods for detection of outbreaks highlight the need for more rigorous and comprehensive evaluation of detection methods, for example, using larger dummy data sets and/or simulated outbreaks, clearly defined evaluation indicators (sensitivity, specificity, and timeliness), and multiple statistical techniques (eg, cumulative sum vs space-time permutations vs geospatial regression analysis) [70,71]. Evidence shows that epidemic features of outbreaks affect the performance of detection methods, for example, low incidence conditions or baseline counts and seasonality [72]. The authors of the papers in this study also reported the need for standard operating procedures to ensure signals were verified by staff to reduce the low positive predictive value or false positivity rate and subsequent workload [37,44-47].

Implementation science is a growing field of research dedicated to understanding the factors necessary for the real-world implementation of health interventions [73]. This study identified lessons learned that mostly focused on technical and organizational factors. These included outbreak verification processes, staff, and resources to support operations. These organizational factors are consistent with those identified in a systematic review of the implementation of eHealth interventions (not web-based apps per se), which also revealed that implementation issues appear consistent over the past decade or so (eg, issues with funding, infrastructure, policies and standards, interoperability) [30]. The growing number of web-based apps being used in infectious disease control demands evidence from an implementation science perspective and at all levels (user, system, and organization) to ensure that

investment in these new technologies provides a cost benefit for the owning organization in the long term.

This study also highlights a distinct lack of evaluation studies for web-based apps of this kind. Only 6 of 15 apps identified in this study had been evaluated, and evaluations were focused on the technical aspect of improving the timeliness and sensitivity of detection of outbreaks, rather than other forms of effectiveness evaluation, for example, user needs assessment or health outcomes evaluation. Previous authors have recommended clear definitions of the processes that impact the timeliness of reporting (ie, implementation factors) and how timeliness is defined and measured by the owning organization [74,75]. However, other forms of evaluation should also be considered. As mentioned by Calba et al [76], the sociological and economic impacts of technology are important. Researchers should also use validated tools or frameworks where possible and ensure that the evaluation is tailored toward the defined attributes, processes, and context of the surveillance system. Researchers involved in the CONSORT-EHEALTH group have developed a unified checklist for reporting evaluations of web-based and mHealth apps that is currently limited to controlled trials [77]. Until further advice is available, we recommend that researchers take note of the need to think more holistically about the evaluation of web-based apps for infectious disease outbreak responses.

Limitations

As is the case with other systematic reviews, our review process was limited by the breadth of the published literature. There may be many more eligible outbreak detection and response apps that have been developed or implemented but have not been published. Publication bias in this subject area likely skews toward apps that have been successfully developed or implemented, as is the case with all the papers found and included in this study [78].

This study is also limited by the lack of a widely applied, standardized terminology for describing the types and functions of different digital health technologies; only recently has such a standardized taxonomy been proposed by the WHO in recognition of this challenge [79]. Thus, although we included as many synonyms or related search terms for *app* as conceivable in an attempt to apply a sensitive and comprehensive search methodology, there may still be published papers on relevant apps that have not been identified in this study.

Finally, the lessons extracted from the papers were based on the reported perspectives and experiences of their academic authors. The extent of the involvement and visibility of these authors in full app development or implementation processes is unclear. As such, the reported lessons may be biased toward more proximal insights derived from the late implementation or evaluation stages, missing important lessons relating to app development or initial implementation.

Conclusions

Digital health technologies, such as web- and mobile-based apps, present unique and beneficial opportunities for timely and effective responses to communicable disease outbreaks. This has certainly been underscored by the rapid digital innovation and implementation in response to the current COVID-19 pandemic, the most visible of which are mobile contact tracing apps [80,81]. However, to fully capitalize on the potential of these apps, there are important lessons in design, implementation, and evaluation. Public health officials who wish to design new or improve existing web-based apps for this purpose should ensure that outbreak detection is automatic and signals are verified by users [37,39,41-48,51,52,55,56], the app is easy to use [37,38,41-47,49,50,53,55,57], and staff and resources are available to support the operations of the app [27,37-39,44-52]. They should also conduct comprehensive and rigorous evaluations [37,40-47,54,56]. In addition, public health organizations should maximize the functionality of these web-based apps to support response actions and detection and notification. We recommend that future authors describing the development or implementation of mHealth web-based apps consider using the WHO criteria [82] to facilitate comparison across apps for outbreak responses. Further research is also needed on the development (with user needs assessments) and implementation (with segmentation for the personal, technical, and organizational factors affecting technology adoption, including the user environment) of web-based apps used in the control of infectious diseases. Finally, although evaluation studies were reported for 6 web-based apps [37-40,44-47,50-53,57] and some demonstrated a significant reduction in time from detection to notification [38-40], these were limited to process evaluations using data collected via the app. Our results suggest that the evaluation of web-based apps requires a more holistic approach for effectiveness evaluation. This includes using validated tools where possible and data from the user, the app, and the organizational environment (of the user and the organization hosting the app).

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist for this systematic review.
[PDF File (Adobe PDF File), 630 KB - publichealth_v7i4e24330_app1.pdf]

Multimedia Appendix 2
Summary of papers reporting on web-based apps for infectious disease outbreak response included in this review.
[PDF File (Adobe PDF File), 755 KB - publichealth_v7i4e24330_app2.pdf]

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Abbreviations

IT: information technology
mHealth: mobile health
WHO: World Health Organization

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Original Paper

The Psychosocial Predictors and Day-Level Correlates of Substance Use Among Participants Recruited via an Online Crowdsourcing Platform in the United States: Daily Diary Study

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Abstract

Background: Alcohol consumption and stimulant use are major public health problems and contribute to morbidity and mortality in the United States. To inform interventions for substance use, there is a need to identify the day-level correlates of substance use by collecting repeated measures data in one's natural environment. There is also a need to use crowdsourcing platforms like Amazon Mechanical Turk (MTurk) to efficiently engage larger populations of people who use alcohol and stimulants in research.

Objective: We aimed to (1) utilize daily diaries to examine the temporal relationship between day-level cravings for alcohol and stimulant/substance use (ie, heavy drinking or any drug use) in a given day over 14 days and (2) assess whether depression, negative affect, and self-esteem measured at baseline predict substance use in a given day over 14 days among people who use alcohol and/or stimulants in the United States.

Methods: Individuals aged ≥18 years in the United States, who reported alcohol or stimulant (ie, cocaine, crack cocaine, and methamphetamine) use in the past year, were recruited using MTurk between March 26 and April 13, 2018. Eligible participants completed a baseline survey and 14 daily surveys online. The baseline survey assessed sociodemographics and psychosocial (ie, depression, affect, self-esteem, and stress) factors. Daily surveys assessed substance use and cravings for alcohol and stimulants. Four multivariable random-intercept logistic regression models were built to examine psychosocial constructs separately along with other significant predictors from bivariate analyses while controlling for age and education.

Results: Among a total of 272 participants, 220 were White, 201 were male, and 134 were men who have sex with men (MSM). The mean age was 36.1 years (SD 10.5). At baseline, 173 participants engaged in any current or past hazardous alcohol consumption, 31 reported using cocaine, 19 reported using methamphetamine, 8 reported using crack cocaine, and 104 reported any noninjection or injection drug use in the past 6 months. Factors independently associated with substance use were depression (adjusted odds ratio [aOR] 1.11, 95% CI 1.02-1.21; *P*=.01), negative affect (aOR 1.08, 95% CI 1.01-1.16; *P*=.01), lower levels of self-esteem (aOR 0.90, 95% CI 0.82-0.98; *P*=.02), and cravings for alcohol (aOR 1.02, 95% CI 1.01-1.03; *P*<.001) and stimulants (aOR 1.03, 95% CI 1.01-1.04; *P*=.01). MSM had higher odds of engaging in substance use in all models (model 1: aOR 4.90, 95% CI 1.28-18.70; *P*=.02; model 2: aOR 5.47, 95% CI 1.43-20.87; *P*=.01; model 3: aOR 5.99, 95% CI 1.55-23.13; *P*=.009; and model 4: aOR 4.94, 95% CI 1.29-18.84; *P*=.01).

Conclusions: Interventions for substance use should utilize evidenced-based approaches to reduce depression, negative affect, and cravings; increase self-esteem; and engage MSM. Interventions may also consider leveraging technology-based approaches to reduce substance use among populations who use crowdsourcing platforms.

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KEYWORDS

Amazon Mechanical Turk; stimulant use; alcohol use; craving; depression; affect; self-esteem; men who have sex with men

Introduction

Alcohol consumption and drug use are major public health problems and contribute to a substantial amount of morbidity and mortality among adults in the United States [1-3]. Both psychosocial stressors and biobehavioral features play key roles in drug and alcohol use behaviors [4-6]. For instance, depression [7], negative affect (eg, guilt and shame) [8,9], stress [10,11], and low self-esteem [12,13] are known to characterize patterns of substance use. Further, craving, which can be described as an urge or desire to use drugs or alcohol, is a key biobehavioral aspect of substance use disorder (SUD) [6,14] and has been linked to drug and alcohol use in several studies [6,15,16]. However, understanding how these psychosocial factors and biobehavioral features influence substance use on a day-to-day basis remains understudied, especially among populations who use crowdsourcing platforms.

The relationship between craving and substance use is difficult to measure with accuracy because of the transient nature of craving [17]. Further, substance use can be episodic and is often shaped by mood and context (eg, social setting) [18]. Therefore, in order to more accurately capture the daily patterns associated with substance use, methodological approaches that overcome these challenges should be leveraged. The daily dairy method [18-20] offers a promising opportunity to identify the day-level correlates of substance use by collecting repeated measures over time in one's natural environment, thereby taking into account within-person variation related to mood and context [17,18,21].

Substance use research generally relies on traditional recruitment methods (eg, targeted sampling and respondent driven sampling), which are expensive and time consuming [22,23]. Additionally, people who use alcohol or other drugs are often difficult to retain in research, which can result in small sample sizes and limited generalizability [23]. Amazon Mechanical Turk (MTurk) is an innovative crowdsourcing platform that can be used to overcome these limitations by efficiently recruiting and engaging larger populations of people who use alcohol or other drugs in research using the internet [23]. Although MTurk has been used more widely over the past decade, it is still underutilized, and its use may improve the scientific rigor of substance use research by overcoming the limitations noted above. In addition, MTurk may reduce underreporting bias by enabling participants to report on sensitive behaviors in private settings [23]. More research, which leverages MTurk and the daily diary method together, is needed to engage larger populations of people who use alcohol or other drugs in research and to identify the day-level correlates of substance use. This may advance our understanding of the public health program needs related to substance use for populations who use crowdsourcing platforms in the United States.

In order to reduce this gap in research, we utilized daily dairies to identify the day-level correlates of substance use in a given day over a 2-week follow-up period among people who use alcohol or stimulants and who were recruited using MTurk in the United States. In addition, we assessed the relationship between key psychological factors measured at baseline and substance use in a given day over the 2-week follow-up period. More specifically, the main two objectives of this study were to (1) examine the relationship between day-level cravings for alcohol and/or stimulants (ie, crack cocaine, cocaine, or methamphetamine) and substance use in a given day, and (2) determine whether certain psychosocial factors, such as depression, negative affect, self-esteem, and stress measured at baseline, were associated with substance use in a given day over the follow-up period. We hypothesized that both day-level cravings for alcohol and stimulants, and psychosocial stressors would be key predictors of substance use among MTurk users. Taken together, this research aimed to identify the daily correlates and baseline predictors of substance use among people who use alcohol and/or stimulants and who were recruited using MTurk, which may help inform the development of interventions for populations who utilize crowdsourcing platforms in the United States.

Methods

Ethical Considerations

Baseline and follow-up data were drawn from the Stimulants and Alcohol use in MTurk Behavioral Assessments Study ("SAMBA"), a study designed to examine substance use and HIV-related sexual risk behaviors among men who have sex with men (MSM) and non-MSM who use alcohol and/or stimulants in the United States. All study procedures and materials were reviewed and approved by the Institutional Review Board at the University of California, San Francisco. All participants provided informed consent using an online consent form during the screening process.

Recruitment, Screening, and Enrollment

A total of 272 participants in the United States were enrolled using MTurk between March 26 and April 13, 2018. Participants were recruited online using MTurk [23], which involved posting an initial "Human Intelligence Task" and then screening participants for eligibility. Participants were considered eligible if they (1) were at least 18 years old, (2) were able to speak English, and (3) reported alcohol or stimulant (ie, cocaine, crack cocaine, or methamphetamine) use in the past year at baseline. The SAMBA Study recruited for the following two eligible groups (1:1 ratio): MSM who use alcohol or stimulants and non-MSM who use alcohol or stimulants. The parent study was interested in examining both substance use and HIV-related risk behaviors, and explicitly sampled MSM because this population is disproportionately impacted by both substance use and HIV-related risk behaviors [24,25].

Online Surveys

All surveys were administered online and completed using computers or smartphones. First, participants completed an initial survey to be screened for eligibility, and if they were considered eligible, they completed a baseline assessment

followed by 14 daily surveys. Participants were compensated US $0.80 for completing the screener, US $5.00 for completing the baseline survey, and US $1.00 for completing each daily diary, and those who completed all 14 daily surveys received a US $6.00 bonus, resulting in a maximum of US $25.80 in compensation per participant. Research staff contacted participants through their individual MTurk accounts and provided a link to complete the assessments using a unique authenticator known as a single sign on token.

Baseline Measures

Sociodemographics

We assessed sociodemographic factors, including age in years and race/ethnicity (White, Asian, African American/Black, Native American/Alaskan Native, and Hawaiian/Pacific Islander). Being a sexual minority male (ie, MSM) was assessed using a dichotomous measure created from the responses to the following questions: (1) "*What was your sex at birth (male/female)?*" and (2) "*Who do you have sex with (men/women/transgender females or transwomen/transgender males or transmen)?*" Data were also collected on relationship status (married/committed, single, and divorced), employment status (full time, part time, and unemployed), having health insurance (yes/no), ever testing for HIV (yes/no), and annual income (≥US $125,000, US $75,000-124,999, US $40,000-74,999, and ≤US $40,000). Having at least a 4-year degree was assessed by creating a dichotomous variable that included those who attained a bachelor's degree or completed any postgraduate studies versus those who completed 12th grade/general education degree or an associate of arts degree/some college.

Alcohol Use

We measured alcohol consumption in the past 6 months (yes/no) and current or past hazardous drinking (yes/no) using the three-item Alcohol Use Disorders Identification Test-Concise (AUDIT-C), where scores ≥4 for males and ≥3 for females indicate hazardous drinking [26,27]. The AUDIT-C consists of three questions that are designed to help identify problematic alcohol use, and scores range from 0 to 12 (a score of 0 reflects no alcohol use in the past year) [26,27]. A higher AUDIT-C score represents a higher likelihood that the participant's drinking is negatively affecting health [26,27].

Drug Use

Methamphetamine use, cocaine use, crack cocaine use, and any drug use, which included reporting any injection or noninjection drug use in the past 6 months (yes/no), were also assessed.

Psychosocial Measures at Baseline

Self-esteem was assessed using the 10-item Rosenberg Self-Esteem Scale (RSES) [28,29], where higher scores represent higher levels of self-esteem (α=.92). Participants recorded their level of agreement with statements assessing general feelings related to esteem on a 4-point scale ranging from "strongly agree" to "strongly disagree." Items 2, 5, 6, 8, and 9 were reverse coded to ensure that higher scores represent higher levels of self-esteem. Final scores were assessed by summing the scores from all 10 items.

Positive affect and negative affect were measured using the 20-item Positive and Negative Affect Schedule (PANAS) [30], where scores range from 10 to 50 and higher scores indicate higher levels of positive (α=.90) or negative (α=.94) affect. Using a 5-point scale (1=very slightly or not at all to 5=extremely), participants recorded their level of agreement with the 20 emotions assessed on the PANAS. Positive affect was measured by summing scores from items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. Negative affect was measured by summing scores from items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20.

Stress was measured using the 10-item Perceived Stress Scale (PSS) [31], where scores range from 0 to 40 and higher scores represent higher levels of perceived stress. Using a 5-point scale (0=never to 4=very often), participants reported how often they experienced different feelings and thoughts in the past month. Items 4, 5, 7, and 8 were reverse coded to ensure that higher scores represent higher levels of stress. All items were summed to calculate total stress scores. For descriptive purposes, low stress (scores range from 0 to 13), moderate stress (scores range from 14 to 26), and high stress (scores range from 27 to 40) were also measured using the PSS.

Depression was measured using the 10-item Center for Epidemiologic Studies Depression Scale (CESD-10) [32], where scores range from 0 to 30 and scores ≥10 are considered to indicate depression (α=.91). Using a 4-point scale (0=rarely or none of the time/less than 1 day to 3=all of the time/5-7 days), participants reported how often in the past week they experienced different emotional states. Item 10 ("I could not get going") was not included in the survey in error, so scoring for this item was performed by taking the average scores from items 1 to 9. Items 5 and 8 were reverse coded to ensure that higher scores represent higher levels of depression. All 10 items were summed to calculate total depression scores.

Daily Diary Measures

Outcome

Our outcome of interest was a dichotomous measure of substance use in a given day that was created by combining heavy drinking and any drug use in the past 24 hours (yes/no). This measure included all individuals who reported heavy drinking or any drug use in the past 24 hours over the 14-day follow-up period (not at baseline). Heavy drinking in the past 24 hours (yes/no) was a dichotomous measure defined according to the National Institute on Alcohol Abuse and Alcoholism guidelines, which state that six or more drinks for males and five or more drinks for females per day can be considered heavy drinking [33]. Any drug use (including any injection and noninjection drug use) in the past 24 hours (yes/no) was a dichotomous measure derived from the following two questions: "In the past 24 hours, have you used any noninjection drugs recreationally or to get high (crystal meth/speed, crack or powder cocaine, marijuana, heroin, gamma-hydroxybutyric acid, prescription medications [such as oxycontin and xanax], hallucinogens [such as lysergic acid diethylamide], or others)?" and "Have you injected any drug in the past 24 hours?" All data for the outcome were collected after baseline via 14 daily diaries.

Cravings for Alcohol and Stimulants

In addition to alcohol and drug use, participants were asked to report their day-level cravings for alcohol and/or stimulants (ie, cocaine, crack cocaine, and methamphetamine) in the past 24 hours as appropriate. Craving scales ranged from 0 to 100, where 100 represents the strongest craving one has ever experienced and 0 represents no craving at all. Data on cravings were collected after baseline via 14 daily diaries.

Statistical Analysis

Descriptive statistics were used to describe the study sample. For categorical variables, frequencies and percentages were used, and depending on distributional assumptions for continuous data (ie, normal distribution versus nonnormal distribution), means and SDs or medians and IQRs were used.

Logistic mixed effects regression models were used to analyze the associations between substance use and both time-invariant and time-varying factors over 14 days. Time-varying covariates were measured via 14 daily surveys, and day-level cravings for alcohol and stimulants (ie, cocaine, crack cocaine, and methamphetamine) were assessed. All models included a random intercept to account for repeated measures per person [34]. Measurements at timepoints for which there were no missing outcomes or covariate information were included in the model (there was a small amount of missing data, and this pattern is summarized below) [34].

We first built bivariate models to test each factor on substance use individually (a conservative Bonferroni multiple comparison correction for 24 tests would be $P<.002$). For those factors that were significantly ($P<.051$) associated with substance use, multivariable models were then built to determine if they independently contributed to substance use while controlling for potential confounders. Multivariable models were controlled for age and education because they have been identified as correlates of substance use in prior research [35,36]. Due to the high level of correlation among the psychosocial measures examined in this study (depression, affect, self-esteem, and stress), their effects on substance use were estimated in separate models, which also included the other exposures that were significant in bivariate analyses. A manual backward selection approach [37] that considered multicollinearity between all exposures was used to build all four final models. Variables that did not retain a P value that was <.051 were removed from the final models in order to achieve parsimony and enhance the fit of each model. The main effect of time over the follow-up was explored in all four models using an indicator variable for day of follow-up, but was not significant in any of the models and therefore was not included.

For all longitudinal data, including the outcome substance use in a given day and cravings for alcohol and stimulants in the past 24 hours, the overall percentage of missing data was calculated by summing the total number of missing responses and then dividing that number by the total number of potential responses (272×14=3808). The overall percentage of surveys completed was calculated by summing the number of surveys completed and dividing that number by the total number of surveys (3808). The average number of surveys completed per person was calculated by dividing the total number of surveys completed by the total sample size. All analyses were conducted using Stata 14.2 (Stata Corp).

Results

Screening, Enrollment, and Survey Completion Rates

A total of 3897 individuals responded to the MTurk task posted for this study. Of these, 2910 were screened out because they did not meet the eligibility criteria and another 41 were not included because they did not complete the screening survey. Of the 946 individuals who were considered eligible according to screening data, 161 were MSM and 785 were non-MSM. Of the 161 eligible MSM, 152 agreed to participate, and of the 785 eligible non-MSM, 781 agreed to participate, resulting in a total of 13 individuals who declined or opted out. However, this study only had the capacity to enroll 272 participants and had to waitlist the remaining 661. All of the participants who were enrolled consented at baseline. Completion rates for the 14 daily surveys were as follows: day 1, 99.3%; day 2, 98.2%; day 3, 99.3%; day 4, 95.9%; day 5, 94.1%; day 6, 91.9%; day 7, 95.9%; day 8, 95.2%; day 9, 95.9%; day 10, 94.8%; day 11, 92.6%; day 12, 90.8%; day 13, 92.3%; and day 14, 89.7%.

Baseline Characteristics

Baseline characteristics of the study sample are described in Table 1. Among a total of 272 participants, 201 (73.9%) were male and 134 (65.3%) were MSM. The mean age was 36.1 years (SD 10.5). The majority of the sample identified as being White (220/272, 80.8%), followed by African American/Black (22/272, 8.0%), Asian (17/272, 6.2%), other (10/272, 3.6%), and Native American or Alaskan Native (3/272, 1.1%). Most participants were married or in a committed relationship (158/272, 58.0%). Less than half of the sample reported being single (112/272, 41.1%), and only 2 (0.7%) participants were divorced. Most participants (180/272, 66.1%) reported being fully employed, and over half (163/272, 59.9%) reported having at least a 4-year degree. Annual income varied, with slightly over a third (99/272, 36.4%) earning less than US $40,000, 89 (32.7%) earning US $40,000-74,999, 64 (23.5%) earning US $75,000-124,999, and 20 (7.3%) earning US $125,000 or more. The majority (229/272, 84.1%) of the sample reported having health insurance, and over half (170/272, 62.5%) reported ever being tested for HIV.

Table 1. Baseline sociodemographic characteristics, substance use, and psychosocial factors among people who use alcohol and/or stimulants recruited from MTurk between March 26 and April 13, 2018, in the United States (N=272).

Variable	Value
Sociodemographic factors	
Age (years), mean (SD)	36.1 (10.4)
Race/ethnicity, n (%)	
White	220 (80.8%)
Asian	17 (6.2%)
African American	22 (8.0%)
Native American or Alaskan Native	3 (1.1%)
Other	10 (3.6%)
Gender/self-reported sex, n (%)	
Male	201 (73.9%)
Female	71 (26.1%)
Men reporting sex with other men, n (%)	134 (65.3%)
Relationship status, n (%)	
Single	112 (41.1%)
Married/committed	158 (58.0%)
Divorced	2 (0.7%)
Employment status, n (%)	
Full-time employment	180 (66.1%)
Part-time employment	45 (16.5%)
Unemployed	47 (17.2%)
Higher education (bachelor's degree/any postgraduate studies), n (%)	163 (59.9%)
Income (US $), n (%)	
≥125,000 (reference)	20 (7.3%)
75,000-124,999	64 (23.5%)
40,000-74,999	89 (32.7%)
<40,000	99 (36.4%)
Has health insurance, n (%)	229 (84.1%)
Reported ever testing for HIV, n (%)	
Yes	170 (62.5%)
No	95 (34.9%)
Do not know	7 (2.5%)
Substance use	
Alcohol consumption in the past 6 months, n (%)	261 (99.2%)
AUDIT-C score, mean (SD)[a]	4.2 (2.4)
Hazardous alcohol consumption[b], n (%)	173 (63.8%)
Methamphetamine use in the past 6 months, n (%)	19 (10.1%)
Cocaine use in the past 6 months, n (%)	31 (15.3%)
Crack cocaine use in the past 6 months, n (%)	8 (4.4%)
Any drug use in the past 6 months including injection drug use, n (%)	104 (38.2%)
Substance use cravings[c]	
Day-level craving for alcohol in the past 24 hours, median (IQR)	5 (0-26)

Variable	Value
Day-level craving for methamphetamine in the past 24 hours, median (IQR)	54 (20-88)
Day-level craving for cocaine in the past 24 hours, median (IQR)	39 (1-71)
Day-level craving for crack cocaine in the past 24 hours, median (IQR)	52 (51-87)
Psychosocial factors	
Self-esteem score[d], median (IQR)	30 (26-35)
Affect[e]	
Positive affect, median (IQR)	31 (26-37)
Negative affect, median (IQR)	15 (11-20)
Perceived stress score[f], median (IQR)	17 (11-21)
Low stress, n (%)	93 (34.1%)
Moderate stress, n (%)	152 (55.8%)
High stress, n (%)	27 (9.9%)
Depression score[g], median (IQR)	7.7 (3.3-12.2)

[a]Alcohol Use Disorders Identification Test-Concise (AUDIT-C) scores were calculated using the three-item AUDIT-C.

[b]Hazardous drinking was measured at baseline using the three-item AUDIT-C. Scores range from 0 to 12. Scores of 4 or more for men indicate hazardous drinking and scores of 3 or more for women indicate hazardous drinking.

[c]Day-level craving scores range from 0 to 100.

[d]Self-esteem was measured using the "Rosenberg Self-Esteem Scale" (RSES). Higher scores represent higher self-esteem.

[e]Affect was measured using the "Positive and Negative Affect Schedule" (PANAS). Scores range from 10 to 50, with higher scores indicating higher levels of positive or negative affect. Positive and negative affect were measured by summing different items from the PANAS scale.

[f]Stress was measured using the "Perceived Stress Scale" (PSS). Scores range from 0 to 40, with higher scores representing higher perceived stress. Scores ranging from 0 to 13 are considered low stress, 14 to 26 are considered moderate stress, and 27 to 40 are considered high stress.

[g]Depression was measured using the 10-item Center for Epidemiologic Studies Depression Scale Revised (CESD-10). A score of ≥10 is considered to indicate depression.

Nearly all (261/272, 99.2%) participants reported consuming alcohol in the past 6 months. The mean AUDIT-C score for any current or past drinking was 4.2 (SD 2.4), and 173 (63.8%) participants engaged in any current or past hazardous alcohol consumption. In the past 6 months, 31 (15.3%) participants reported using cocaine, 19 (10.1%) reported using methamphetamine, 8 (4.4%) reported using crack cocaine, and 104 (38.2%) reported any noninjection or injection drug use. On a scale from 0 to 100, median day-level craving scores at baseline for alcohol, methamphetamine, cocaine, and crack cocaine were 5 (IQR 0-26), 54 (IQR 20-88), 39 (IQR 1-71), and 52 (IQR 51-87), respectively.

The median score for self-esteem was 30 (IQR 26-35). On a scale from 10 to 50, median scores for positive affect and negative affect were 31 (IQR 26-37) and 15 (IQR 11-20), respectively. On a scale from 0 to 40, the median perceived stress score was 17 (IQR 11-21), and just over half (152/272, 55.8%) of the sample reported experiencing moderate stress, followed by low stress (93/272, 34.1%) and high stress (27/272, 9.9%). On a scale from 0 to 30, where a score ≥10 is considered to indicate depression, the median score was 7.7 (IQR 3.3-12.2).

Missing Data

Overall, there was a minimal amount of missing data. Out of a total of 3,808 possible responses, there were 201 (5.2%) missing responses for the primary outcome of interest (substance use in the past 24 hours over the follow-up period) and for day-level cravings for alcohol in the past 24 hours. With regard to day-level cravings for cocaine, crack cocaine, and methamphetamine in the past 24 hours, there were 253 (6.6%) missing responses for each measure of craving.

Bivariate Analyses

Results from bivariate logistic regression models examining the predictors of substance use in a given day measured at baseline and each day over the follow-up period are summarized in Table 2, in addition to descriptive data stratified by substance use on day 1. Part-time employment was associated with a higher odds of substance use in a given day over the follow-up compared with full-time employment. Those who had a bachelor's degree or completed some postgraduate work had a lower odds of engaging in substance use in a given day over the follow-up period compared with those who reported completing less education. Those who earned less than US $40,000 annually had a higher odds of substance use in a given day compared with those who earned US $125,000 or more annually. MSM had a higher odds of substance use in a given day compared with those who were not MSM.

Table 2. Bivariate random-intercept logistic regression models of the predictors of substance use in a given day among people who use alcohol and/or stimulants recruited from MTurk between March 26 and April 13, 2018, in the United States (N=272).

Variable	Substance use in the past 24 hours on day 1[a] (n=50)	No substance use in the past 24 hours on day 1[a] (n=220)	Unadjusted odds ratio (95% CI)	*P* value[b]
Sociodemographic factors at baseline[c]				
Age (years), mean (SD)	35.50 (10.44)	36.32 (10.34)	0.99 (0.94-1.03)	.66
Race/ethnicity, n (%)				
White (reference)	40 (80.0%)	178 (80.9%)	N/A[d]	N/A
Asian	1 (2.0%)	16 (7.3%)	0.19 (0.26-1.40)	.10
African American	5 (10.0%)	17 (7.7%)	3.61 (0.62-21.05)	.15
Native American or Alaskan Native	1 (2.0%)	2 (0.9%)	13.61 (0.10-1726.21)	.29
Hawaiian or Pacific Islander	3 (6.00%)	7 (3.2%)	3.57 (0.28-44.84)	.32
Relationship status, n (%)				
Married/committed (reference)	28 (56.0%)	128 (58.2%)	N/A	N/A
Single	22 (44.0%)	90 (40.9%)	1.53 (0.59-3.96)	.37
Divorced	0 (0%)	2 (0.9%)	N/A	N/A
Employment status, n (%)				
Full-time employment (reference)	31 (62.0%)	149 (67.7%)	N/A	N/A
Part-time employment	13 (26.0%)	32 (14.5%)	5.70 (1.54-21.00)	.009
Unemployed	6 (12.0%)	39 (17.7%)	0.63 (0.18-2.18)	.46
Higher education (bachelor's degree or any post-graduate), n (%)	24 (48.0%)	138 (62.7%)	0.23 (0.08-0.59)	.003
Income (US $), n (%)				
≥125,000 (reference)	4 (8.0%)	16 (7.3%)	N/A	N/A
75,000-124,999	3 (6.0%)	61 (27.7%)	0.39 (0.05-2.67)	.33
40,000-74,999	14 (28.0%)	75 (34.1%)	1.03 (0.16-6.53)	.97
<40,000	29 (58.0%)	68 (30.9%)	6.84 (1.09-42.81)	.04
Has health insurance, n (%)	42 (84.0%)	185 (84.1%)	0.44 (0.12-1.64)	.22
Ever tested for HIV, n (%)	36 (72.0%)	132 (60.0%)	0.69 (0.46-1.04)	.07
Men reporting sex with other men, n (%)	37 (82.2%)	96 (60.8%)	7.35 (2.40-22.56)	<.001
Substance use cravings at day one[e,f]				
Day-level craving for alcohol in the past 24 hours, median (IQR)	10.5 (0-50)	3 (0-15)	1.03 (1.02-1.04)	<.001
Day-level craving for methamphetamine in the past 24 hours, median (IQR)	0 (0-9)	0 (0-0)	1.03 (1.01-1.05)	<.001
Day-level craving for cocaine in the past 24 hours, median (IQR)	0 (0-1)	0 (0-0)	1.04 (1.02-1.06)	<.001
Day-level craving for crack cocaine in the past 24 hours, median (IQR)	0 (0-0)	0 (0-0)	1.04 (1.02-1.06)	<.001
Psychosocial factors at baseline[c]				
Self-esteem score[g], median (IQR)	27.5 (23-32)	30 (27-36)	0.87 (0.81-0.93)	<.001
Positive affect score[h], median (IQR)	30 (25-34)	32 (26-38)	0.94 (0.89-1.00)	.07

Variable	Substance use in the past 24 hours on day 1[a] (n=50)	No substance use in the past 24 hours on day 1[a] (n=220)	Unadjusted odds ratio (95% CI)	*P* value[b]
Negative affect score[h], median (IQR)	19.5 (15-32)	14 (11-18.5)	1.14 (1.08-1.21)	<.001
Perceived stress score[i], median (IQR)	20 (15-23)	16 (10-20)	1.13 (1.06-1.20)	<.001
Depression score[j], median (IQR)	11.66 (4.44-17.77)	6.66 (2.22-12.22)	1.19 (1.11-1.27)	<.001

[a]In the bivariate logistic regression models, substance is the outcome and is a composite variable that includes those who reported heavy drinking and/or any drug use in the past 24 hours over a 2-week follow-up period. Substance use is the outcome and includes those who reported heavy drinking and/or any drug use in the past 24 hours on day 1.

[b]*P* values were derived from random effects logistic regression.

[c]Time invariant covariates measured at baseline.

[d]N/A: not applicable.

[e]Time varying covariates measured at day 1 over the follow-up period.

[f]Day-level cravings in the past 24 hours were assessed on a scale ranging from 0 to 100, where 0 is no craving at all and 100 is the strongest craving one has ever experienced.

[g]Self-esteem was measured using the "Rosenberg Self-Esteem Scale" (RSES). Higher scores represent higher self-esteem.

[h]Affect was measured using the "Positive and Negative Affect Schedule" (PANAS). Scores range from 10 to 50, with higher scores indicating higher levels of positive or negative affect. Positive and negative affect were measured by summing different items from the PANAS scale.

[i]Stress was measured using the "Perceived Stress Scale" (PSS). Scores range from 0 to 40, with higher scores representing higher perceived stress. Scores ranging from 0 to 13 are considered low stress, 14 to 26 are considered moderate stress, and 27 to 40 are considered high stress.

[j]Depression was measured using the 10-item Center for Epidemiologic Studies Depression Scale Revised (CESD-10). A score of ≥10 is considered to indicate depression.

Every 1-point increase in self-esteem was associated with a lower odds of engaging in substance use in a given day. Every 1-point increase in negative affect was associated with a higher odds of engaging in substance use in a given day. Similarly, increases in perceived stress and depression were associated with higher odds of engaging in substance use in a given day. Higher day-level craving scores in the past 24 hours for alcohol, cocaine, crack cocaine, and methamphetamine were all associated with a higher odds of engaging in substance use in a given day over the follow-up period.

Multivariable Analyses

Results from all four multivariable logistic regression models examining baseline predictors and daily correlates of substance use in a given day while controlling for age in years and education are summarized in Table 3. In model 1, factors significantly associated with substance use in a given day were self-esteem (adjusted odds ratio [aOR] 0.90, 95% CI 0.82-0.98; *P*=.02), day-level craving scores for alcohol and cocaine (aOR 1.02, 95% CI 1.01-1.03; *P*<.001 and aOR 1.03, 95% CI 1.01-1.04; *P*=.01, respectively), and being in the MSM group (aOR 4.90, 95% CI 1.28-18.70; *P*=.02). In model 2, factors significantly associated with substance use in a given day were negative affect (aOR 1.08, 95% CI 1.01-1.16; *P*=.01), day-level craving scores for alcohol and cocaine (aOR 1.02, 95% CI 1.01-1.03; *P*<.001 and aOR 1.02, 95% CI 1.01-1.04; *P*=.001, respectively), and being in the MSM group (aOR 5.47, 95% CI 1.43-20.87; *P*=.01). In model 3, factors significantly associated with substance use in a given day were day-level craving scores for alcohol and cocaine (aOR 1.02, 95% CI 1.01-1.03; *P*<.001 and aOR 1.03, 95% CI 1.01-1.04; *P*=.001, respectively), and being in the MSM group (aOR 5.99, 95% CI 1.55-23.13; *P*=.009). In model 4, factors significantly associated with substance use in a given day were depression (aOR 1.11, 95% CI 1.02-1.21; *P*=.01), day-level craving scores for alcohol and cocaine (aOR 1.02, 95% CI 1.01-1.03; *P*<.001 and aOR 1.02, 95% CI 1.01-1.04; *P*=.001, respectively), and being in the MSM group (aOR 4.94, 95% CI 1.29-18.84; *P*=.01).

Table 3. Multivariable random-intercept logistic regression models of the predictors of substance use in a given day among people who use alcohol and/or stimulants recruited from MTurk between March 26 and April 13, 2018, in the United States (N=272).

Variable	Adjusted odds ratio (95% CI) Model 1[a,b]	*P* value[c]	Adjusted odds ratio (95% CI) Model 2[a,d]	*P* value[c]	Adjusted odds ratio (95% CI) Model 3[a,e]	*P* value[c]	Adjusted odds ratio (95% CI) Model 4[a,f]	*P* value[c]
Sociodemographic factors measured at baseline[g]								
Mean age in years	1.01 (0.95-1.07)	.64	1.01 (0.95-1.07)	.62	1.01 (0.95-1.07)	.73	1.00 (0.95-1.06)	.78
Higher education (bachelor's degree/any postgraduate)	0.18 (0.05-0.61)	.006	0.17 (0.05-0.59)	.005	0.17 (0.05-0.60)	.006	0.19 (0.05-0.65)	.009
Men reporting sex with other men	4.90 (1.28-18.70)	.02	5.47 (1.43-20.87)	.01	5.99 (1.55-23.13)	.009	4.94 (1.29-18.84)	.01
Substance use day-level cravings measured over the follow-up[h,i,j]								
Day-level craving for alcohol in the past 24 hours	1.02 (1.01-1.03)	<.001	1.02 (1.01-1.03)	<.001	1.02 (1.01-1.03)	<.001	1.02 (1.01-1.03)	<.001
Day-level craving for cocaine in the past 24 hours	1.03 (1.01-1.04)	.01	1.02 (1.01-1.04)	.001	1.03 (1.01-1.04)	.001	1.02 (1.01-1.04)	.001
Psychosocial factors measured at baseline[g]								
Self-esteem score[k]	0.90 (0.82-0.98)	.02	N/A[l]	N/A	N/A	N/A	N/A	N/A
Negative affect score[m]	N/A	N/A	1.08 (1.01-1.16)	.01	N/A	N/A	N/A	N/A
Perceived stress score[n]	N/A	N/A	N/A	N/A	1.06 (0.98-1.16)	.11	N/A	N/A
Depression score[o]	N/A	N/A	N/A	N/A	N/A	N/A	1.11 (1.02-1.21)	.01

[a]All adjusted models (1-4) are controlled for age in years and education (eg, having at least a BA degree).

[b]Total effect of self-esteem on substance use in a given day.

[c]*P* values were derived from random effects logistic regression.

[d]Total effect of negative affect on substance use in a given day.

[e]Total effect of perceived stress on substance use in a given day.

[f]Total effect of depression on substance use in a given day.

[g]Time invariant covariates measured at baseline.

[h]Time varying covariates measured at day 1 over the follow-up period.

[i]Day-level cravings in the past 24 hours were assessed on a scale ranging from 0 to 100, where 0 is no craving at all and 100 is the strongest craving one has ever experienced.

[j]Substance use includes those who reported heavy drinking and/or any drug use in the past 24 hours over a 2-week period.

[k]Self-esteem was measured using the "Rosenberg Self-Esteem Scale" (RSES). Higher scores represent higher self-esteem.

[l]N/A: not applicable.

[m]Negative affect was measured by summing certain items from the "Positive and Negative Affect Schedule" (PANAS).

[n]Stress was measured using the "Perceived Stress Scale" (PSS). Scores range from 0 to 40, with higher scores representing higher perceived stress.

[o]Depression was measured using the 10-item Center for Epidemiologic Studies Depression Scale Revised (CESD-10). A score of ≥10 is considered to indicate depression.

Discussion

Principal Findings

This daily diary study, which measured the predictors and day-level correlates of substance use in a given day among people who use alcohol and/or stimulants in the United States and who were recruited via MTurk, identified several important findings. Higher day-level craving scores for alcohol and stimulants predicted substance use in a given day over the 14-day follow-up period. Negative affect and depression measured at baseline were both associated with substance use in a given day. We also found that higher levels of self-esteem measured at baseline were associated with a lower odds of engaging in substance use in a given day over the follow-up period. These findings may have important implications for behavioral interventions that aim to reduce day-to-day patterns of heavy drinking and drug use among people who use alcohol and stimulants in the United States.

Using the daily dairy method, our study found day-level cravings for alcohol and stimulants to be correlated with substance use in a given day. Our study adds to existing research that supports the link between craving and substance use [15-17] by showing how cravings measured daily in one's natural environment predict substance use among MTurk users in the United States.

As such, results from this study may help further our understanding of how day-level fluctuations in cravings shape substance use patterns. Additionally, these findings point to the potential of the daily diary method in identifying high-risk days for substance use via monitoring cravings on a daily basis. This may be a promising opportunity to deploy mobile health (mHealth) or other technology-based interventions to address craving using empirically driven approaches [38]. For example, mHealth platforms, where participants can respond to drinking and drug use queries and receive timely feedback on how to avoid drug or alcohol use, have shown promise [39].

Negative affect was independently associated with substance use in a given day over the 2-week follow-up period in this study, which is consistent with prior research [40-43]. Based on this finding and former research, we believe that behavioral interventions should consider utilizing strategies to promote emotional regulation through enhancing positive emotion and sensitizing individuals to natural rewards [44]. Future studies should test whether an increase in positive affect leads to an increase in emotional regulation and a decrease in substance use. Further, utilizing technology-based interventions that address substance use in real-time and leverage mobile platforms or computers to deploy interventions may increase accessibility to efficacious treatments for people with SUD [45]. Technology-based interventions have also been proven to be cost-effective and thus a practical option in resource-limited settings [46].

Depression was associated with substance use in a given day in this study. Individuals who experience depression and engage in substance use tend to have worse treatment outcomes for both depression and substance use compared to those who experience one of these conditions alone [47]. Moreover, depression accelerates the onset of SUD and predicts relapse among people who use drugs [48]. Thus, it is recommended to treat the underlying mechanisms of both depression and substance use using transdiagnostic approaches that integrate treatments for both disorders [47]. For instance, cognitive behavioral therapy, mindfulness mediation, and acceptance-based approaches have all shown promise in addressing both depression and substance use [47], and should be considered in future intervention work. Moreover, to best address the needs of populations who use crowdsourcing platforms, delivering combined therapies that simultaneously address depression and substance use using technology-based approaches may be beneficial [38,39,49].

Higher levels of self-esteem were associated with a reduced odds of engaging in substance use over the follow-up period in our study. Previous studies have shown that self-esteem is protective against substance use and mediated by adaptive coping mechanisms among multiracial youth and college students in the United States [12,13]. Our study adds to this literature [12,13] by showing that higher levels of self-esteem are protective against substance use among MTurk-recruited adults who use alcohol and stimulants in the United States. Based on our findings and prior research [12,13], interventions for substance use should consider leveraging evidenced-based techniques, such as cognitive behavioral therapy and motivational interviewing, to enhance self-esteem and increase adaptive coping skills using technology-based platforms to engage larger populations of MTurk users [46].

MSM had significantly higher odds of engaging in substance use in a given day over the follow-up period compared to those who were not MSM in our study. Drug and alcohol use are common among MSM and have been linked to chronic stress due to sexual stigma, depression, sexual anxiety, gay community attachment, and internalized homophobia [50]. MSM also report using drugs and alcohol to enhance their sense of belonging, help cope with everyday life stress, and increase their sense of pleasure [51]. In order to reduce substance use among MSM, it is imperative to develop culturally appropriate substance use treatment programs [52] that take the underlying drivers of substance use specific to MSM into account [50].

Perceived stress was not independently associated with substance use in a given day in our study. One possible explanation for this is that our baseline measure of stress was not collected close enough to the repeated measures outcome of interest to detect an association. Stress may be a more transient experience that should be captured using repeated measures data. We recommend that future studies leveraging a repeated measures deign collect data on stress closer to the outcome measure of substance use to better understand the potential temporal effect of stress on substance use. Further, since the relationship between stress and substance use has been established in other studies [10,11], we recommend interpreting our findings with caution and continuing to address stress by enhancing adaptive coping mechanisms in interventions for substance use.

Limitations

This study has limitations. We relied on self-reported data of sensitive behaviors, such as drug and alcohol use, that were collected via daily diaries, which may be subject to social desirability bias and recall bias. These biases may threaten the reliability and validity of our findings by dampening the effect or pushing the results toward the null. However, it should be noted that the daily diary method is known to enhance the ecological validity of substance use research by collecting repeated measures over time in one's natural environment [17]. The lack of racial and ethnic diversity in our sample may limit the generalizability of our results to other populations of people who use alcohol and/or stimulants. Future MTurk studies should develop strategies to recruit more diverse samples of people who use alcohol and stimulants to broaden the applicability of the research findings [53,54]. Aside from MSM, we were not powered to detect any potential relationship between other sexual minority groups, including women who have sex, and substance use, which may limit the generalizability of our findings to sexual minorities other than MSM. All psychosocial measures were collected at baseline only; therefore, no time-varying effect can be inferred from the detected associations. Further, the relationship between stress and substance use may not have been detected because stress was not measured close enough to the repeated measures outcome. Item 10 of the CESD-10 ("I could not get going") was not included in the study survey in error, so scoring for this item was performed by taking the average scores from items 1 to 9,

which may compromise the validity of this item. Regression analyses were performed using data for complete cases only (ie, all cases with missing outcome or covariate data were excluded). Complete case analysis assumes that data are missing completely at random, which means that the cause of missing data is independent of the observed (ie, the measured outcome of interest) and unobserved (ie, other unmeasured causes) parameters of interest [34]. Although this is a strong assumption, it should be noted that the largest overall percentage of missing responses was very minimal (6.6%, for day-level cravings for stimulants in the past 24 hours) and approximately meets the rule of thumb for such an analysis [55]. Despite these limitations, this study provides several important insights into the predictors and day-level correlates of substance use among people who use alcohol and/or stimulants in the United States and who were recruited via MTurk.

In summary, day-level cravings for alcohol and stimulants, depression, negative affect, and being in the MSM group predicted substance use, and higher levels of self-esteem were protective against substance use in our sample of people who used alcohol and/or stimulants. Interventions that target biobehavioral circuitries, such as craving, should be investigated in conjunction with programs that are designed to reduce negative psychosocial stressors like depression. Substance use treatment programs may also consider employing cognitive behavioral strategies to enhance self-esteem and improve adaptive coping. Further, culturally tailored approaches should be developed to effectively engage MSM in interventions. Finally, we recommend delivering interventions for substance use using mHealth or other technology-based platforms, in order to increase the accessibility to efficacious treatments for people living with SUD in the United States.

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Conflicts of Interest

None declared.

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Abbreviations

aOR: adjusted odds ratio
AUDIT-C: Alcohol Use Disorders Identification Test-Concise
CESD-10: Center for Epidemiologic Studies Depression Scale
mHealth: mobile health
MSM: men who have sex with men
MTurk: Amazon Mechanical Turk
PANAS: Positive and Negative Affect Schedule

PSS: Perceived Stress Scale
SAMBA: Stimulants and Alcohol use in MTurk Behavioral Assessments Study
SUD: substance use disorder

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Original Paper

Exploring the Association Between Physical Activity and Risk of Mental Health Disorders in Saudi Arabian Adults: Cross-sectional Study

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Abstract

Background: The relationship between physical activity and mental health, especially the symptoms of major depressive disorder (MDD) and generalized anxiety disorder (GAD), has received increasing attention in recent years.

Objective: The aim of this study was to explore the association between fulfilling the World Health Organization (WHO) global recommendations on physical activity and the risk and symptoms of MDD and GAD in the Saudi population.

Methods: This study was a secondary analysis of data from a large nationwide cross-sectional survey conducted via phone interviews in June and July 2020. In this study, a proportional quota sampling technique was used to obtain an equal distribution of participants, stratified by age and gender, across the 13 regions of Saudi Arabia. The main mental health screening tool used for the risk of MDD was the Patient Health Questionnaire-9 (PHQ-9). Risk of GAD was measured using the Generalized Anxiety Disorder-7 (GAD-7) scale. Participants self-reported whether they fulfill the WHO global recommendations on (1) moderate-intensity aerobic physical activity (MIPA) and (2) vigorous-intensity aerobic physical activity (VIPA). The results were then analyzed based on the following two categories: fulfilling the WHO global recommendations or not.

Results: The data analysis included 8333 participants recruited in the main study between June and July 2020. The response rate was 81.45% (8333/10,231). Of them, 50.3% (4192/8333) were female, and the mean age was 36.5 years, with a median age of 36 years and a range from 18 to 90 years. The average total PHQ-9 score was 5.61, and the average total GAD-7 score was 4.18. For men, the average total PHQ-9 and GAD-7 scores were associated with fulfilling recommendations for MIPA; however, there were no associations for VIPA in both sexes. Fulfilling the WHO's recommendations for MIPA was associated with considerably fewer depressive symptoms in six of the nine items in the PHQ-9. Moreover, fulfilling recommendations for MIPA was associated with considerably fewer anxiety symptoms in six of the seven items in the GAD-7. However, fulfilling recommendations for VIPA was significantly associated with more depressive symptoms in one of the PHQ-9 items ("Thoughts that you would be better off dead or thoughts of hurting yourself in some way;" $P<.001$).

Conclusions: This study has shown that fulfilling guidelines on MIPA is associated with less overall risk of MDD and GAD in males and fewer depressive and anxiety symptoms generally in a nonclinical population. In the general population, an increase in MIPA may improve well-being and general mental health.

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KEYWORDS

Saudi Arabia; physical activity; mental health; depression; anxiety; risk; symptoms; cross-sectional; survey

Introduction

The World Health Organization (WHO) has recognized health as "A state of complete physical, mental, and social well-being and not the absence of disease or weakness" [1]. Globally, poor mental health and well-being are considered a major cause of disease, with depression considered a leading contributor [2]. According to the WHO, one in four people globally is affected by a mental disorder at some point in their life, which means 450 million people currently have such conditions [3].

Physical activity is recognized as a key factor in the prevention and management of mental illness, including, but not limited to, mental disorders such as major depressive disorder (MDD), generalized anxiety disorder (GAD), and posttraumatic stress disorder [2]. Increased physical activity can be used as a complementary strategy with other treatment modalities to prevent and manage mental health conditions, as it can delay onset and reduce a wide range of symptoms [4]. However, the WHO's recommendation for physical activity is that adults should participate in at least 150 minutes of moderate-intensity aerobic physical activity (MIPA) per week, 75 minutes of vigorous-intensity aerobic physical activity (VIPA) per week, or an equivalent combination of the two [5]. According to the WHO, the Eastern Mediterranean Region has the highest prevalence of physical inactivity (35%), and Saudi Arabia has the highest rate of physical inactivity among the Gulf Cooperation Council countries [6]. In particular, a recent study found that the prevalence of physical inactivity in Saudi Arabia (not meeting the WHO recommendations) ranged between 66.8% and 81.2%. Females and males did not differ in the frequency of physical activity [7].

A recent meta-analysis of prospective cohort studies demonstrated in subgroup analyses that depression could be reduced by 22% if participants complete 150 minutes per week of MIPA [8]. Despite this, the study was not able to describe the relationship between physical activity and mental health due to the small sample size; however, it was concluded that higher levels of physical activity were associated with a lower risk of developing depression [8]. A systematic review study found that a light amount of physical activity (<150 min/week) was also associated with a reduced likelihood of depression [9]. It is important to know whether mental health benefits can be obtained with a lower level of physical activity, particularly among those at risk of mental illness, as well as those who prefer light physical activity to MIPA [2]. However, a study conducted between July 2012 and June 2014 at psychiatric clinics in five regions of Saudi Arabia showed that higher rates of physical activity were positively correlated with primary bipolar disorders and use of antianxiety medications but negatively correlated with primary anxiety disorders, use of antidepressant medications, and use of multiple psychotropic medications [10]. However, these two studies were in hospital and university settings. No study has characterized physical activity and mental health in Saudi Arabia in community settings with national-level coverage. More studies are needed to characterize physical inactivity in Saudi Arabia and its associations with the risk of mental health disorders and mental health symptoms, as different symptoms have different risk factors and impairments [11]. Thus, the aim of this study was to explore the association between fulfilling the WHO global recommendations on physical activity and the risks and symptoms of MDD and GAD in the Saudi population.

Methods

Design

This study was a secondary analysis of a multiwave, cross-sectional, national-level mental health screening (Saudi Mental Health Surveillance System) completed via computer-assisted phone interviews conducted in two waves between June and July 2020. The full methodology and rationale were previously published as a study protocol article [12].

Participants and Recruitment

Adults aged 18 years or above from Saudi Arabia were recruited via a random phone number list generated from the Sharik Association for Health Research, a research participant database [13]. The Sharik database includes individuals interested in participating in health research, currently has more than 70,000 potential participants, is growing daily, and covers the 13 administrative regions of Saudi Arabia [13].

Sample Size

This surveillance system used a proportional quota sampling technique to achieve an equal distribution of participants, stratified by age, gender, and region within and across the 13 administrative regions of Saudi Arabia. The Saudi Mental Health Surveillance System uses two age groups based on Saudi Arabia's median adult age of 36 years. This led to a quota of 52 for this study.

The sample size was calculated based on the depth of the subanalysis needed for the surveillance system, which compares age and gender groups across regions with a medium effect size of approximately 0.3, 80% power, and a 95% CI [14]. Therefore, each quota group required 78 participants and a total sample of 312 per region for a grand total of 4056 participants per wave. Once the quota sample was reached, participants with similar characteristics were not eligible to participate in the study. The sampling process was controlled automatically by the data collection system with no human interference [15].

Variables

The data used in this secondary analysis included general demographic variables, such as age, gender, and region, and other health-related variables, such as a history of mental health conditions and physical activity.

Physical activity was assessed by asking the participants on how many days they performed the recommended levels, duration, and intensity of physical activities within the previous week, using two brief assessment tools for physical activity. For VIPA, the question was "how many times a week do you usually do 20 minutes or more of vigorous-intensity physical activity that makes you sweat or puff and pant?" (eg, heavy lifting, digging, jogging, aerobics, and fast bicycling). For MIPA, the question was "how many times a week do you usually do 30 minutes or more of moderate-intensity physical

activity or walking that increases your heart rate or makes you breathe harder than normal?" (eg, carrying light loads, bicycling at a regular pace, and doubles tennis) [16]. The answers for these two questions ranged from 0 days in the last week to 7 days in the last week. The main mental health screening tool used for the risk of MDD was the Patient Health Questionnaire (PHQ-9) [17-20]. Risk of GAD was measured using Generalized Anxiety Disorder-7 (GAD-7) [21].

Outcome Measures

To categorize the participants' physical activity, this study used the WHO's global recommendations on physical activity for adults (18-64 years old), which are in line with guidelines from the Centers for Disease Control and Prevention and the American Heart Association [22,23] as follows: (1) VIPA, 75 minutes per week or (2) MIPA, 150 minutes per week. Based on participants' self-reported responses to the interview questionnaire (ie, number of exercise minutes, frequency, and intensity level per week), two categorical outcome variables were created that reflect whether guidelines were met as follows: MIPA (1, at least 150 minutes of MIPA per week; 0, less than 150 minutes) and VIPA (1, at least 75 minutes of VIPA per week; 0, less than 75 minutes).

The PHQ-9 score is the total score of nine questions, each of which is answered on a 4-point Likert scale ranging from 0 to 3, for a final total score between 0 and 27. Similarly, the GAD-7 score is calculated as the total score of seven questions, each of which is answered on a 4-point Likert scale ranging from 0 to 3, for a final total score between 0 and 21.

Statistical Analysis

Quantitative variables are presented by mean if they have a normal distribution or by median and range, as appropriate, and compared using the *t* test. Qualitative variables are presented as percentages and CIs and compared using Pearson chi-square test. As this study used automated electronic data collection, there are no missing values. The QPlatform also includes a data integrity check to prevent users from entering invalid data [15].

Ethical Considerations

Ethical approval was obtained from the Sharik Association for Health Research institutional review board (approval number 01-2020).

Results

The data set included 8333 participants from two waves (June and July 2020). The response rate was 81.4% (8333/10,231). The mean age was 36.5 years, with a median age of 36 years and a range from 18 to 90 years. Table 1 shows the main participant characteristics.

Table 1. Participant characteristics.

Characteristic	Value (N=8333), n (%)
Gender	
Male	4141 (49.7)
Female	4192 (50.3)
Region	
Asir	643 (7.7)
Baha	625 (7.5)
Eastern Region	645 (7.7)
Hail	646 (7.8)
Jazan	645 (7.7)
Al Jouf	638 (7.7)
Madinah	641 (7.7)
Makkah	648 (7.8)
Najran	643 (7.7)
Northern Boarder	639 (7.7)
Qassim	648 (7.8)
Riyadh	643 (7.7)
Tabuk	629 (7.5)
Previously diagnosed with major depressive disorder	
Yes	191 (2.3)
No	8142 (97.7)
Previously diagnosed with generalized anxiety disorder	
Yes	130 (1.6)
No	8203 (98.4)

The average total PHQ-9 score was 5.61, and the average total GAD-7 score was 4.18. As shown in the *t* test analysis presented in Table 2 and Table 3, the average total PHQ-9 and GAD-7 scores were associated with fulfilling the recommendation for MIPA but not for VIPA.

Table 2. Independent samples *t* test of the association of moderate-intensity aerobic physical activity with the Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7 total scores.

Variable	150+ min MIPA[a]/week		*t* (df)	*P*
	No (n=6961)	Yes (n=1372)		
Mean PHQ-9[b] score	5.69	5.15	3.96 (8331)	.001
Mean GAD-7[c] score	4.33	3.95	3.06 (8331)	.002

[a]MIPA: moderate-intensity aerobic physical activity.

[b]PHQ-9: Patient Health Questionnaire-9.

[c]GAD-7: Generalized Anxiety Disorder-7.

Table 3. Independent samples *t* test of the association of vigorous-intensity aerobic physical activity with the Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7 total scores.

Variable	75+ min VIPA[a]/week		*t* (df)	*P*
	No (n=7326)	Yes (n=1007)		
Mean PHQ-9[b] score	5.63	5.40	1.48 (8331)	.137
Mean GAD-7[c] score	4.28	4.20	0.50 (8331)	.614

[a]VIPA: vigorous-intensity aerobic physical activity.

[b]PHQ-9: Patient Health Questionnaire-9.

[c]GAD-7: Generalized Anxiety Disorder-7.

In terms of the differences between males and females, in the PHQ-9 score for males, there were significant differences with MIPA (t_{4139}=3.65, *P*<.001), but not with VIPA (t_{4139}=1.21, *P*=.23). However, for females, there were no significant differences with MIPA (t_{4190}=1.31, *P*=.19) or VIPA (t_{4190}=−0.16, *P*=.87).

In the GAD-7 score for males, there were significant differences with MIPA (t_{4139}=2.38, *P*=.02), but not with VIPA (t_{4139}=0.26, *P*=.79). However, for females, there were no significant differences with MIPA (t_{4190}=1.43, *P*=.15) or VIPA (t_{4190}=−0.39, *P*=.69).

MIPA was associated with considerably fewer depressive symptoms in six of the nine items in the PHQ-9 (Table 4). Moreover, MIPA was associated with considerably fewer anxiety symptoms in six of the seven items in the GAD-7 (Table 5). However, none of the anxiety symptoms (GAD-7 items) was associated with VIPA. On the other hand, VIPA was associated with fewer depressive symptoms in three of the nine items in the PHQ-9, including “Little interest or pleasure in doing things” (*P*=.02), “Trouble falling or staying asleep, or sleeping too much” (*P*=.008), and “Feeling tired or having little energy” (*P*=.01). However, VIPA was associated with more depressive symptoms in one of the PHQ-9 items (“Thoughts that you would be better off dead or thoughts of hurting yourself in some way;” *P*<.001).

Table 4. Independent samples *t* test of the association between moderate-intensity aerobic physical activity and depressive symptoms (Patient Health Questionnaire-9 items).

PHQ-9[a] items	150+ min MIPA[b]/week[c]		*t* (df)	*P*
	No (n=6961)	Yes (n=1372)		
Little interest or pleasure in doing things	0.79	0.67	4.78 (8331)	<.001
Feeling down, depressed, or hopeless	0.81	0.70	4.64 (8331)	.001
Trouble falling or staying asleep, or sleeping too much	0.95	0.93	1.03 (8331)	.30
Feeling tired or having little energy	0.96	0.88	3.06 (8331)	.002
Poor appetite or overeating	0.72	0.68	1.57 (8331)	.12
Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0.46	0.42	1.65 (8331)	.10
Trouble concentrating on things, such as reading the newspaper or watching television	0.47	0.43	2.02 (8331)	.044
Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0.37	0.32	2.82 (8331)	.005
Thoughts that you would be better off dead or thoughts of hurting yourself in some way	0.17	0.13	2.89 (8331)	.004

[a]PHQ-9: Patient Health Questionnaire-9.

[b]MIPA: moderate-intensity aerobic physical activity.

[c]The scores of PHQ-9 items are provided.

Table 5. Independent samples *t* test of the association between moderate-intensity aerobic physical activity and anxiety symptoms (Generalized Anxiety Disorder-7 items).

GAD-7[a] items	150+ min MIPA[b]/week[c]		*t* (df)	*P*
	No (n=6961)	Yes (n=1372)		
Feeling nervous, anxious, or on edge	0.77	0.72	2.33 (8331)	.02
Not being able to stop or control worrying	0.54	0.46	3.56 (8331)	<.001
Worrying too much about different things	0.61	0.55	2.28 (8331)	.02
Trouble relaxing	0.70	0.64	2.27 (8331)	.02
Being so restless that it's hard to sit still	0.41	0.36	2.75 (8331)	.006
Becoming easily annoyed or irritable	0.80	0.77	1.10 (8331)	.27
Feeling afraid, as if something awful might happen	0.50	0.44	2.70 (8331)	.007

[a]GAD-7: Generalized Anxiety Disorder-7.

[b]MIPA: moderate-intensity aerobic physical activity.

[c]The scores of GAD-7 items are provided.

Data Availability Statement

The data are available from Sharik Association for Health Research upon request.

Discussion

Principal Findings

This study explored the association between WHO global recommendations on physical activity for mental health and the risks of MDD and GAD in a Saudi community population sample. It is one of the first and largest studies to explore the association between physical activity and risk of mental health disorders (MDD and GAD) in general population settings in Saudi Arabia. The study found that the average total PHQ-9 and GAD-7 scores were associated with fulfilling recommendations for MIPA among men only; however, there were no associations for VIPA in both sexes. Further analysis showed that the associations of fulfilling MIPA with PHQ and GAD were only significant for males. MIPA was associated with considerably fewer depressive symptoms in six of the nine items in the PHQ-9. Moreover, MIPA was associated with considerably fewer anxiety symptoms in six of the seven items in the GAD-7 scale. None of the anxiety symptoms (GAD-7 items) was associated with VIPA. On the other hand, VIPA was associated with considerably fewer depressive symptoms in three of the nine items in the PHQ-9. However, VIPA was associated with more depressive symptoms in the self-harm and suicide ideation item of the PHQ-9.

MIPA has been shown to have a significant association with better mental health in several other studies across many countries, confirming its cross-cultural effectiveness [2,4,8]. According to recent meta-analysis study findings, MIPA has significant effects on the severity of depressive symptoms among nonclinical populations (age >18 years) after supervised or unsupervised training. This effect of even low-intensity physical activity may be attributable to the exercise-induced release of neurotrophic growth factors that are responsible for nerve growth and synaptic plasticity in the brain [24]. However, other studies found different effects of physical activity on mental health in relation to gender [26].

VIPA is generally associated with better mental well-being, including coping, autonomy, and personal growth [26,27]. However, some evidence suggests that VIPA may have no association with depression and anxiety, although VIPA is associated with better scores for some depressive symptoms [27-30]. One explanation is that VIPA may be associated with more negative affective states during participation, compared with MIPA, which can predict dropout and therefore reduce the likelihood of meeting physical activity guidelines [2,31]. In addition, the strenuous nature of VIPA may also undermine competence, particularly for those who are inactive [2,31]. Finally, due to its extreme nature, VIPA may not be suitable for everyone and, apart from a few experimental studies, might not be adopted for enough time to show effects on MDD and GAD in the general population.

One strength of this study was the exploration of the association between physical activity and individual symptoms of depression/anxiety, as mental health symptoms may differ in their etiology, risk factors, impairment, etc, and thus may show differential associations with physical activity [11,25]. Analyzing individual symptoms and their causal associations is an initial step toward personalized treatment of mental health disorders that recognizes the heterogeneity of MDD and GAD [11]. A previous study explored the association between individual symptoms of MDD and physical activity and found that eight out of 26 symptoms were relevant in young adults diagnosed with MMD [25].

This study was limited by its cross-sectional design, which prevented the analysis from generating the direction of the association between physical activity and the risks of MDD and GAD. The study was also limited by its bivariate analysis, which may be affected by other behavioral factors. However, it provided initial insights on the effect of physical activity on mental health in a general community setting in Saudi Arabia, which adds to the global literature in this area of research. The findings of this study may be relevant to other countries with

high levels of physical inactivity like Saudi Arabia, but generalization of the results to other countries may be limited.

Conclusion

This study found that fulfilling guidelines on MIPA (150 min/week) is associated with lower depression scores among male participants and generally fewer depressive and anxiety symptoms. Increasing the general population's awareness of the need to increase moderate physical activity levels may improve the population's mental health.

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Authors' Contributions

NFB, NAA, and MHB participated in the conceptual design and formulation of the research questions. All authors participated in the development and review of the manuscript. NAA supervised and managed the data collection process. NAA and NFB analyzed the data.

Conflicts of Interest

None declared.

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Abbreviations

GAD: generalized anxiety disorder
GAD-7: Generalized Anxiety Disorder-7
MDD: major depressive disorder
MIPA: moderate-intensity aerobic physical activity
PHQ-9: Patient Health Questionnaire-9
VIPA: vigorous-intensity aerobic physical activity
WHO: World Health Organization

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Original Paper

Association of Opioid Use Disorder With 2016 Presidential Voting Patterns: Cross-sectional Study in New York State at Census Tract Level

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Abstract

Background: Opioid overdose-related deaths have increased dramatically in recent years. Combating the opioid epidemic requires better understanding of the epidemiology of opioid poisoning (OP) and opioid use disorder (OUD).

Objective: We aimed to discover geospatial patterns in nonmedical opioid use and its correlations with demographic features related to despair and economic hardship, most notably the US presidential voting patterns in 2016 at census tract level in New York State.

Methods: This cross-sectional analysis used data from New York Statewide Planning and Research Cooperative System claims data and the presidential voting results of 2016 in New York State from the Harvard Election Data Archive. We included 63,958 patients who had at least one OUD diagnosis between 2010 and 2016 and 36,004 patients with at least one OP diagnosis between 2012 and 2016. Geospatial mappings were created to compare areas of New York in OUD rates and presidential voting patterns. A multiple regression model examines the extent that certain factors explain OUD rate variation.

Results: Several areas shared similar patterns of OUD rates and Republican vote: census tracts in western New York, central New York, and Suffolk County. The correlation between OUD rates and the Republican vote was .38 (P<.001). The regression model with census tract level of demographic and socioeconomic factors explains 30% of the variance in OUD rates, with disability and Republican vote as the most significant predictors.

Conclusions: At the census tract level, OUD rates were positively correlated with Republican support in the 2016 presidential election, disability, unemployment, and unmarried status. Socioeconomic and demographic despair-related features explain a large portion of the association between the Republican vote and OUD. Together, these findings underscore the importance of socioeconomic interventions in combating the opioid epidemic.

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KEYWORDS

opioid use disorder; opioid poisoning; racial and ethnic disparities; geographic variance; sociodemographic factors; presidential election

Introduction

The United States is experiencing an epidemic of nonmedical opioid use involving both prescribed pain relievers and illegal drugs such as heroin and fentanyl. In 2017, the US Department of Health and Human Services declared the opioid crisis a public health emergency [1]. Geographic variation is a crucial factor in studying patterns in opioid deaths. Previous studies have

shown that certain state- or county-level characteristics such as rurality, poverty, educational attainment, health care access, and racial demographics are associated with higher opioid use [2-4]. Opioid use disorder (OUD) is defined as a problematic pattern of opioid use leading to problems or distress with at least 2 use-related symptoms over a 12-month period, including impaired control (eg, craving, desire to cut down, taking more than intended), social impairment (eg, social or interpersonal problems, reduction in important activities), risky use (use in hazardous situations, continued use that worsens a physical or mental problem), or noniatrogenic tolerance and/or withdrawal [5]. The public face of the opioid epidemic has been represented by the increasing prevalence of opioid-related drug overdoses and resulting fatalities, typically due to respiratory depression [1]. Whether fatal or not, these diagnoses of opioid overdoses are commonly represented in health databases as opioid poisoning (OP) events [6].

An earlier study observed similarities between geographic variation of opioid use and Republican voters at the county level [7]. Rather than being directly causal, this association is likely driven by external factors shared by both opioid users and voters for the Republican candidate in the 2016 election. Understanding the nature of this relationship helps to place the opioid epidemic in its larger sociopolitical context and further illuminates the importance of addressing socioeconomic factors in order to fight the opioid epidemic. Prior analysis suggested higher rates of county-level public health measures such as physically unhealthy days, mentally unhealthy days, age-adjusted mortality rate, teen births, diabetes, and obesity were associated with shifting to the Republican presidential candidate in the 2016 election [8]. Because OUD and OP are associated with both physical and mental distress, which can be proxied by the above measures, we explored the relationship of OUD and OP to demographic and other variables including voting for the Republican candidate [9].

While the prevalence of OUD is greater than that of OP, there is certainly overlap in OP and OUD populations, since OUD is a major risk factor for opioid overdose; however, significant OP also occurs in subpopulations not identified as high risk (high risk being those with chronic opioid use, nonmedical opioid use, OUD) [6,10]. As such, we chose to investigate these related but nonidentical populations at the census tract (CT) level in respect to voting patterns in the 2016 presidential election.

Our aim is to better understand the interconnected relationship between opioid use, Republican voting, and other demographic factors in New York State. Our analysis is at the CT level, which provides a much higher resolution than previous studies. Census tracts generally contain between 2500 to 8000 people [11], far fewer than the 100,000-inhabitant average at the county level. This fine-grained analysis makes our spatial correlations much more powerful, better revealing how different factors contribute to OUD and OP in communities across New York State.

Methods

This study was approved by the Stony Brook University institutional review board and the Office of Quality and Patient Safety, Department of Health of New York State. Informed consent was not needed as the study had no contact with participants and the data were obtained from a New York State administrative database. The primary research question and analysis plan were not preregistered on a publicly available platform, and thus the results should be considered exploratory.

Data Collection

The presidential voting results of 2016 were obtained from the Harvard Election Data Archive [12]. These data provided the number of votes for each candidate at an election precinct level, a geographic region generally smaller than the CT level. Several counties (eg, Wyoming County) had incomplete or incoherent data, so those counties were contacted directly to provide election data. The dataset was joined to a geospatial, precinct-level shapefile in ArcGIS Desktop 10.7.1 (Esri). The precinct-level voting data was extrapolated to the larger CT level by area-based estimation (Multimedia Appendix 1). The CT voting counts were a linear combination of the precinct-level voting counts and precinct area percentage within that CT (CT components add up to 1). The number of votes for each candidate was then normalized by US Census population estimates of each CT.

The demographic data were taken from the American Community Survey (ACS) by the US Census Bureau. CT level education, age, marriage, unemployment, income, population, race, gender, disability, and health care data (Medicare and Medicaid eligibility) were provided in the 2012-2016 ACS 5-year estimates [13]. These data were mapped to a CT shapefile. Urban-ness is taken from the 2010 Census Summary File and is calculated as the number of households living in an urban area divided by the total number of households in the CT [14].

The opioid-related patient information was extracted from the Statewide Planning and Research Cooperative System (SPARCS) database, a central administrative repository for health event claims data for New York State patients [6]. We extracted patients based on International Classification of Diseases (ICD) codes (primary and secondary diagnosis codes, ICD-9 from January 1, 2012, to September 30, 2015, and ICD-10 from October 1, 2015, to December 31, 2016). Two cohorts of patients were extracted; first, patients diagnosed with OP (Multimedia Appendix 2) between 2012 and 2016, and second, patients diagnosed with OUD (Multimedia Appendix 3) between 2010 and 2016. For converting home addresses to geolocations (latitude and longitude), we used EaserGeocoder, an open source geocoding software [15]. The geocoding process runs in-house, and therefore no sharing of patient data is needed. It was not possible to convert all patient addresses to geolocations, as some of them were either invalid or PO Box addresses instead of street addresses. These patient geolocations were added to the CT shapefile, then grouped and counted within a CT. OP and OUD rates per 100,000 persons were calculated for each CT. The SPARCS data also have patient-level demographic and other characteristics such as gender, age, race, and type of payment. We included 63,958 patients who had at least one OUD diagnosis between 2010 and 2016, and 36,004 patients with at least one OP diagnosis between 2012 and 2016.

There are 4919 total CTs in New York State according to ACS 2012-2016 5-year estimates. The 2016 voting data from Harvard Dataverse included data for 4900 (99.6%) CTs. After removing CTs with populations less than 100, 4836 (98.3%) CTs remained. These CTs were then used in the spatial mappings, of which 63 CTs had missing education data, 129 had missing income data, 61 had missing marital/race/gender data, and 69 had missing disability data. Excluding these CTs with missing values left 4777 (97.1%) CTs remaining for CT characteristic analyses.

Analysis

The analyses were divided into 2 parts, one at the patient level using the SPARCS dataset and the other at the CT level while combining the CT dataset and the SPARCS dataset. First, descriptive statistics of patient-level characteristics were calculated for OUD and all patients in the SPARCS dataset. A logistic regression model was used to determine the associations between patient-level characteristics (eg, sex, age group, race, and payment type) with OUD. Odds ratios and their 95% confidence intervals were estimated based on the logistic regression. Second, maps for crude rates of opioid overdose normalized by population for OP and OUD and maps for 2016 Republican presidential vote rates were generated for CTs with ArcGIS. The OUD rates were heavily positively skewed due to the high resolution of the geography level and low counts of opioid use for each CT. Spearman rank order correlations were calculated to evaluate the association between OP/OUD and presidential election voting rates. The averages for CT-level demographics and socioeconomic factors were calculated and compared between the CTs with OUD rates in the lowest (1% to 25%) quartile and CTs with OUD rates in the highest (76% to 100%) quartile using *t* tests. To assess the extent to which the Republican presidential vote association with OUD is explained by CT-level characteristics, 3 regression models were built with the OUD rate as the dependent variable. Model 1 included only the percentage of voting for the Republican presidential candidate. Model 2 adjusted for CT demographic and socioeconomic features, and model 3 additionally aggregated medical factors and median age. Multicollinearity among covariates was evaluated using variation inflation factor.

The standardized regression coefficients and partial R^2 were reported. Statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing) and Python 3.7 (Python Software Foundation).

Results

The patient-level characteristics of OUD and all patients in the SPARCS dataset are shown in Table 1. All patient-level characteristics are significantly associated with OUD. A male patient is 1.735 times more likely to have OUD than a female. The young adult (aged 18 to 24 years) age group is the most active in nonmedical opioid use, so this serves to be a good reference for odds ratio [16]. Compared with the young adult age group, all other age groups are less likely to have OUD (all OR <1.00, P<.001).

Table 1. Characteristics of Statewide Planning and Research Cooperative System database patients associated with opioid use disorders in New York State, 2010-2016.

Characteristics	All SPARCS[a] (in and out) patients 2010-2016 (N=210,935,831), n (%)	OUD[b] patients 2010-2016 (n=63,958), n (%)	Odds ratio (95% CI)	*P* value
Sex				
Female	119,850,432 (56.18)	27,590 (43.13)	1 (Ref)	—[c]
Male	91,076,257 (43.18)	36,366 (56.86)	1.73 (1.71-1.76)	<.001
Age in years				
<18	26,893,357 (12.75)	1713 (2.68)	0.12 (0.11-0.12)	<.001
18-24	17,276,865 (8.19)	9435 (14.75)	1 (Ref)	—
25-39	38,832,961 (18.41)	19,402 (30.34)	0.92 (0.89-0.94)	<.001
40-64	74,991,993 (35.55)	24,078 (37.65)	0.59 (0.58-0.60)	<.001
≥65	46,078,300 (21.84)	9330 (14.59)	0.37 (0.36-0.38)	<.001
Race				
White, non-Hispanic	90,255,132 (42.79)	42,764 (66.86)	1 (Ref)	—
Black, non-Hispanic	41,978,134 (19.90)	6881 (10.76)	0.35 (0.34-0.36)	<.001
Hispanic	50,616,600 (24.00)	9176 (14.35)	0.38 (0.37-0.39)	<.001
Other	26,489,568 (12.56)	5097 (7.97)	0.41 (0.39-0.42)	<.001
Payment type				
Insurance company	43,520,092 (20.63)	14,378 (22.48)	1.91 (1.87-1.95)	<.001
Medicare	28,390,633 (13.46)	14,564 (22.77)	1.26 (1.23-1.29)	<.001
Medicaid	17,920,248 (8.50)	6390 (9.99)	1.34 (1.31-1.38)	<.001
Self-pay	28,652,602 (13.58)	8810 (13.77)	1.16 (1.13-1.19)	<.001
Other	43,520,092 (20.63)	14,378 (22.48)	1.91 (1.87-1.95)	<.001

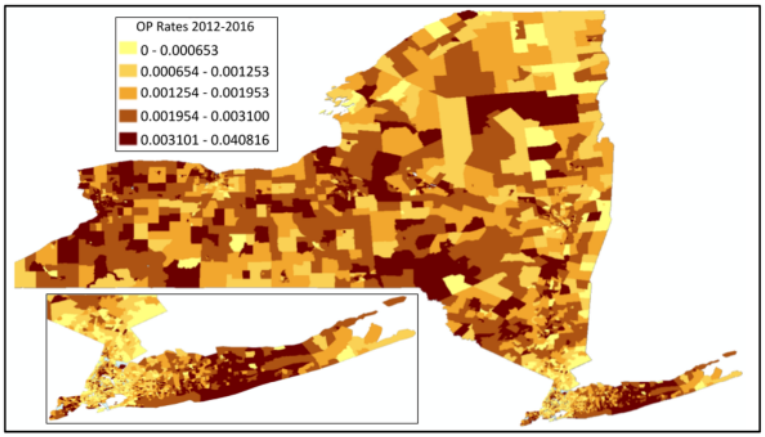
[a]SPARCS: Statewide Planning and Research Cooperative System.

[b]OUD: opioid use disorder.

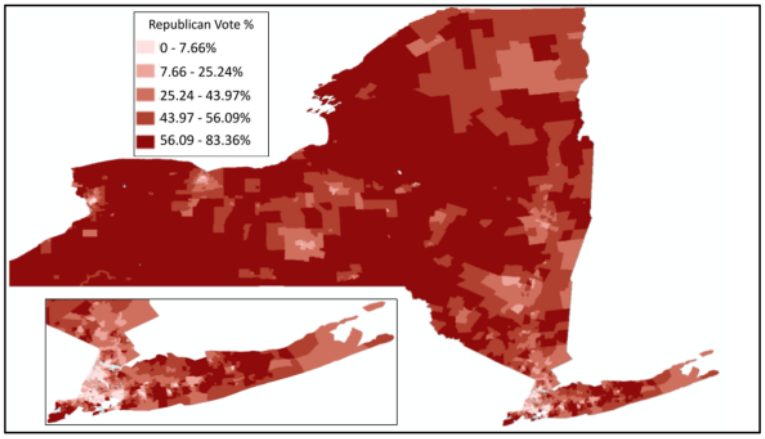
[c]Not applicable.

Figure 1 illustrates opioid use and Republican voting in 4836 of 4919 CTs in New York State. Each map has color ranges ordered by quintiles at the CT level. The first map (A) shows OP rates 2012-2016 with a closer look into New York City and Long Island, which have rates among the highest in the state [13]. About 1 in 5 CTs had more than 310 OP diagnoses per 100,000 persons, while a similar proportion had fewer than 65 diagnoses per 100,000 persons. The areas of higher OP diagnoses were Suffolk County on eastern Long Island, Erie County in western New York, Oneida/Onondaga Counties in central New York, and Delaware/Broome Counties in the Southern Tier. Metro areas varied in OP rates. The second map (B) portrays the percentage of the presidential vote for the Republican candidate for each CT. Note that large urban areas had, for the most part, lower support for the Republican candidate. Several areas shared similar patterns to the OP rates shown in map A: primarily, CTs in western New York, central New York, and Suffolk County. The third map (C) shows OUD rates 2010-2016 at the CT level. The results are similar to map A. The spearman correlation between maps A and B was 0.38 (*P*<.001), between maps B and C was 0.38 (*P*<.001), and between maps A and C was 0.86 (*P*<.001).

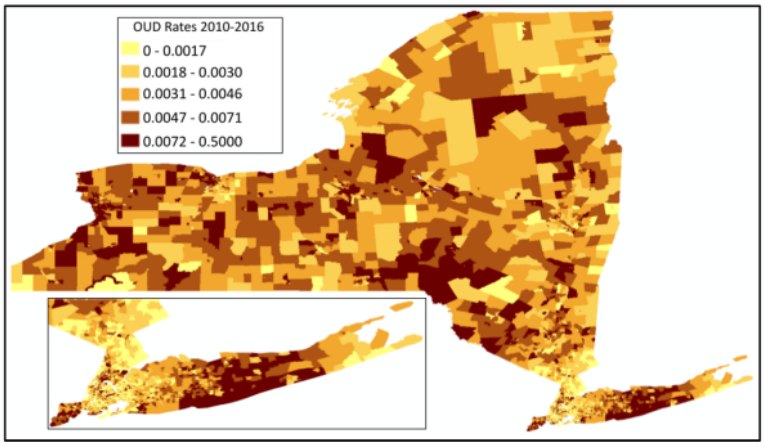
Figure 1. Opioid use and Republican presidential vote 2016 in New York State at census tract level: (A) 2012-2016 opioid poisoning rates by census tract per 100,000 people, (B) Republican presidential vote rate by census tract, 2016, (C) 2010-2016 opioid use disorder rates by census tract per 100,000 people.



(A) 2012-2016 opioid poisoning rates by census tract per 100,000 people.



(B) Republican presidential vote rate by census tract, 2016.



(C) 2010-2016 opioid use disorder rates by census tract per 100,000 people.

Next, we examined the CT-level characteristics between the Republican presidential vote and opioid use. In Table 2, we tested the differences in the average of various socioeconomic and demographic features at the CT level between the low- and high-OUD CTs. CTs were ranked by OUD rates, and the lowest and highest quartiles were used for comparison. The Republican presidential vote demonstrated the highest differences between high- and low-OUD rate CTs, with the former voting at an average rate of 42.86% (SE 0.56%, $P<.001$) for the Republican candidate, more than twice the average rate of 20.85% (SE 0.55%) for lower OUD rate CTs. Other characteristics with relatively large interquartile differences include percentage of population with disabilities, percentage of white population, and percentage of households in urban areas.

Table 2. Characteristics compared between census tracts with lower opioid use versus census tracts with higher opioid use in New York State, 2010-2016.

Characteristics	Total (n=4777), mean (SE)	Lower OUD[a] rate tracts (n=1193), mean (SE)	Higher OUD rate tracts (n=1194), mean (SE)	Mean difference higher-lower (95% CI)	*P* value
Disability %	11.59 (0.07)	9.31 (0.11)	14.45 (0.17)	5.14 (4.74 to 5.54)	<.001
Republican vote %	33.66 (0.32)	20.85 (0.55)	42.86 (0.56)	22.01 (20.47 to 23.55)	<.001
Marriage %	44.39 (0.19)	43.45 (0.38)	41.79 (0.38)	–1.66 (–2.71 to –0.61)	.002
Urban %	87.45 (0.43)	95.61 (0.55)	86.09 (0.90)	–9.52 (–11.59 to –7.45)	<.001
Male %	48.52 (0.06)	48.14 (0.13)	48.74 (0.12)	0.60 (0.25 to 0.95)	.0007
White %	63.69 (0.46)	47.90 (0.92)	74.71 (0.77)	26.81 (24.46 to 29.16)	<.001
Unemployment %	7.96 (0.07)	7.95 (0.14)	8.67 (0.16)	0.72 (0.30 to 1.14)	.0007
Medicare eligible %	10.47 (0.07)	11.93 (0.16)	9.40 (0.12)	–2.53 (–2.92 to –2.14)	<.001
Medicaid eligible %	12.92 (0.07)	13.79 (0.16)	12.15 (0.13)	–1.64 (–2.04 to –1.24)	<.001
High school diploma %	27.27 (0.14)	24.17 (0.30)	31.60 (0.23)	7.43 (6.68 to 8.20)	<.001
Median age	39.15 (0.10)	37.20 (0.20)	39.87 (0.20)	2.67 (2.12 to 3.22)	<.001
Median income ($)	65,913.31 (467.12)	69,461.49 (1003.40)	55,756.10 (790.90)	–13,705.39 (–16,210.84 to –11,199.94)	<.001

[a]OUD: opioid use disorder.

Finally, we analyzed the extent to which the Republican presidential vote explains the variation of OUD rates with adjustment for CT-level characteristics. Table 3 shows 3 multiple linear regression models with adjustment for CT characteristics. Model 1 only includes the percentage of Republican vote, which shows a positive relationship and explains 5% of the county-level variation in opioid use. Model 2 accounts for several CT characteristics in addition to the Republican vote and explains 24% of the variation in OUD rates. The percentage of Republican vote explains 3% of the variation in OUD rates. Model 3 includes all of the characteristics in Table 2, adding health care–related factors (Medicare eligibility and disability) as well as median age. Medicaid was not included because it had a high collinearity with Medicare (variation inflation factor = 7.5, correlation = 0.88). The model explains 30% of the variation in OUD rates, and the percentage of Republican votes explains 1% of the variation in OUD rates. From models 2 and 3, the most prominent variables that explain the variation in CT OUD rates are disability rates, percentage of Republican vote, and marriage rates.

Table 3. Socioeconomic and demographic factors associating the Republican vote with opioid use disorder rates per 100,000 people, 2010-2016.

Characteristics	R^2	Partial R^2	Standardized regression coefficient	Standard error	*P* value
Model 1	.05	—[a]	—	—	—
Intercept	—	—	<.001	.01	1
Republican vote %	—	.05	.23	.01	<.001
Model 2	.24	—	—	—	—
Intercept	—	—	<.001	.01	1
Marriage %	—	.07	–.40	.02	<.001
Republican vote %	—	.03	.32	.03	<.001
White %	—	.03	.28	.03	<.001
Urban household %	—	.02	.14	.01	<.001
High school diploma %	—	.01	.13	.02	<.001
Unemployment %	—	.01	.12	.02	<.001
Male %	—	.004	.06	.01	<.001
Median income, per $1000	—	.002	–.02	.02	.35
Model 3	.30	—	—	—	—
Intercept	—	—	<.001	.01	1
Marriage %	—	.04	–.32	.02	<.001
Disability %	—	.05	.27	.02	<.001
Republican vote %	—	.01	.24	.03	<.001
White %	—	.02	.22	.02	<.001
Urban %	—	.03	.17	.01	<.001
High school diploma %	—	.01	.13	.02	<.001
Male %	—	.01	.09	.01	<.001
Medicare eligible	—	.006	–.07	.01	<.001
Unemployment %	—	.003	.06	.02	<.001
Median income $	—	.002	.06	.02	.001
Median age	—	.0005	.03	.02	.12

[a]Not applicable.

Discussion

Principal Findings

The demographic findings for OUD in New York State were generally consistent with recently published epidemiology of the US opioid epidemic in that young adult white males are overrepresented [16].

We have explored the specific geographic relationships between opioids, voting patterns, and demographic features like disability and unemployment. Disability may be the easiest factor to explain. In the United States, the largest proportion of years lived with a disability is attributable to chronic noncancer pain, and globally, musculoskeletal (ie, back and neck) pain is the third leading cause of disability-adjusted life-years [17]. As chronic pain is well described as the most common source of chronic disability in the United States, and opioid treatment is also well described as increasing the odds ratio for the development of OUD, especially with chronic exposure [18,19], it is reasonable to expect that the odds ratio for OUD is increased in patients with chronic disabling conditions. Additionally, OUD related to use of prescription pain medications is highly disabling, which offers another linkage to our finding [20].

Next, the small but significant contribution of differences in marriage status is also meaningful in the context of social and economic changes that have paralleled and likely contributed to the arc of the opioid epidemic over the past 25 years [21]. In our analysis, the interquartile differences demonstrated a small but significant negative correlation between marriage percentage and OUD. Monnat and Brown [22] describe “landscapes of despair”—the small cities and rural areas where over several decades social and family conditions have been deteriorating as economic distress (eg, job loss due to manufacturing and natural resource industry decline) has been mounting. They found, consistent with our findings, the highest percentage of 2016 Republican voting over the 2012 baseline in the top

quartile of counties with the lowest well-being, which included higher separation and divorce rates as compared with the quartile of counties with the highest well-being [22]. These locales are also where the 2016 Republican candidate overperformed compared with Republican voting patterns in the 2012 election: counties with the highest rate of deaths of despair (ie, those with the highest drug, alcohol, and suicide mortality rates attributable in large measure to economic distress and a large working class) [23]. The interquartile comparisons between high- and low-OUD rate CTs in Table 2 resonate with these landscapes of despair in that in addition to the large difference (>100%) in Republican vote, they generally demonstrate face validity in the valence of the correlations in the high-OUD tracts: higher percentage White, more disability, unemployment, high school diploma as terminal degree, and male gender with less marriage, urbanicity, and median income.

Understanding these landscapes of despair is crucial because opioids are an anodyne to both physical and emotional pain. Whereas life expectancy continues to rise in wealthy market economies, recent studies reveal a grim picture of increasing morbidity and all-cause mortality of middle-aged white non-Hispanic US men and women since 1999, mostly due to drug and alcohol poisonings, suicide, and alcohol-related liver diseases, especially among those with high school education or less [24,25]. In addition, compared with college-educated people, since 1950, those without a bachelor's degree have a higher prevalence of pain at each age, a prevalence that is increasing with each successive birth cohort [26]. Among validated voters in 2016, the Republican candidate won by more than 2 to 1 (64% to 28%) among white voters who had not completed college (44% of all voters), which aligns with the demographics of OUD [27]. These facts may also help explain the relationship between opioids and voting patterns. A political candidate might have appealed to the residents of these landscapes by resonating with their emotional and physical needs, their sense of lost status, opportunity, and agency, and presenting themself as a kind of anodyne by promising to uplift them economically and/or sociopolitically [28].

We have shown that Republican voting percentage is independently associated with OUD in model 1 and remains significant in model 2 and 3 with adjustment for other covariates. This is sufficient to show Republican voting percentage is an important associated factor of OUD. Although a causal relationship cannot be inferred, our model clusters lower odds of having a marital partner, increased disability, voting Republican, and high school diploma as a terminal degree with risk for OUD, as well as being male, white, urban, and unemployed. Our findings highlight the relationship between OUD and factors related to despair, suggesting that socioeconomic growth may be necessary to successfully fight the opioid epidemic, in addition to traditional interventions like improved access to OUD treatment. Disability, unemployment, and nonmarried status do not have to cause despair but are likely to do so in communities that lack a safety net, both economically and socially. Understanding and responding to the needs of these "landscapes of despair" may be key to reversing the opioid epidemic and may also affect the political direction of the United States.

Limitations

Our study has a few limitations regarding the method and underlying assumptions about the population. It is important to note that the population base containing the sample that voted Republican in 2016 is not the same as the population base data we used to determine OUD but rather they were generalized and configured to the CT level. In addition, for the purposes of constructing our statistical analyses, we assumed in these populations that socioeconomic and demographic factors affect OUD rates. All associations in our study were found to be mild. This could partially be due to the retrospective study design and inaccuracy in the aggregated census data. In the future, a well-designed prospective study may reveal more accurately the influence of socioeconomic and demographic factors on OUD. Last, in order to converge the datasets appropriately, we assumed that the population in which we drew data to determine OUD was also alive and voting in the 2016 election.

Conclusions

The association between the 2016 Republican presidential vote and OUD highlights the demographic, geographic, and socioeconomic characteristics that underpin both features. Studying opioid use at a finer grain geospatial level provides a unique opportunity for a more precise understanding of the opioid epidemic at large scale.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Illustration of data conversion from precinct level to census tract level. The blue-outlined polygon is a census tract and the black-outlined polygons are precincts. To convert precinct level election data to the census tract level, precinct areas within each census tract were calculated (table in figure). The linear combination of voting counts and area percentage provides an estimate of the vote counts at the census tract level.

[PNG File , 555 KB - publichealth_v7i4e23426_app1.png]

Multimedia Appendix 2
International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes related to opioid poisoning.
[DOCX File , 17 KB - publichealth_v7i4e23426_app2.docx]

Multimedia Appendix 3
International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes related to opioid use disorder.
[DOCX File , 18 KB - publichealth_v7i4e23426_app3.docx]

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Abbreviations

ACS: American Community Survey
CT: census tract
ICD: International Classification of Diseases
OUD: opioid use disorder
OP: opioid poisoning
SPARCS: Statewide Planning and Research Cooperative System

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Original Paper

Monitoring Information-Seeking Patterns and Obesity Prevalence in Africa With Internet Search Data: Observational Study

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Abstract

Background: The prevalence of chronic conditions such as obesity, hypertension, and diabetes is increasing in African countries. Many chronic diseases have been linked to risk factors such as poor diet and physical inactivity. Data for these behavioral risk factors are usually obtained from surveys, which can be delayed by years. Behavioral data from digital sources, including social media and search engines, could be used for timely monitoring of behavioral risk factors.

Objective: The objective of our study was to propose the use of digital data from internet sources for monitoring changes in behavioral risk factors in Africa.

Methods: We obtained the adjusted volume of search queries submitted to Google for 108 terms related to diet, exercise, and disease from 2010 to 2016. We also obtained the obesity and overweight prevalence for 52 African countries from the World Health Organization (WHO) for the same period. Machine learning algorithms (ie, random forest, support vector machine, Bayes generalized linear model, gradient boosting, and an ensemble of the individual methods) were used to identify search terms and patterns that correlate with changes in obesity and overweight prevalence across Africa. Out-of-sample predictions were used to assess and validate the model performance.

Results: The study included 52 African countries. In 2016, the WHO reported an overweight prevalence ranging from 20.9% (95% credible interval [CI] 17.1%-25.0%) to 66.8% (95% CI 62.4%-71.0%) and an obesity prevalence ranging from 4.5% (95% CI 2.9%-6.5%) to 32.5% (95% CI 27.2%-38.1%) in Africa. The highest obesity and overweight prevalence were noted in the northern and southern regions. Google searches for diet-, exercise-, and obesity-related terms explained 97.3% (root-mean-square error [RMSE] 1.15) of the variation in obesity prevalence across all 52 countries. Similarly, the search data explained 96.6% (RMSE 2.26) of the variation in the overweight prevalence. The search terms yoga, exercise, and gym were most correlated with changes in obesity and overweight prevalence in countries with the highest prevalence.

Conclusions: Information-seeking patterns for diet- and exercise-related terms could indicate changes in attitudes toward and engagement in risk factors or healthy behaviors. These trends could capture population changes in risk factor prevalence, inform digital and physical interventions, and supplement official data from surveys.

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KEYWORDS

obesity; overweight; Africa; chronic diseases; hypertension; digital phenotype; infodemiology; infoveillance

Introduction

Globally, obesity and overweight are the fifth leading cause of death, associated with at least 2.8 million adult deaths each year [1,2]. In Africa, the burden of obesity and overweight has increased significantly over the last two decades [3-6]. Among sub-Saharan African women, the prevalence of obesity increased by 12% between 1975 and 2016, while the prevalence of overweight increased by 24% [7-9]. Among men, obesity prevalence increased by 5%, while overweight prevalence increased by 15% in the same period [7-9].

Insufficient exercise and unhealthy diets (partly due to a nutrition transition from nutrient-dense foods to energy-dense foods) coupled with tobacco use and excessive alcohol consumption (factors predominantly associated with an urban lifestyle) are to blame for the increase in noncommunicable disease burden in Africa [10,11]. Specifically, urbanization and related economic advancements including higher income, higher education, and higher socioeconomic status have been associated with higher obesity prevalence [12-16]. Aging, cultural norms (eg, in some cultures female fatness symbolizes beauty, prosperity, and fertility), and television viewing habits have also correlated with increasing obesity prevalence [16-20].

Persons who are obese or overweight are at a higher risk of developing other medical conditions including hypertension, cardiovascular disease, type 2 diabetes, and stroke [21-24]. Joubert et al [25] noted that 68% of hypertensive disease, 38% of ischemic heart disease, 78% of type 2 diabetes, and 45% of ischemic stroke among adults in South Africa were due to obesity. The burden of obesity-associated noncommunicable diseases is expected to continue to increase in sub-Saharan African countries. Data suggest that millions of people living with diabetes in sub-Saharan Africa are unaware of their status and many lack access to necessary information and medications [4,26-29]. Furthermore, obesity-related diseases have been associated with an increased risk of severe COVID-19 disease [30].

The rise in prevalence of noncommunicable diseases in Africa creates new challenges that many health care systems are not currently equipped to manage. Furthermore, the lack of high-quality data also creates a barrier in quantifying public health needs and addressing the impact of diseases [31]. This data limitation includes a substantial gap in the standard and availability of health data, especially where health information is not digitized or comprehensive [31].

Usually, data on behavioral risk factors are collected through surveys, which can be costly and capture only a single time point. In contrast, digital data from internet sources can capture timely changes in attitudes toward and engagement in risky behaviors. While computational and statistical approaches have been successfully used to process data from digital sources for monitoring infectious disease reports and chronic disease risk factors, few studies have focused on Africa [31-43]. As more people in Africa use internet platforms and mobile phones for seeking and sharing information, it is important to understand how behavioral data shared on digital platforms can be used to support and develop timely disease and risk factor surveillance platforms. Here, we assess how diet- and exercise-related searches submitted on an internet search engine can be used for monitoring information-seeking patterns and obesity prevalence in 52 African countries.

Methods

Data Collection

Search data were collected for 108 search terms (Multimedia Appendix 1) from Google application programming interfaces. The search terms included terms related to chronic diseases, risk factors, diet, and physical activity. To generate a comprehensive list of terms, we used the Google Trends website [44] to identify terms that had similar search trends for chronic diseases and their associated risk factors. We collected the yearly search volume for each country from 2010 to 2016 for 52 countries in English [45]. Google normalizes the search volume for each term relative to the search activity in the country and the specific time period. Two countries (South Sudan and Sudan) were excluded because obesity prevalence estimates were unavailable for these countries.

We also downloaded age-standardized obesity and overweight prevalence estimates for adults aged 18 years and older from 2010 to 2016 from the World Health Organization (WHO) website [46,47]. These estimates were obtained using data from population-based studies on cardiometabolic risk factors, multicountry and national measurement surveys, as well as the WHO STEPwise approach to surveillance (STEPS) surveys for estimating BMI [48]. Overweight was defined as a BMI >25 kg/m^2 and obese was defined as a BMI ≥30 kg/m^2 [49]. The reported credible intervals (CIs) for the estimates represented the 2.5th and 97.5th percentiles of the posterior distributions.

Machine Learning Methods

We used machine learning methods to identify search patterns that were associated with changes in obesity and overweight prevalence across African countries. Specifically, we employed support vector machine (SVM), random forest (RF), gradient boosting, and Bayes generalized linear model (GLM). The machine learning methods were selected to assess a broad range of approaches from decision tree methods, kernel-based approaches, and least squares regression methods. We implemented these methods using the SuperLearner package in R [50,51], which generates estimates for each individual method and an ensemble of the methods.

RF regression is an extension of bootstrap aggregating (“bagging”). It involves the construction of de-correlated decision trees, which are averaged to reduce the variance of the prediction function. Trees are preferred candidates for bagging because they capture the complex interaction structures in the data and have relatively low bias if grown deep. Since each generated tree in bagging is identically distributed, the average of B such trees is the same as the likelihood of any one of the trees. The gradient boosting algorithm also involves the generation of ensembles of predictive trees. However, trees are built using the gradient boosting approach, which involves a sequential iterative fitting procedure to reduce bias by assigning higher weights to poorly fit samples and optimization via a loss

function. An advantage of the gradient boosting algorithm is that nonlinearities and interactions do not need to be explicitly specified.

In contrast, SVM regression is similar to multiple linear regression when the relationship between X and y is linear: $y = f(x) = W \cdot X + b$. However, SVM regression involves the application of kernel functions (eg, gaussian, polynomial, radial basis, and sigmoid kernel) to model nonlinearity between X and y. The SVM regression model parameters are selected to minimize an epsilon-insensitive cost function. The model parameters were selected by applying cross-validation to the training data.

Lastly, Bayes GLMs are a class of GLMs that are a generalization of linear regression models such that the distribution of the dependent variable is of the exponential family (eg, gaussian, poisson, binomial, categorical, multinomial, or beta). In the Bayesian approach, inferences are based on the posterior distribution, prior knowledge is captured quantitatively through the prior distribution, and the data are represented through the likelihood function [52,53]. Two advantages of Bayesian models include the incorporation of domain knowledge via the prior and uncertainty quantification via the posterior distribution.

Data Analysis

First, we estimated the Pearson correlation coefficient (r) between the search data and obesity and overweight prevalence across Africa from 2010 to 2016. Next, we excluded all search terms that had zero variance (ie, 20 search terms) and search terms not significantly correlated with obesity/overweight prevalence at a significance level of $P<.05$. Additionally, because there were zero reported searches for some terms in some countries, we excluded all terms with less than 50% of observations greater than zero, implying that only the most significant and comprehensive variables were used in the modeling. We then fitted separate models to estimate obesity and overweight prevalence using the search data. The coefficient of determination (R^2) and root-mean-square error (RMSE) were used to assess the model fit. The out-of-sample estimation involved splitting the data into 2 sets: data from 2010 to 2014 were used to train the model, while data from 2015 to 2016 were used to evaluate the model. In machine learning, the data used to train the model are usually different from the data used to validate it. The training data are used to fit the model (ie, train the algorithm to identify patterns) and the evaluation data are used to assess the predictive performance of the fitted model by comparing the model estimates to true values. The aim is to allow the model to be generalizable to future sets of data. However, in the absence of future data, the evaluation data are used. We also report the correlation between the out-of-sample predictions and WHO-estimated obesity and overweight prevalence. The following R packages were used: SuperLearner, randomForest, kernlab, and arm [51,54].

Results

Information-Seeking Patterns

Some countries had sparse or no data for some of the search terms. Search patterns were similar for several of the terms: lose weight and weight (r=0.93, 95% CI 0.91-0.94), diet and weight (r=0.92, 95% CI 0.90-0.93), diet and weight loss (r=0.89, 95% CI 0.87-0.91), food and weight (r=0.88, 95% CI 0.85-0.90), food and weight loss (r=0.86, 95% CI 0.83-0.88), breakfast and diet (r=0.85, 95% CI 0.82-0.87), weight and ginger (r=0.84, 95% CI 0.81-0.87), weight and breakfast (r=0.83, 95% CI 0.80-0.86), weight loss and weight gain (r=0.83, 95% CI 0.79-0.86), exercise and food (r=0.81, 95% CI 0.77-0.84), ginger and weight loss (r=0.81, 95% CI 0.77-0.84), weight loss and fasting (r=0.81, 95% CI 0.77-0.84), gym and diet (r=0.81, 95% CI 0.77-0.84), lose weight and food (r=0.81, 95% CI 0.77-0.84), lose weight and gym (r=0.81, 95% CI 0.77-0.84), and food and ginger (r=0.80, 95% CI 0.75-0.83). Most of these associations were between terms that capture the same underlying intention. For instance, someone searching for information on how to lose weight might also search for gym, diet, or weight loss plans.

Estimated obesity prevalence was lowest for Ethiopia and highest for Libya during the study period (Figure 1). Obesity prevalence was most statistically significantly correlated with similar and different search terms across the countries with highest obesity and overweight prevalence (Figure 2). For example, for Libya, statistically significant correlations were observed between obesity prevalence and searches for yoga (r=0.95, 95% CI 0.71-0.99), exercise (r=0.89, 95% CI 0.43-0.98), and gym (r=0.91, 95% CI 0.49-0.99). Similarly, for Egypt, significant correlations were observed between obesity prevalence and searches for gym (r=0.98, 95% CI 0.83-0.99), breakfast (r=0.96, 95% CI 0.73-0.99), and yoga (r=0.95, 95% CI 0.67-0.99). In contrast, significant correlations for South Africa were between obesity prevalence and searches for how to exercise (r=0.99, 95% CI 0.91-0.99), green tea (r=0.98, 95% CI 0.89-0.99), and weight gain (r=0.97, 95% CI 0.83-0.99). For Algeria, we observed significant correlations between obesity prevalence and searches for gym (r=0.93, 95% CI 0.58-0.99), yoga (r=0.92, 95% CI 0.54-0.99), and weight (r=0.89, 95% CI 0.44-0.98). Searches for Fitbit were significantly associated with obesity prevalence in some countries (eg, Egypt and Algeria); however, the search volume was much lower than the search volume of other terms listed, suggesting less interest. Findings were similar between overweight prevalence and the search terms.

Figure 1. Estimated adult obesity prevalence in Africa from the World Health Organization in (A) 2010 and (B) 2016.

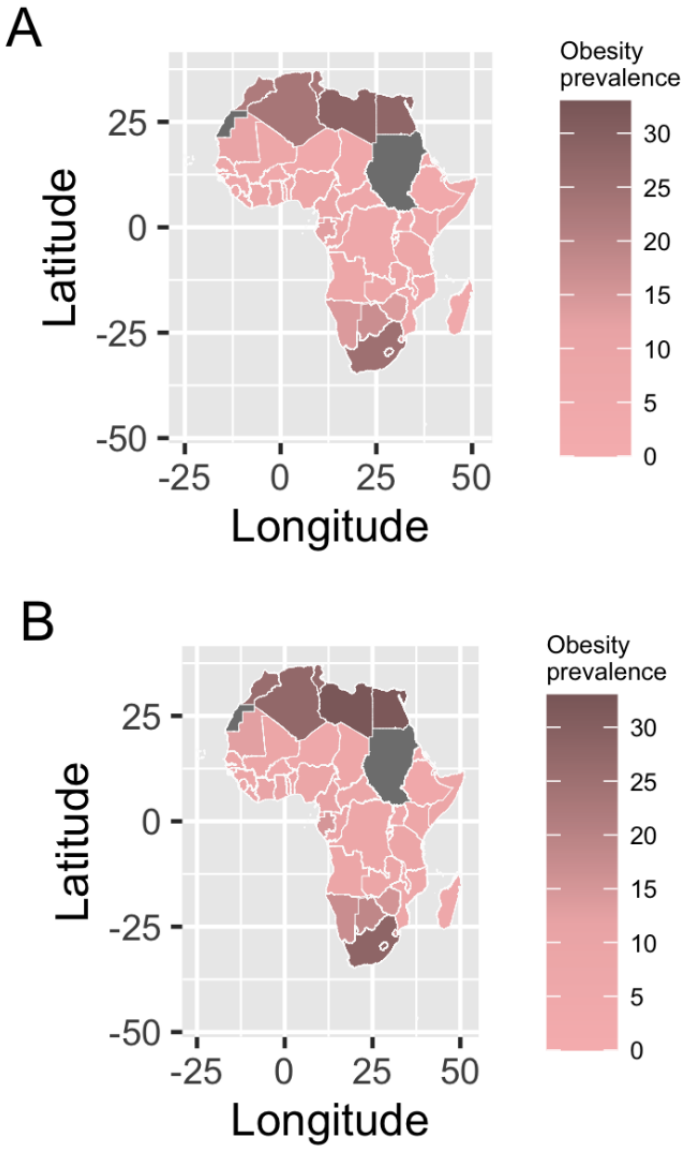
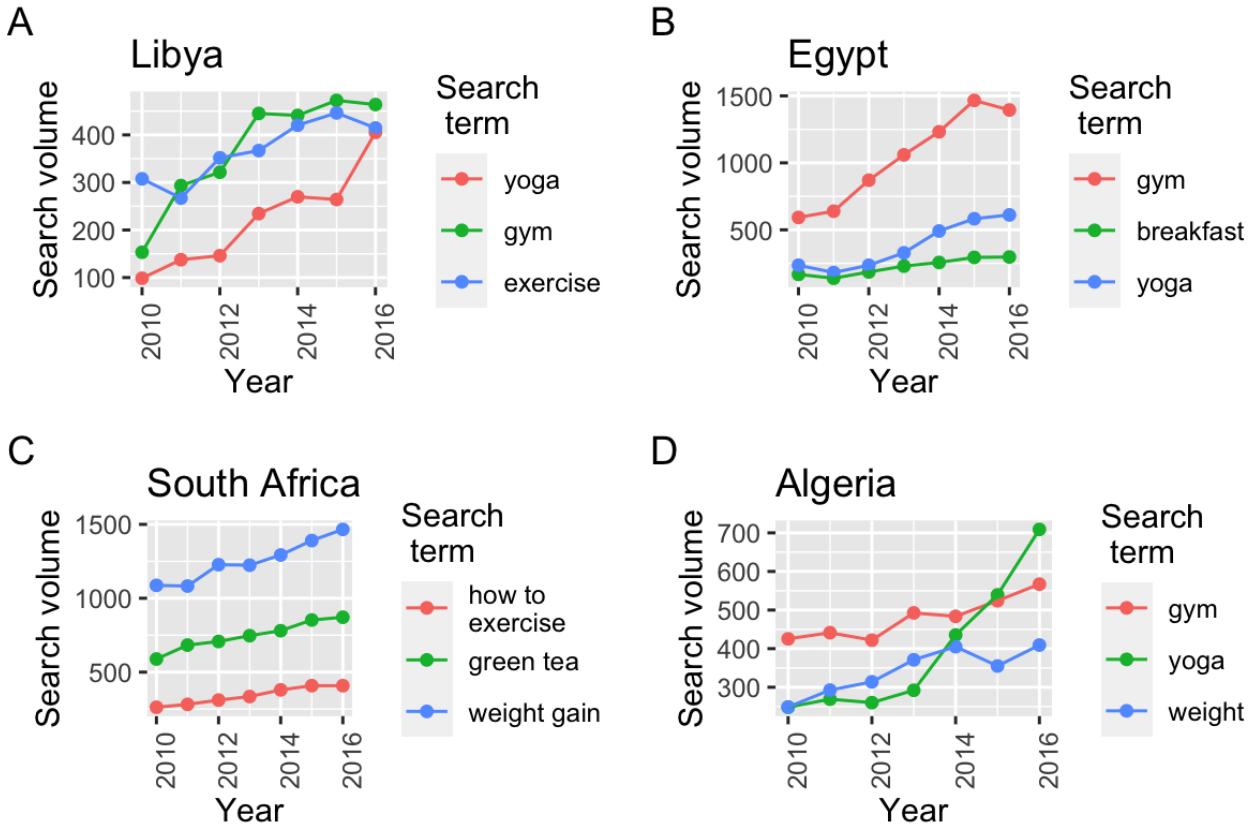


Figure 2. Search trends for the terms most correlated with obesity and overweight prevalence estimates from the World Health Organization for countries with the highest obesity and overweight prevalence in Africa: (A) Libya, (B) Egypt, (C) South Africa, and (D) Algeria.



Estimating Obesity With Search Trends

Twelve of the terms that were significantly correlated with obesity prevalence (ie, hypertension, breakfast, diet, nutrition, obese, green tea, weight gain, lose weight, weight loss, weight, gym, and malnutrition) were used in modeling to estimate obesity prevalence. The estimated variances explained by the various models were 0.97, 0.92, 0.77, and 0.30 for RF (Figure 3), gradient boosting, SVM, and Bayes GLM, respectively; the corresponding RMSEs were 1.15, 1.87, 3.53, and 5.60, respectively. Likewise, the correlations between the out-of-sample estimates (ie, data not used to train the model) and obesity prevalence were 0.96, 0.94, 0.87, and 0.56 for RF, gradient boosting, SVM, and Bayes GLM, respectively.

Similarly, 8 search terms (hypertension, breakfast, diet, nutrition, obese, lose weight, gym, and malnutrition) were used in modeling to estimate overweight prevalence. The RF model was also the best performing model for estimating overweight prevalence (Figure 4). The estimated variances explained by the various models were 0.96 (RMSE 2.26), 0.91 (RMSE 3.56), 0.62 (RMSE 7.72), and 0.23 (RMSE 9.99) for RF, gradient boosting, SVM, and Bayes GLM, respectively; the corresponding correlations between the out-of-sample model estimates and overweight prevalence were 0.95, 0.94, 0.78, and 0.49, respectively.

Figure 3. Estimation of obesity prevalence using search data and the random forest algorithm. (A) Association between model-estimated obesity prevalence and World Health Organization (WHO) obesity prevalence. (B) Association between model-predicted obesity prevalence and WHO obesity prevalence. The decision tree approaches had the lowest errors in estimating obesity prevalence.

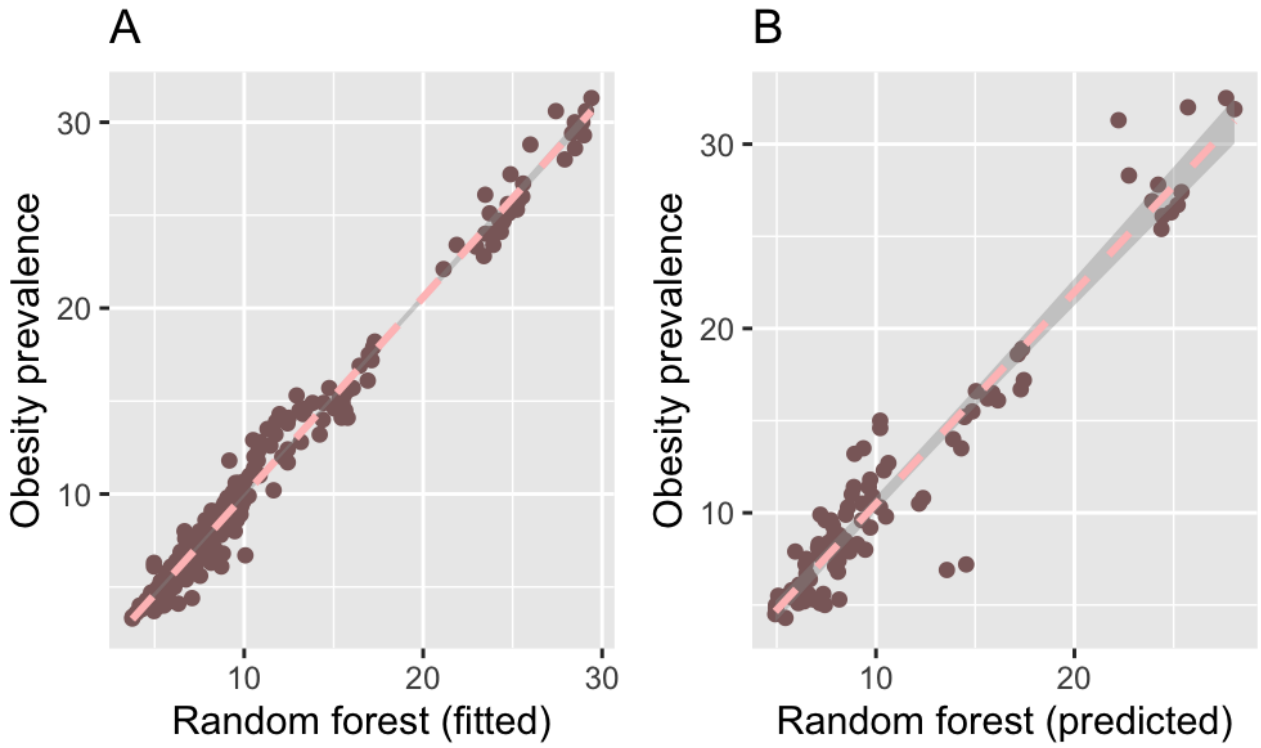
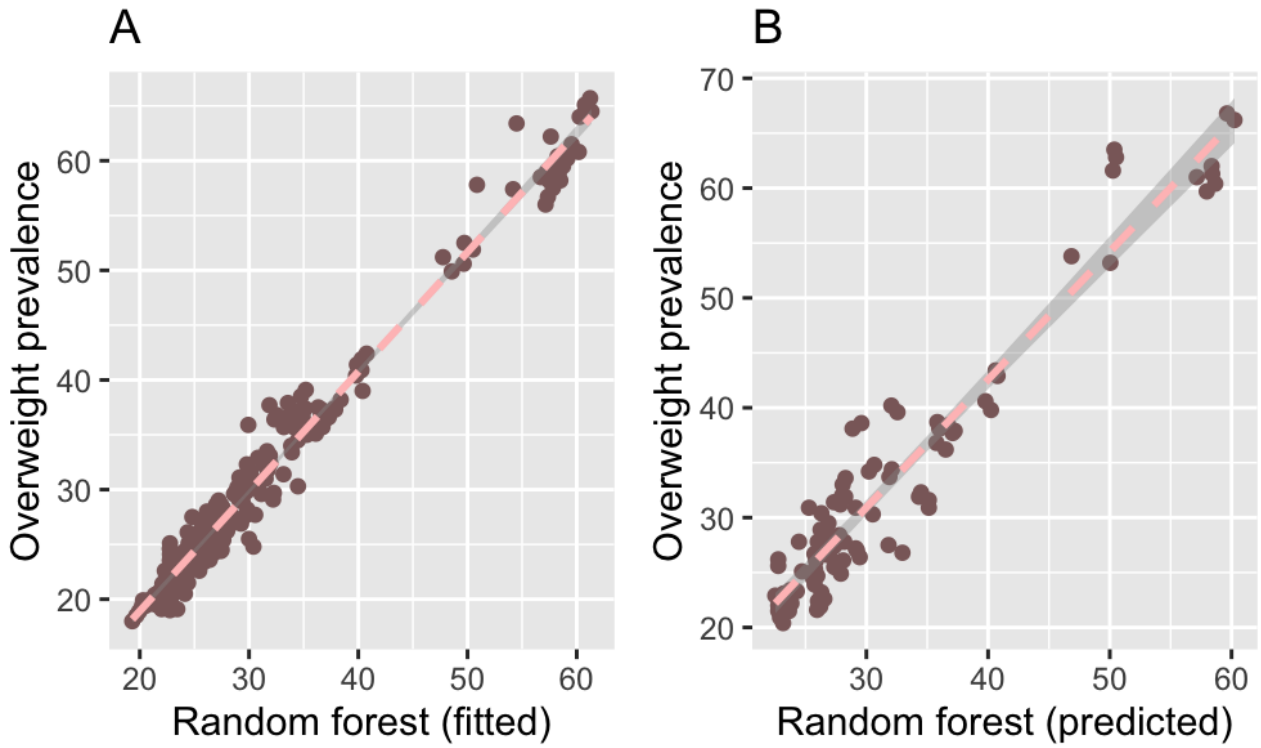


Figure 4. Estimation of overweight prevalence using search data and the random forest algorithm. (A) Association between model-estimated overweight prevalence and World Health Organization (WHO) overweight prevalence. (B) Association between model-predicted overweight prevalence and WHO overweight prevalence. The decision tree algorithms had the most accurate estimates of overweight prevalence.



Discussion

Our study assessed the potential use of information-seeking trends of obesity- and overweight-related terms for monitoring these conditions in Africa. Several of the search terms were correlated with changes in obesity and overweight prevalence and, when modeled together, produced estimates that were significantly correlated with data from the WHO. Data from internet sources, including social media and search engines, can capture detailed information on individuals' well-being that can collectively reflect community perceptions of health. Web searches, unlike social media, can more accurately reflect information-seeking patterns on sensitive or stigmatized health topics since individuals tend to consider it private [55].

As African nations become more urbanized, digital data and tools could be useful for monitoring changes in behavioral risk factors, which could help public health officers, policy makers, health providers, and nutritionists to make informed decisions on chronic disease prevention efforts in Africa. Similarly, health care professionals can also use digital platforms to seek information on advances in medical practice, disseminate health information, and communicate with and support patients [56,57]. However, digital health implementation in some African countries is constricted by systemic hurdles such as weak health systems and a lack of coordination of mushrooming pilot projects [58].

A research agenda around monitoring risk factors for noncommunicable diseases using digital platforms should focus on quantifying changes with the intent to participate in behavioral risk factors, postings of engagement on social media, and information seeking on poor diet, physical inactivity, and other risk factors. Interventions can target younger populations—who tend to use digital platforms and are at risk—to promote healthy behaviors (eg, to stop smoking or reduce intake of sugary drinks). By monitoring changes in discussion trends on digital platforms, interventions designed for both online and offline targeting could be more beneficial, thereby avoiding the unintended effects of poorly designed campaigns. Furthermore, in regions where large data sets are available, systems can be developed for quantifying the prevalence of these risk factors at a granular level (ie, subnational or subregional)—using a combination of digital data, hospital data, and demographic data—where survey estimates are unavailable or delayed.

A major limitation of this study is that we did not collect data in other languages spoken in Africa (including Swahili, Portuguese, Sesotho, Zulu, Afrikaans, Xhosa, Tswana, Hausa, Tsonga, Afar, French, Arabic, and Somali). However, other studies suggest that English is used on the internet in many African countries [31,45]. Also, the obesity and overweight data are estimates that might not accurately reflect current obesity rates due to limitations in data and methods. Furthermore, the differences in search patterns between countries suggest a need for country-specific analysis. For example, there are local dieting fads (such as herbal life in South Africa) that should be monitored to capture local context. However, the number of observations was insufficient for fitting individual models to each country. Additionally, access to the internet might be influenced by socioeconomic status, which means that individuals seeking information on Google might not be representative of the total population [59-61].

However, our approach demonstrates that the adoption of internet technologies in Africa provides opportunities for studying and improving health. Obesity and overweight are health challenges faced by countries in Africa, and population information-seeking behaviors can inform how we design interventions. Information-seeking patterns on obesity-related risk factors could capture changes in attitudes, behaviors, and risk factor prevalence that could supplement official estimates from surveys.

Authors' Contributions

EON designed the study. EON and OO analyzed the data and drafted the manuscript. EON, OO, and VM interpreted the results. All authors contributed to editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
A list of terms used to extract data from Google.
[PDF File (Adobe PDF File), 70 KB - publichealth_v7i4e24348_app1.pdf]

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Abbreviations

CI: credible interval
GLM: generalized linear model
RF: random forest
RMSE: root-mean-square error
STEPS: STEPwise approach to surveillance
SVM: support vector machine
WHO: World Health Organization

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Original Paper

Respondent Characteristics and Dietary Intake Data Collected Using Web-Based and Traditional Nutrition Surveillance Approaches: Comparison and Usability Study

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Abstract

Background: There are many constraints to conducting national food consumption surveys for national nutrition surveillance, including cost, time, and participant burden. Validated web-based dietary assessment technologies offer a potential solution to many of these constraints.

Objective: This study aims to investigate the feasibility of using a previously validated, web-based, 24-hour recall dietary assessment tool (Foodbook24) for nutrition surveillance by comparing the demographic characteristics and the quality of dietary intake data collected from a web-based cohort of participants in Ireland to those collected from the most recent Irish National Adult Nutrition Survey (NANS).

Methods: Irish adult participants (aged ≥18 years) were recruited to use Foodbook24 (a web-based tool) between March and October 2016. Demographic and dietary intake (assessed by means of 2 nonconsecutive, self-administered, 24-hour recalls) data were collected using Foodbook24. Following the completion of the study, the dietary intake data collected from the web-based study were statistically weighted to represent the age-gender distribution of intakes reported in the NANS (2008-2010) to facilitate the controlled comparison of intake data. The demographic characteristics of the survey respondents were investigated using descriptive statistics. The controlled comparison of weighted mean daily nutrient intake data collected from the Foodbook24 web-based study (329 plausible reporters of a total of 545 reporters) and the mean daily nutrient intake data collected from the NANS (1051 plausible reporters from 1500 reporters) was completed using the Wilcoxon–Mann-Whitney U test in Creme Nutrition software.

Results: Differences between the demographic characteristics of the survey participants across the 2 surveys were observed. Notable differences included a lower proportion of adults aged ≥65 years and a higher proportion of females who participated in the web-based Foodbook24 study relative to the NANS study (P<.001). Similar ranges of mean daily intake for the majority of nutrients and food groups were observed (eg, energy [kilocalorie per day] and carbohydrate [gram per day]), although significant differences for some nutrients (eg, riboflavin [mg/10 MJ], P<.001 and vitamin B12 [µg/10 MJ], P<.001) and food groups were identified. A high proportion of participants (200/425, 47.1%) reported a willingness to continue using Foodbook24 for an additional 6 months.

Conclusions: These findings suggest that by using targeted recruitment strategies in the future to ensure the recruitment of a more representative sample, there is potential for web-based methodologies such as Foodbook24 to be used for nutrition surveillance efforts in Ireland.

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KEYWORDS

diet; survey and questionnaire; technology; nutrition surveillance

Introduction

Dietary assessment is of paramount importance for the surveillance of public health [1]. Conventional methods include food records (prospective), 24-hour dietary recalls (24HDRs), food frequency questionnaires (FFQs), and diet history methodology (retrospective measures). The selection of the dietary assessment methodology to be used in any given situation is dependent on many factors, including the main objective of the study, the level of detail required, and the resources available [2]. One of the most commonly used methods, the 24-hour multipass dietary recall [3] approach, involves a trained researcher interviewing participants about what they consumed in the previous 24 hours. Techniques such as probing for commonly forgotten items, asking questions about food preparation, and using portion size assessment aids (photos and food models) to assess the amounts consumed are used to prompt accurate recall of dietary intake. Although this method is recommended by the European Food Safety Authority (EFSA) for the collection of dietary intake information [4], the cost and feasibility of this method add challenges. Therefore, many studies opt to collect dietary intake data using FFQs, which are less accurate but require less researcher and participant burden.

Previous research on the use of web-based dietary assessment tools has demonstrated the feasibility of their use in terms of large-scale dietary intake data collection [5-9] and has suggested the potential for the collection of dietary intake information at a lower cost and with less attrition compared with traditional interviewer-led methods [10]. The use of validated, web-based dietary assessment methodologies also allows for estimated intake to (1) be updated frequently through repeated measurements, (2) be investigated across seasons, (3) improve the capture of episodically consumed items, and (4) allow for intraperson and interperson variability to be easily assessed [11]. However, Shim et al [12] noted that even with the use of novel technologies in dietary assessments, the results highlight that participants still have difficulty in reporting diet accurately (underreporting and social desirability bias). A concern is that the data collected using these approaches is flawed with measurement error and, as a result, cannot be confidently relied on to inform public health policy or nutrition- and health-related research [13].

These criticisms are not unique to technology-based self-reported methods but are, in fact, unique to all self-report dietary assessment methodologies, including paper-based measures such as estimated food diaries and interviewer-administered 24HDRs [14]. However, rather than adding to the error, some research demonstrates that technology-based dietary assessment technologies offer a structured data collection approach that reduces the impact of inconsistencies related to erroneous data entry and allows probing into multiple details of the consumption to occur in a harmonized manner and reduce nonresponse bias, as they might be viewed more favorably by participants [15].

National food consumption surveys are necessary to estimate dietary intake at the population level to provide an evidence base for developing and evaluating health policy and to investigate food safety risks, such as contaminant exposure [1]. A recent review of national nutrition surveys conducted in 53 countries of the World Health Organization European region highlights that none of the surveys identified used mobile phones to collect dietary information, whereas Belgian, German, and Portuguese surveys employed electronic interviews; the Spanish Anthropometry, Intake and Energy Balance Study used tablets; and the Norwegian Ungkost and Swedish Riksmaten used a web-based food diary [16]. However, efforts are underway to harmonize the collection of dietary intake data across Europe by further developing a computerized system (GloboDiet) to assist a reviewer in the administration and analysis of 24-hour recalls with participants [17]. In 2017, the third wave for National Diet and Nutrition Survey (NDNS) Rolling Programme in the United Kingdom (2018-2022) has included plans to consider technological dietary assessment approaches; it is hoped that this will highlight the potential of web- and computer-based approaches in national consumption surveys going forward [1].

The feasibility of a self-administered web-based platform to collect nationally representative data in Ireland has yet to be investigated. The collection of nationally representative consumption data incurs a large financial cost, with the most recent National Adult Nutrition Survey (NANS; 2008-2011) in Ireland, costing approximately €5 million (US $5.9 million) to coordinate and execute [18]. Many dietary assessment methods used in nutrition surveillance require highly skilled interviewers, which increases survey costs and thus impacts the frequency of data collection at a national level (on average every 3-10 years depending on the country, except for the United States, where national food consumption data are collected on a yearly basis in the National Health and Nutrition Examination Survey) [19]. Therefore, there is potential for the use of self-administered web-based dietary assessment platforms to assist with the rolling collection of food consumption data at a national level.

Foodbook24 is a self-administered web-based tool that was developed for an Irish adult population and consists of different components that facilitate the collection of dietary intake data without direct interaction with a researcher. The development, validity, and user acceptability of the Foodbook24 tool are described elsewhere [20,21]. Participants were invited to complete dietary assessments using Foodbook24 via email, and a series of email reminders were scheduled to prompt participants to log in and complete each component. Dietary assessment via Foodbook24 can be completed using a range of technology devices, including smartphones, tablet devices, and laptop or desktop computers, thereby providing efficient routes of access to participants and enabling greater and more affordable geographical reach [1].

In this regard, this study aims to investigate the feasibility of using a web-based dietary assessment tool for the purposes of

nutrition surveillance in Ireland by (1) comparing the demographic characteristics of participants that sign up to use the web-based Foodbook24 tool relative to the most recent Irish NANS and (2) investigating the quality of dietary intake data collected via the web-based Foodbook24 tool relative to the most recent Irish NANS by means of a controlled comparison.

Methods

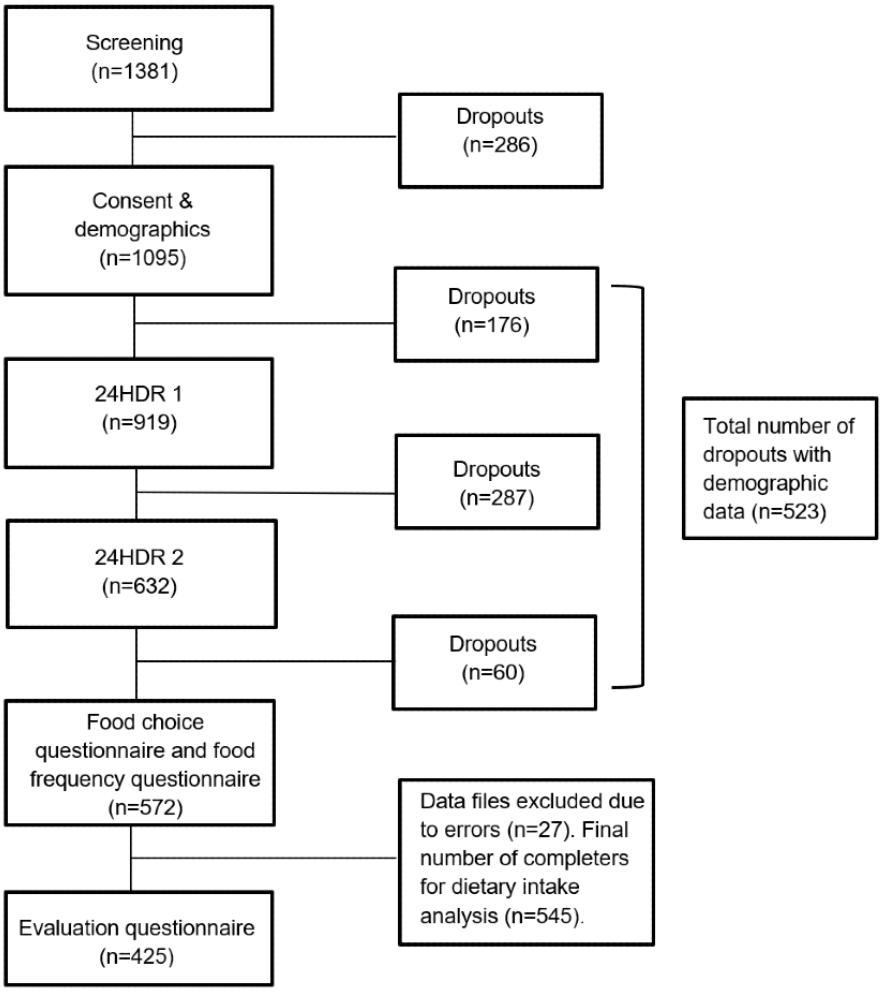
Foodbook24

The Foodbook24 project was a collaborative research project between the University College Dublin and University College Cork with the aim of developing and validating a web-based dietary assessment tool for the Irish adult population. In brief, the design of the Foodbook24 tool was informed by guidelines issued on the collection of national food consumption data by the EFSA in 2009 [4], interviews with key stakeholder organizations or institutions in Ireland, and an extensive review of the literature concerning web-based dietary assessment platforms [22]. The final proposed design of Foodbook24 was a self-administered web-based tool consisting of different components that facilitate the collection of dietary intake data without direct interaction with a researcher. These components included a screening and consent stage, demographic questionnaire, 2×24-hour multiple-pass dietary recall (administered on nonconsecutive days), and food frequency and food choice questionnaires (FCQs). Foodbook24 was validated in a population of Irish adults by comparing intakes recorded by Foodbook24 against those recorded by a semiweighed food diary and using biological markers of nutrient intake in blood and urine samples [20]. The results of this study demonstrated the validity of Foodbook24 and user acceptability, as Foodbook24 was preferred by participants (80/118, 67.8%) compared with the traditional diary method.

Foodbook24 Study

The Foodbook24 study was conducted between March and October 2016. Participants were recruited via the Foodbook24 website, which was aided by advertising of the study in newspapers, posters, e-flyers, social media, and word of mouth. This study was conducted in accordance with the guidelines laid down in the Declaration of Helsinki 1983, and ethical approval was obtained from the University College Dublin Human Research Ethics Committee (LS 15-77 Gibney-Timon). A targeted recruitment strategy to ensure the recruitment of a nationally representative sample of Irish adults (as used in NANS) was not used in this study to allow for the investigation of the demographic characteristics of participants interested in taking part in a study using web-based methodologies. A total of 1385 participants were screened to participate in the web-based study via the Foodbook24 website, and 1095 participants provided demographic data. Participants were eligible to take part in the study if they were aged ≥18 years, fluent in both written and verbal English, had regular access to the internet, and agreed to the information collected as part of the study while ensuring their confidentiality, to be used for the purposes of food and health research. Once participants were screened and provided informed consent using the web-based tool, they had the choice to complete the demographics questionnaire and the first (of two) 24HDR immediately or they had the option to complete these at a later time. A series of email reminders were scheduled to remind participants to log in to the tool and complete the next required component of the tool (Figure 1). The two 24HDRs were separated by a minimum of a 7-day period (may have been longer depending on when participants logged in to complete the second recall), and 2 days after the second recall, the final 2 stages (FFQ and FCQ) were made available for participants to complete; the data of these questionnaires were not included in this publication. Participants who completed all stages of Foodbook24 were asked to complete an evaluation questionnaire once the study had concluded. A total of 425 participants completed the optional questionnaire. The questionnaire consisted of a 16-item evaluation questionnaire administered on the internet. The focus of the questionnaire was to assess the participants' overall experience using the 24-hour recall component of the tool only and their acceptability of some of the software design features, method preference, and future use. If participants fully complied with the study protocol, study involvement was complete within 10 days. Although financial compensation was not offered for participation in this study, participants who completed all aspects of the study received a personalized dietary feedback report. This report was developed by the research team using the food and nutrient output generated from the tool and further analysis using specialized databases and decision trees that were developed to calculate which food groups contributed the most to nutrient intake. The resulting dietary feedback report was subsequently emailed to the participants.

Figure 1. Stages of the Foodbook24 tool in the web-based study. 24HDR: 24-hour dietary recall.



National Adult Nutrition Survey (2008-2011)

The NANS investigated habitual food and beverage consumption, lifestyle, health indicators, and attitudes toward food and health in a representative sample (n=1500) of adults aged 18 to 90 years recruited in the Republic of Ireland between 2008 and 2010 [18]. Eligible respondents were adults aged ≥18 years who were free living (living independently in the community) and who were not pregnant or breastfeeding, and a response rate of 60% (1500/2500) was observed. A targeted recruitment strategy was employed in the NANS to ensure representative population samples were recruited. The names and addresses of Irish adults were randomly selected from a database owned by Data Ireland (An Post) to contact potential participants by post. The researchers then contacted potential participants to discuss the study. For groups that were not highly represented via this recruitment strategy, particularly those aged 18 to 35 years, the second level of recruitment was introduced. Analysis of the demographic features in this sample has shown it to be a representative sample of Irish adults with respect to age, gender, social class, and geographical location when compared with census data [18]. Food intake was determined using a 4-day semiweighed food record. At present, this is the most recent nationally representative nutrition survey data available in Ireland.

Data and Statistical Analysis

Nutrient and Food Group Analysis

Food intake data collected from NANS were analyzed using WISP version 4.0 (Tinuviel Software). The food composition data linked to the NANS data set are derived from UK food composition tables [23] and the Irish Food Composition Database [24]. Foodbook24 automatically generates a food and nutrient intake output for each user. The food composition data that underpin the Foodbook24 software were developed via a reduction process that involved the merging of food codes of a similar description and/or composition linked to the NANS data set [25]. Data collected from all participants in the NANS included at least one (of 4) day of dietary intake data recorded on a weekend day, whereas only 31.9% (174/545) of Foodbook24 participants completed one data collection time point on a weekend day.

Underreporting

The Henry equation was used to identify misreporters of energy intake (EI) in both surveys. Basal metabolic rate (BMR) was calculated using standard equations based on gender, weight, and age [26]. The mean daily EI and nutrient intake were calculated for all participants in both surveys. In Foodbook24, the nutrient output file was automatically generated, and the data were further aggregated in SPSS (IBM Corporation) to

compute the mean daily intakes. Data collected from the NANS were analyzed in WISP to derive mean daily nutrient intake values. Participants whose ratio of EI to their calculated BMR (EI/BMR) fell below 1.1 were classified as underreporters [27], and those with an EI/BMR of >2.5 were classified as overreporters of dietary intake. Individuals identified as misreporters (underreporters and overreporters) were excluded from further analysis, resulting in 329 plausible reporters (of a possible 545 reporters; misreporting rate of 39%) from the Foodbook24 web-based study and 1051 plausible reporters (of a possible 1500 reporters; misreporting rate of 30%) from the NANS.

Controlled Comparison of Dietary Intake Data

As there was a large difference in the final number and characteristics of reporters in both surveys, a weighted adjustment was applied to compare population nutrient and food intake recorded in both surveys. Sampling weights were applied to the Foodbook24 data to account for differential probabilities of participant characteristics and nonresponse, applying appropriate sampling weights based on age and gender [28]. The NANS study data were not weighted, as the recruitment strategy ensured a nationally representative sample from the outset. The weighted adjustment and the subsequent modeling of dietary intake collected from the Foodbook24 web-based survey were completed using the Crème Nutrition (R) software.

Statistical Analysis

Descriptive statistics (demographic data and evaluation questionnaire data) for both survey populations were computed and compared using a Chi-square analysis in SPSS (version 20). The dietary intake data recorded in both studies were averaged across days, creating mean daily food and nutrient intake, for analysis. The mean, SD, median, and IQR of each nutrient and food group were calculated using Crème Nutrition. The Wilcoxon–Mann-Whitney U test was used to compare the weighted Foodbook24 food and nutrient intake data against intake data recorded from the NANS.

Results

Study Populations

A total of 1095 adult participants (766 females and 329 males) signed up to the Foodbook24 web-based study, and 1500 adult participants (740 males and 760 females) were recruited to complete the NANS. As evident from Figure 1, certain stages of the web-based study had higher attrition rates than others, for example, between recall 1 and 2; however, a higher level of adherence was observed for the remainder of the survey after this point. The initial high level of attrition, which can be described as dropout attrition, observed in this study may be partly explained by the fact that for a large number of participants, emails informing them about the next steps required to participate in the study were mistaken as spam mail and therefore were not seen or considered. Table 1 displays the demographic characteristics of the total population of web-based participants compared with those of the NANS participants. The different recruitment approaches resulted in significant differences between the 2 cohorts for all demographic characteristics with notable differences for the representation of the above 65 years age group, male participants, participants who are obese, participants from the manual skilled social class, and participants with a tertiary-level education. Table 1 also shows the demographic characteristics of the Foodbook24 web study completers (those that completed all aspects of the study) and dropouts (those that dropped out without completing all aspects of the study). The analysis demonstrates that a higher proportion of females and participants with a higher level of education completed the study compared with those who dropped out. A subsequent analysis (from Table 2 onward) focuses only on web-based participants who completed 2×24-hour recalls and who were considered adequate energy reporters (n=329) and adequate reporters from the NANS (n=1051).

Table 1. Demographic characteristics of participants involved in the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).

Demographic	Foodbook24 web-based study total population (n=1095)	Foodbook24 web-based study completers (n=572)	Foodbook24 web-based study dropouts (n=523)	National Adult Nutrition Survey (n=1500)	*P* value (difference between Foodbook24 completers and dropouts)	*P* value (difference between 2 surveys)
Age (years), range	18-89	__[a]	—	18-90	—	—
Age (years), n (%)					.25	<.001[b]
18-35	501 (45.8)	253 (44.2)	248 (47.4)	531 (35.4)		
36-50	358 (32.7)	187 (32.7)	171 (33.7)	436 (29.1)		
51-64	200 (18.3)	110 (17.7)	90 (17.3)	306 (20.4)		
>65	36 (3.3)	22 (3.9)	14 (2.6)	226 (15.1)		
Gender, n (%)					<.001[c]	<.001[b]
Female	766 (70)	416 (73)	350 (67)	765 (51)		
Male	329 (30)	156 (27)	173 (33)	735 (49)		
BMI[d], n (%)					.07	<.001[b]
Underweight (<18.5)	28 (2.6)	16 (2.8)	12 (3.4)	10 (0.7)		
Normal weight (18.5-24.9)	608 (55.5)	300 (52.4)	300 (57.4)	492 (32.8)		
Overweight (25-29.9)	331 (30.2)	184 (32.1)	147 (28.1)	532 (35.5)		
Obese (>30)	127 (11.6)	69 (12.06)	58 (11.1)	318 (21.2)		
Social class[d], n (%)					.24	<.001[b]
Professional or manager or tech	740 (67.6)	392 (68.5)	348 (66.4)	670 (44.7)		
Nonmanual skilled	163 (14.9)	83 (14.5)	80 (15.3)	267 (17.8)		
Manual skilled	22 (2.0)	9 (1.5)	13 (2.5)	213 (14.2)		
Semiskilled/unskilled	131 (12.4)	59 (10.0)	72 (13.7)	285 (19.0)		
Retired/unemployed	24 (2.1)	13 (2.2)	11 (1.75)	64 (4.3)		
Education[d], n (%)					.05[c]	<.001[b]
Primary	16 (1.5)	15 (2.6)	11 (2.1)	139 (9.3)		
Secondary	188 (17.2)	86 (15.0)	102 (19.6)	650 (43.3)		
Tertiary	890 (81.3)	480 (84.0)	410 (78.2)	682 (45.5)		

[a]Not available.

[b]Significant difference in demographic information between the Foodbook24 and National Adult Nutrition Survey studies, as defined by Chi-square analysis.

[c]Significant difference in demographic information between the Foodbook24 study completers and dropouts, as defined by Chi-square analysis.

[d]Excludes missing values.

Table 2. Nutrient intake of adequate reporters from the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).

Nutrient	Foodbook24, mean daily intake[a] (SD)	National Adult Nutrition Survey, mean daily intake[b] (SD)	*P* value	Difference (%)
Energy (kcal/day)	2174.74 (521.63)	2227.46 (623.56)	.37	2.42
Carbohydrate (g/day)	246.98 (69.98)	252.55 (76.64)	.61	2.25
Starch (g/day)	140.53 (56.24)	146.73 (46.95)	<.001[c]	4.41
Total sugars (g/day)	98.33 (35.6)	101.11 (43.83)	.68	2.83
Dietary fiber (g/day)	24.08 (10.72)	20.67 (8.03)	<.001[c]	−14.17
Fat (g/day)	88.35 (29.75)	84.66 (28.62)	<.001[c]	−4.18
Monounsaturated fat (g/day)	31.26 (11.2)	30.97 (11.25)	.31	−0.93
Polyunsaturated fat (g/day)	14.2 (6.24)	14.8 (6.67)	.16	4.2
Saturated fat (g/day)	36.46 (15.47)	33.35 (12.88)	<.001[c]	−8.53
Protein (g/day)	85.71 (30.51)	89.66 (26.43)	<.001[c]	4.61
Percent energy (protein)	15.83 (3.80)	16.44 (3.41)	<.001[c]	3.67
Percent energy (carbohydrate)	43.17 (8.02)	45.57 (7.29)	<.001[c]	5.27
Percent energy (total sugars)	15.37 (5.83)	18.19 (6.17)	<.001[c]	15.47
Percent energy (fat)	36.52 (7.52)	34.21 (6.30)	<.001[c]	−6.74
Percent energy (monounsaturated fat)	13.07 (3.46)	12.46 (2.67)	.20	−4.93
Percent energy (polyunsaturated fat)	6.11 (2.11)	6.07 (2.29)	<.001[c]	−0.64
Percent energy (saturated fat)	14.71 (4.40)	13.44 (3.44)	<.001[c]	−9.41
Calcium (mg/10 MJ)	1029.46 (356.17)	1124.308 (438.46)	<.001[c]	8.43
Carotene (µg/10 MJ)	5185.62 (4799.66)	4545.71 (3990.98)	.84	−14.07
Copper (mg/10 MJ)	1.42 (0.45)	1.44 (1.83)	.05	1.71
Folate (µg/10 MJ)	322.44 (125.82)	434.35 (326.35)	<.001[c]	25.76
Iron (mg/10 MJ)	14.51 (4.07)	17.21 (19.80)	.42	15.70
Magnesium (mg/10 MJ)	363.79 (87.89)	344.85 (100.62)	<.001[c]	−5.49
Potassium (mg/10 MJ)	462.74 (357.46)	593.44 (829.67)	.66	22.02
Retinol (µg/10 MJ)	1.83 (0.66)	3.76 (9.22)	<.001[c]	51.40
Riboflavin (mg/10 MJ)	2905.23 (940.71)	2923.08 (642.762)	<.001[c]	0.61
Sodium (mg/10 MJ)	2.36 (6.19)	3.57 (9.61)	.06	33.80
Vit B12 (µg/10 MJ)	2.52 (0.90)	4.74 (9.12)	<.01[c]	46.76
Vitamin B6 (mg/10 MJ)	136.64 (93.86)	149.52 (289.00)	<.014[c]	8.61
Vitamin C (mg/10 MJ)	3.24 (2.73)	5.51 (7.53)	<.001[c]	41.24
Vitamin D (µg/10 MJ)	13.09 (5.08)	16.57 (35.40)	<.02[c]	20.96
Vitamin E (mg/10 MJ)	10.71 (3.24)	12.25 (8.10)	<.001[c]	12.53

[a]Mean daily intake of energy and nutrients reported in the Foodbook24 web-based study.

[b]Mean daily intake of energy and nutrients reported in the National Adult Nutrition Survey in Ireland.

[c]Significant difference in the reporting of nutrient intake between the 2 dietary assessment surveys, as defined by the Wilcoxon–Mann-Whitney U test.

Nutrient Intakes From Adequate Reporters From the Web-Based Foodbook24 Study Compared With Those From the NANS

Table 2 shows nutrient intakes (mean [SD]) for dietary intake data recorded by adequate reporters in the Foodbook24 web-based study (weighted data, n=329) and the NANS (n=1051) study with *P* values from the Wilcoxon–Mann-Whitney U test. Multimedia Appendix 1 displays medians and IQRs of nutrient intakes. Comparable estimates were observed for energy, carbohydrate, polyunsaturated fats, carotene, iron, potassium, and sodium intakes, as highlighted by similar IQRs for intake and no significant difference between intakes. Larger differences were mainly associated with micronutrient intakes, such as retinol, vitamin B12, and vitamin C.

In Tables 3 and 4, the nutrient intakes (mean [SD]) for dietary intake data recorded by adequate reporters in the Foodbook24 web-based study (weighted data) and the NANS studies with *P* values from the Wilcoxon–Mann-Whitney U test are shown for female and male participants, respectively. Multimedia Appendices 2 and 3 display the medians and IQR of nutrient intakes. For female participants, there were no significant differences observed in energy and intake of carbohydrate, polyunsaturated fat, carotene, iron, potassium and sodium recorded in both studies. For male participants, no significant differences were observed in the intake of energy, carbohydrates, starch, monounsaturated and polyunsaturated fats, carotene, iron, magnesium, potassium, retinol, sodium, and vitamin D. Smaller differences in micronutrient intake were observed in male participants from both surveys compared with female participants.

Table 3. Nutrient intakes of female adequate reporters from the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).

Nutrients	Foodbook24, mean daily intake[a] (SD)	National Adult Nutrition Survey, mean daily intake[b] (SD)	*P* value	Difference (%)
Energy (kcal/day)	1899.20 (388.60)	1891.82 (425.81)	.25	−0.39
Energy (KJ/day)	7946.26 (1625.93)	7915.38 (1781.59)	.25	−0.39
Carbohydrate (g/day)	218.76 (57.31)	218.39 (55.61)	.63	−0.17
Total sugars (g/day)	80.28 (33.29)	90.28 (34.98)	<.001[c]	11.08
Starch (g/day)	118.32 (39.39)	123.58 (34.09)	<.001[c]	4.26
Protein (g/day)	74.23 (21.75)	75.89 (18.73)	.005[c]	2.19
Fat (g/day)	77.79 (23.54)	73.24 (21.00)	.01[c]	−6.20
Monounsaturated fat (g/day)	27.76 (8.95)	26.56 (8.51)	.02 [c]	−4.49
Polyunsaturated fat (g/day)	12.94 (4.80)	13.52 (5.61)	.17	4.29
Saturated fat (g/day)	31.64 (12.87)	28.54 (9.58)	<.001[c]	−10.84
Percent energy (protein)	15.71 (3.59)	16.36 (3.31)	<.001[c]	3.95
Percent energy (carbohydrate)	43.34 (8.26)	46.48 (6.57)	<.001[c]	6.74
Percent energy (total sugars)	15.95 (6.11)	19.09 (5.89)	<.001[c]	16.41
Percent energy (fat)	36.67 (7.53)	34.90 (6.06)	<.001[c]	−5.09
Percent energy (monounsaturated fat)	13.15 (3.50)	12.61 (2.60)	<.001[c]	−4.31
Percent energy (polyunsaturated fat)	6.16 (2.05)	6.45 (2.38)	.10	4.55
Percent energy (saturated fat)	14.76 (4.35)	13.61 (3.43)	<.001[c]	−8.48
Dietary fiber (g/day)	22.42 (7.74)	18.99 (7.12)	<.001[c]	−18.06
Calcium (mg/10 MJ)	1039.28 (362.02)	1200.53 (525.56)	<.001[c]	13.43
Carotene (µg/10 MJ)	5539.38 (5076.67)	5345.24 (4511.80)	.63	−3.63
Copper (mg/10 MJ)	1.430 (0.43)	1.58 (2.38)	.03[c]	9.71
Folate (µg/10 MJ)	322.27 (121.01)	453.04 (339.78)	<.001[c]	28.86
Iron (mg/10 MJ)	14.49 (4.03)	18.88 (25.06)	.25	23.23
Magnesium (mg/10 MJ)	366.60 (83.52)	358.21 (120.25)	<.001[c]	−2.34
Potassium (mg/10 MJ)	3737.89 (882.44)	3758.36 (988.83)	.34	0.54
Retinol (µg/10 MJ)	460.97 (363.38)	575.55 (566.87)	.30	19.91
Riboflavin (mg/10 MJ)	1.81 (0.66)	4.46 (11.85)	<.001[c]	59.27
Sodium (mg/10 MJ)	2891.48 (941.44)	2915.64 (626.97)	.09	0.83
Vit B12 (µg/10 MJ)	4.93 (3.07)	10.46 (57.43)	<.001[c]	52.90
Vitamin B6 (mg/10 MJ)	2.46 (0.86)	5.57 (11.99)	<.001[c]	55.80
Vitamin C (mg/10 MJ)	146.27 (96.64)	186.36 (378.23)	<.001[c]	21.51
Vitamin D (µg/10 MJ)	3.21 (2.63)	6.25 (7.56)	<.001[c]	48.61
Vitamin E (mg/10 MJ)	13.10 (4.85)	20.13 (44.56)	<.001[c]	34.92

[a]Mean daily intake of energy and nutrients reported in the Foodbook24 web-based study.

[b]Mean daily intake of energy and nutrients reported in the National Adult Nutrition Survey in Ireland.

[c]Significant difference in the reporting of nutrient intake between the 2 dietary assessment surveys as defined by the Wilcoxon–Mann-Whitney U test.

Table 4. Nutrient intakes of male adequate reporters from the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).

Nutrients	Foodbook24, mean daily intake[a] (SD)	National Adult Nutrition Survey, mean daily intake[b] (SD)	*P* value	Difference (%)
Energy (kcal/day)	2497.07 (398.62)	2582.557 (602.03)	.10	3.31
Energy (KJ/day)	10447.76 (1667.85)	10805.42 (2518.92)	.10	3.31
Carbohydrate (g/day)	282.79 (60.18)	286.26 (80.02)	.67	1.21
Total sugars (g/day)	90.55 (33.49)	111.94 (49.12)	.04[c]	19.11
Starch (g/day)	168.40 (53.36)	169.27 (46.99)	.48	0.52
Protein (g/day)	101.28 (31.85)	104.73 (27.72)	.02[c]	3.30
Fat (g/day)	100.49 (27.74)	96.24 (30.50)	.04[c]	−4.41
Monounsaturated fat (g/day)	35.79 (11.34)	35.33 (11.89)	.22	−1.29
Polyunsaturated fat (g/day)	16.55 (7.15)	16.33 (7.48)	.46	−1.38
Saturated fat (g/day)	40.56 (14.64)	38.14 (13.94)	.01[c]	−6.36
Percent energy (protein)	16.20 (4.35)	16.52 (3.51)	<.001[c]	1.92
Percent energy (carbohydrate)	42.64 (7.26)	44.66 (7.86)	<.001[c]	4.53
Percent energy (total sugars)	13.63 (4.47)	17.28 (6.33)	<.001[c]	21.11
Percent energy (fat)	36.07 (7.51)	33.53 (6.46)	<.001[c]	−7.58
Percent energy (monounsaturated fat)	12.83 (3.32)	12.30 (2.72)	<.001[c]	−4.29
Percent energy (polyunsaturated fat)	5.95 (2.28)	5.68 (2.13)	<.001[c]	−4.79
Percent energy (saturated fat)	14.55 (4.59)	13.28 (3.44)	<.001[c]	−9.62
Dietary fiber (g/day)	26.63 (12.70)	22.41 (8.79)	<.001[c]	−18.80
Calcium (mg/10 MJ)	1000.01 (338.42)	1047.35 (309.90)	.003[c]	4.52
Carotene (µg/10 MJ)	4124.35 (3677.76)	3738.54 (3191.90)	.77	−10.32
Copper (mg/10 MJ)	1.40 (0.49)	1.31 (0.99)	.04[c]	−6.96
Folate (µg/10 MJ)	322.93 (140.06)	415.48 (311.39)	<.001[c]	22.28
Iron (mg/10 MJ)	14.56 (4.19)	15.53 (12.18)	.38	6.25
Magnesium (mg/10 MJ)	355.36 (99.96)	331.37 (73.51)	.28	−7.24
Potassium (mg/10 MJ)	3501.05 (799.94)	3443.25 (669.11)	.33	−1.68
Retinol (µg/10 MJ)	468.03 (341.16)	611.51 (1029.34)	.17	23.46
Riboflavin (mg/10 MJ)	1.86 (0.69)	3.05 (5.31)	<.001[c]	39.13
Sodium (mg/10 MJ)	2946.47 (943.10)	2930.59 (658.83)	.57	−0.54
Vit B12 (µg/10 MJ)	4.98 (2.93)	6.27 (6.57)	<.001[c]	20.53
Vitamin B6 (mg/10 MJ)	2.71 (0.99)	3.91 (4.56)	<.001[c]	30.55
Vitamin C (mg/10 MJ)	107.75 (78.65)	112.33 (144.26)	<.001[c]	4.08
Vitamin D (µg/10 MJ)	3.32 (3.01)	4.77 (7.44)	.08	30.39
Vitamin E (mg/10 MJ)	13.08 (5.73)	12.97 (22.14)	<.001[c]	−0.82

[a]Mean daily intake of energy and nutrients reported in the Foodbook24 web-based study.

[b]Mean daily intake of energy and nutrients reported in the National Adult Nutrition Survey in Ireland.

[c]Significant difference in the reporting of nutrient intake between the 2 dietary assessment surveys as defined by the Wilcoxon–Mann-Whitney U test.

Food Group Intakes From Adequate Reporters From the Web-Based Foodbook24 Study Compared With Those From the NANS

Table 5 displays the daily food group intakes (means, SDs, and percentages of consumers; gram per day) for dietary intake data recorded by adequate reporters in the Foodbook24 web-based (weighted data) and the NANS studies with *P* values from the Wilcoxon–Mann-Whitney U test. Multimedia Appendix 4 displays the medians and IQRs of food group intakes. The results of the analysis demonstrated comparable intake ranges across both surveys; however, for some food groups, there were significant differences in the mean daily food group intake. Intakes of *ready-to-eat breakfast cereals*, *white sliced bread and rolls*, *alcoholic beverages*, *carbonated beverages*, *milk*, *potatoes*, *beef*, and *bacon products* were consumed in significantly less amounts in the Foodbook24 web-based survey than in the NANS. However, an increase in the percentage of consumers for *butter*, *citrus fruits*, *coffee*, *lamb*, *bacon, and pork dishes*, *nonchocolate confectionery*, *nuts*, *other bread* (eg, *linseed*), *other cereals* (eg, *porridge*), *other fruits* (eg, *kiwis*), and *vegetable and pulse dishes* was evident in the Foodbook24 web-based survey compared with NANS.

Table 5. Food group intakes (grams) of adequate reporters from the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).

Food group	Foodbook24, mean (SD)[a]	Consumers, n (%)[b]	National Adult Nutrition Survey, mean (SD)[c]	Consumers, n (%)[d]	*P* value
Bread, cereals, rice, and pasta					
Other breads (eg, linseed bread)	20.37 (35.65)	128 (39.09)	13.84 (26.9)	374 (35.59)	.06
Other breakfast cereals (eg, porridge)	85.64 (113.76)	151 (45.76)	40.72 (84.75)	293 (27.88)	<.001[e]
Rice and pasta, flours, grains, and starch	54.27 (86.67)	153 (46.67)	34.95 (53.31)	498 (47.38)	.23
Ready-to-eat breakfast cereals	18.11 (28.49)	135 (41.21)	24.53 (30.53)	646 (61.47)	<.001[e]
White sliced bread and rolls	15.49 (35.33)	83 (25.15)	55.64 (55.19)	832 (79.16)	<.001[e]
Wholemeal and brown bread and rolls	61.6 (69.87)	214 (65.15)	56.23 (56.94)	774 (73.64)	.90
Beverages					
Alcoholic beverages	174.89 (334.14)	126 (38.18)	356.49 (620.15)	638 (60.7)	<.001[e]
Coffees	187.85 (219.41)	181 (55.15)	124.85 (211.12)	490 (46.62)	<.001[e]
Teas	424.99 (395.92)	237 (72.12)	465.96 (430.98)	874 (83.16)	.13
Water	682.87 (928.29)	219 (66.67)	536.84 (588.48)	857 (81.54)	.72
Carbonated beverages	25.27 (90.16)	34 (10.3)	84.44 (167.19)	380 (36.16)	<.001[e]
Diet carbonated beverages	30.72 (126.05)	27 (8.18)	22.03 (81.75)	127 (12.08)	.39
Dairy					
Cheeses	12.47 (20.97)	170 (51.82)	15.06 (19.02)	707 (67.27)	.27
Butter (over 80% fat)	11.03 (15.02)	184 (56.06)	4.36 (10.61)	396 (37.68)	<.001[e]
Whole milk	27.5 (89.88)	56 (16.97)	116.95 (181.83)	669 (63.65)	<.001[e]
Low-fat spreads (under 40% fat)	2.14 (5.36)	53 (16.06)	4.47 (11.18)	296 (28.16)	.01[e]
Low-fat, skimmed, and fortified milks	43.66 (121.78)	91 (27.58)	99.76 (151.47)	526 (50.05)	<.001[e]
Other milks and milk-based beverages	12.53 (89.42)	26 (7.88	16.08 (56.25)	137 (13.04)	.10
Yogurts	30.56 (57.81)	121 (36.67)	33.07 (52.22)	447 (42.53)	.04
Fruit and vegetables					
Bananas	37.88 (50.93)	145 (43.94)	28.9 (42.62)	485 (46.15)	.10
Citrus fruits	26.65 (71.24)	87 (26.36)	15.35 (42.56)	213 (20.27)	.10
Green vegetables	13.61 (28.33)	100 (30.3)	13.89 (21.78)	474 (45.1)	<.001[e]
Other fruits (berries, apples, etc)	125.42 (126.42)	247 (75.15)	53.74 (78.34)	609 (57.94)	<.001[e]
Other vegetables	42.58 (50.17)	224 (68.18)	26.72 (32.17)	745 (70.88)	<.001[e]
Vegetable and pulse dishes	29.21 (47.43)	177 (53.94)	20.56 (43.67)	477 (45.39)	<.001[e]
Potatoes (boiled/baked/mashed)	55.26 (92.45)	128 (38.79)	79.41 (80.51)	801 (76.21)	<.001[e]
Meat, eggs, and fish					
Beef and veal	15.01 (34.12)	64 (19.39)	19.41 (31.66)	408 (38.82)	<.001[e]
Beef and veal dishes	24.65 (64.85)	56 (16.97)	35.03 (57.67)	373 (35.49)	<.001[e]
Bacon and ham	9.93 (24.78)	92 (27.88)	22.46 (25.58)	797 (75.83)	<.001[e]
Chicken, turkey, and game	33.41 (64.58)	113 (34.24)	28.76 (37.02)	595 (56.52)	<.001[e]
Poultry and game dishes	32.32 (98.08)	73 (22.12)	23.24 (48.99)	274 (26.07)	.53
Eggs and egg dishes	33.51 (58.53)	131 (39.7)	17.62 (24.61)	550 (52.33)	.91

Food group	Foodbook24, mean (SD)[a]	Consumers, n (%)[b]	National Adult Nutrition Survey, mean (SD)[c]	Consumers, n (%)[d]	*P* value
Fish and fish products	27.39 (50.42)	102 (30.91)	24.98 (36.58)	520 (49.48)	<.001[e]
Fish dishes	7.35 (31.48)	23 (6.97)	4.59 (19.54)	77 (7.33)	.83
Lamb	3.59 (17.43)	11 (3.33)	5.52 (16.47)	143 (13.61)	.02[e]
Lamb, pork, and bacon dishes	7.19 (30.62)	30 (9.09)	5.45 (25.96)	72 (6.85)	.59
Meat products	8.77 (29.4)	41 (12.42)	17.62 (29.16)	479 (45.58)	<.001[e]
Pork	5.36 (20.96)	20 (6.06)	6.64 (17.69)	179 (17.03)	.01 [e]
Cakes, confectionery, and savory snacks					
Cakes, pastries, and buns	20.96 (36.35)	128 (38.79)	20.53 (32.24)	510 (48.53)	.04[e]
Biscuits, including crackers	27.89 (44.23)	218 (63.33)	14.13 (20.38)	675 (64.22)	<.001[e]
Chocolate confectionery	13.64 (20.55)	166 (50.61)	11.05 (16.74)	554 (52.71)	.89
Ice creams	10.16 (22.75)	74 (22.42)	6.79 (15.72)	260 (24.74)	.61
Nonchocolate confectionery	5.04 (13)	80 (24.24)	3.94 (11.69)	240 (22.84)	.91
Savory snacks	5.27 (13.03)	104 (31.52)	6.73 (12.69)	408 (38.82)	.008[e]
Soups, sauces, and miscellaneous					
Nuts and seeds; herbs and spices	6.04 (13.24)	139 (42.12)	3.44 (10.3)	263 (25.02)	<.001[e]
Soups, sauces, and miscellaneous foods	47.48 (76.06)	244 (74.24)	60.75 (71.79)	920 (87.54)	<.001[e]

[a]Mean daily intake of food groups in grams per day reported in the Foodbook24 web-based study.

[b]Percentage of participants who reported consuming the respective food group in the Foodbook24 web-based study.

[c]Mean daily intake of food groups in grams per day reported in the National Adult Nutrition Survey in Ireland.

[d]Percentage of participants who reported consuming the respective food groups in the National Adult Nutrition Survey in Ireland.

[e]Significant difference in the reporting of food group intake between the 2 dietary assessment surveys, as defined by the Wilcoxon–Mann-Whitney U test.

Participant Evaluation of Foodbook24

The main results of the participants' evaluations (n=425) of Foodbook24 during the web-based study are depicted in Table 6. Most participants were very positive in their evaluation of Foodbook24 with regard to completion time, user-friendliness, and remembering to use the tool. Overall, most found the Foodbook24 system to be user-friendly, with 96.9% (412/425) reporting it easy or *Okay* to use. When asked if participants felt that Foodbook24 changed what they ate and drank, 69.8% (297/425) felt it did not change at all, whereas some (119/425, 28%) felt it changed a little. Participants were asked to use Foodbook24 for longer periods to gain insight into the potential long-term use of the tool. The results highlighted that 36% (153/425) of participants would have continued to use the tool for an additional month (considering the completion of two 24-hour recalls per week), and 47.1% (200/425) of participants reported a willingness to use Foodbook24 for an additional 6 months. A small proportion of participants (34/425, 8%) said they would prefer not to continue using Foodbook24 beyond the web-based study.

Table 6. Participant acceptability of Foodbook24 in the web-based study (N=425).

Question posed to participant	Participant responses, n (%)
Impact of Foodbook24 on diet	
Changed a lot	9 (2.1)
Changed a little	119 (28)
No change at all	297 (69.8)
Completion time	
Too long	42 (9.8)
Okay	327 (76.9)
Short	56 (13.1)
User-friendliness	
Difficult	13 (3)
Okay	127 (29.8)
Easy/very easy	285 (67.0)
Remembering to use Foodbook24	
Difficult	21 (4.9)
Okay	191 (44.9)
Easy/very easy	213 (50.1)
Use of Foodbook24 for longer periods	
1 week	38 (8.9)
1 month	153 (36.0)
6 months	200 (47.1)
No	34 (8.0)

Discussion

Principal Findings

This study addressed the potential of a web-based tool to collect meaningful dietary intake data at a national level by comparing the demographic characteristics and a controlled comparison of dietary intakes between adult participants in the Foodbook24 web-based study and a nationally representative sample of the Irish population NANS study. Overall, our findings suggest key differences in demographic characteristics between survey respondents; however, similar ranges of nutrient and food group data were observed across both studies.

The Recruitment and Retention of Participants to Web-Based Surveys

The successful recruitment and retention of participants in research studies is essential for optimizing validity [29]. Although a relatively large number of respondents signed up to the web-based Foodbook24 study (n=1095), a retention rate of 58% was observed in the web-based Foodbook24 study from consent to the study to the final stage of data collection (FFQ and FCQ stage; Figure 1). The retention rate in the NANS study was not available; however, the NutriNet Sante study reported a similar rate to that within Foodbook24 at 44%, although the numbers recruited as part of the NutriNet study are more substantial. A study examining the retention rates of women enrolled in nutrition studies noted that the use of email, phone, and text message contact improved retention and highlighted the potential of incentives to optimize retention [29].

It is possible that the demographic characteristic differences observed between the web-based Foodbook24 study and the NANS study are large because of the recruitment efforts undertaken in both studies rather than methods by which the surveys were presented and delivered. For the web-based study, targeted recruitment efforts to ensure the recruitment of a nationally representative sample were not undertaken. This allowed for the investigation of the rate and route of recruitment and characteristics of responders to be examined; that is, were older adults signing up to use Foodbook24 without being directly asked to do so? The findings of this research demonstrate that most participants were female with a higher level of education, suggesting that targeted recruitment strategies are needed when recruiting online nutrition studies and surveys if representative samples are to be achieved.

In contrast, the NANS study employed a multistage, stratified recruitment strategy, and although it was costly, this resulted in the successful recruitment of a sample representative of the Irish adult population. To achieve higher participation rates in web-based nutrition surveillance efforts using Foodbook24 in the future, the use of vast, recurrent multimedia campaigns (television, radio, national/regional newspapers, and billboards) should be considered. This recruitment strategy was employed in the NutriNet Sante study, wherein more than 50,000

participants were successfully recruited to web-based nutrition research [30].

Participants' evaluation of Foodbook24 in the web-based study highlighted a willingness to use the tool on a long-term basis (Table 6; participants willing to use Foodbook24 for 6 months: 200/425, 47.1%) for dietary data collection, which is a significant finding. In the United States, the results from a study by Thompson et al [10] showed that 70.02% (757/1081) of adult participants (n=1081) preferred the web-based, self-administered Automated Self-Administered 24 hours (ASA24) tool over the interviewer-led Automated Multiple-Pass Method. These results indicate that technology-based dietary methods may encourage users to participate in nutrition surveys [1].

Demographic Characteristics of Participants in the Web-Based Foodbook24 Study Compared With Those From the NANS Study

The results of the web-based Foodbook24 study compared with the NANS study showed significant differences with respect to the demographic characteristics of the populations recruited. A primary challenge for researchers employing web-based self-report surveys is the ability to engage target populations in the survey, as the method heavily relies on self-selection (referring to when survey participants are allowed to decide whether or not they want to participate in a survey) [31]. The key differences observed included the proportion of those aged ≥65 years, the proportion of males to females recruited, and the distribution of participants in BMI, social class, and education level categories.

There was a significantly lower proportion of older adult participants in the web-based Foodbook24 survey compared with the NANS, although the range of ages of the participants in both studies was very similar, which suggests the potential for the use of Foodbook24 in this population. Ward et al [32] demonstrated the potential use of self-administered, web-based, 24-hour recalls in a population of older adults aged between 60 and 85 years, whereby 67.1% (214/319) completed at least one recall and 47.9% (153/319) completed 2 or more recalls. Ward et al [32] also concluded that further support may be required to obtain multiple recalls in this population, which could be a consideration for Foodbook24 going forward.

Gender is an important determinant of health-risk and health-promoting behaviors [33] and yet research suggests that approximately only 20% of participants in health-related research are male [34]. This finding was apparent in the Foodbook24 web-based study, where only 30.04% (329/1095) of participants who signed up to take part in the study were male. Female participants were found to be more likely to complete all aspects of the Foodbook24 web-based study when the incidence of nonresponse or dropout was investigated. This highlights a clear advantage of a stratified, multistage recruitment approach that was employed in the NANS [15] and other national nutrition surveys such as the NDNS in the United Kingdom, where focused efforts are used to ensure an even proportion of males to females are recruited. Ryan et al [35] noted that there are complex barriers hindering male recruitment to health studies, particularly web-based, and that strategies that involve friends and family to aid recruitment can be successful. The difference in social class and education level observed between the web-based study and NANS is consistent with previous reports, which highlight that individuals with lower education level [36] and social class [37] were less likely to complete web-based surveys, potentially because of computer literacy issues. A higher level of education was also observed in those who completed all aspects of the Foodbook24 web-based study compared with those who dropped out. Kirkpatrick et al [37] recently demonstrated that women with low incomes reported dietary intake data relatively well using ASA24-2016; however, their data were less accurate, relative to women with a higher income. Concentrated efforts to ensure representative samples from all population groups are engaged in future web-based surveys and that training and support are available to those less familiar with technology are warranted [38].

In the Foodbook24 web-based study, a higher proportion (608/1095, 55.52%) of participants reported a BMI within the normal BMI category (18.5-24.9) compared with 32.8% (492/1500) in the NANS study and a lower proportion (127/1095, 11.59%) with obesity compared with 21.2% (318/1500) in the NANS. Web-based anthropometric measurements were self-reported compared with measurements taken by trained researchers in NANS; however, research has shown that self-reported anthropometric data can be reliable when validated against in-person measures [39]. As such, it is difficult to decipher whether the anthropometric data reported as part of the web-based Foodbook24 is actually reflective of the population that took part in the study. However, an element of misreporting is expected, as per previous web-based studies where body measurements are self-reported [40].

Comparison of Dietary Intake Data Collected From the Web-Based Foodbook24 Study and NANS

Although both web-based and interviewer-administered dietary assessment tools are prone to similar measurement errors and correlated person-specific biases [41], research has shown that 24-hour recall tools can provide comparable data to interviewer-administered recalls [10,21,42,43] and are substantially better than FFQs [44,45]. Web-based methodologies for the purposes of nutrition surveillance also provide automated analysis and standardized approaches for the collection of data, which reduces the likelihood of error associated with human data collection and analysis [1].

In this study, the discrepancies observed between intakes from both NANS and the web-based study may be because of different time points of data collection and the changes in food consumption trends between those time points; however, it is important to consider the impact of the different dietary assessment methodologies on nutrient and food group data from both surveys. It is also possible that by presenting the participant with a limited food and beverage list in the Foodbook24 tool compared with open-ended entry options as per the food diary method may also explain some of the discrepancies observed. Future development research to address this potential issue is currently underway. De Keyzer et al [46] compared data collected from repeated 24-hour recalls using EPIC-SOFT, a

European computer program for 24-hour dietary protocols, to data collected from a 5-day estimated food diary for estimating nutrient intakes in a national food consumption survey. The results highlighted a similar level of misreporting using both methods, and similar to this study, group-level intakes of protein, carbohydrates, starch, sugar, water, potassium, and calcium from duplicate 24HDRs did not differ from those obtained by 5-day estimated diet records. However, for micronutrients that are concentrated in fewer food items such as vitamin A, more repeated 24-hour recalls are necessary to obtain representative estimates of absolute usual intakes [47].

The data collected from the web-based study compared with the NANS study clearly highlight the potential of Foodbook24 for the rapid identification of food trends over time if used in a rolling data collection capacity. Higher consumption rates of coffee, pulses, and exotic fruits and lower consumption of food items such as white bread and ready-to-eat breakfast cereals were observed in the web-based data compared with NANS. Alcoholic beverages were reported as consumed less frequently in the web-based study compared with NANS, which is likely because of the fact that alcoholic beverages are more frequently consumed on weekend days [48] and data collection on weekend days only occurred in 31.9% (174/545) of web-based participants compared with 100% (1500/1500) of NANS participants.

Estimating the usual intake of episodically consumed foods based on a limited number of 24HDRs per participant can be challenging for their use in national consumption surveys [49] and is an important consideration for using Foodbook24 in large-scale surveys going forward. Potential strategies to address these issues include the use of repeat, preferably nonconsecutive dietary recalls, concurrent blended/combined dietary assessment tools alongside the application of sophisticated statistical modeling, and the collection of biological samples to assess biomarkers of nutrient and food group intake as an independent measure [50].

Limitations

This study acknowledges the limitations to this analysis, as it was performed using dietary intake data collected using 2 different methodologies (2×nonconsecutive 24-hour recalls vs 4-day semiweighed food diary) at 2 different time points (5 years apart; the Irish NANS was completed in 2011 and the web-based Foodbook24 study was completed in 2016) and in separate adult cohorts (a random adult sample population vs a representative adult population). As such, the differences observed in this analysis may be because of differences in the education, BMI, and social classes of participants involved in the 2 studies, making it inherently difficult to compare. However, a number of efforts have been made to address these limitations, including (1) completing a controlled comparison of dietary intakes by applying sampling weights to the Foodbook24 data to account for differential probabilities of participant characteristics and nonresponse (based on age and gender), and (2) coding and analyzing the data from both cohorts by using the same food grouping structure and compositional food tables to explore the potential of using a web-based platform to collect dietary intake data of a similar quality relative to data collected using a pen- and paper-based dietary assessment method in Ireland.

Future Considerations for Web-Based Methodologies in Nutrition Surveillance

As it stands, open-source web-based surveys delivered via Foodbook24 do not result in the collection of dietary intake data from a representative sample of the Irish adult population. Although web-based methodologies offer standardized collection and analysis of data, the use of these tools to collect data from representative samples of populations is challenging. Future investigations of the comparison of methodologies should also control for factors such as social class or education, as the findings from this analysis demonstrate that responders with lower socioeconomic status and education were not proportionally represented in the web-based study sample. Although further work is warranted, a carefully designed recruitment strategy for the use of Foodbook24 in national nutrition surveys, especially considering population groups that may require extra support and training, has the potential to exceed the recruitment rates of previous national surveys. Platform adaptations, such as the collection of brand-level data and adapted approaches for groups such as older adults and infants, need to be considered for the collection of nationally representative food consumption information. This research demonstrates the capability of Foodbook24 to collect acceptable food and nutrient intake data from large survey populations. These findings support the use of Foodbook24 as a semicontinuous monitoring system in Ireland that would provide a cost-effective platform to collect valuable information to regularly evaluate the dietary intake of the general Irish adult population. This would allow for the rapid identification of food trends and for the development and monitoring of effective policies on nutrition and food safety in the future.

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Authors' Contributions

CT, EG, JW, and AF conceived and designed the experiments. CT analyzed the data and wrote the initial draft of this manuscript. All authors have been involved in the overall development of Foodbook24. All authors contributed to the writing of this manuscript and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Nutrient intakes of adequate reporters from the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).
[DOCX File , 28 KB - publichealth_v7i4e22759_app1.docx]

Multimedia Appendix 2
Nutrient intakes of female adequate reporters from the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).
[DOCX File , 17 KB - publichealth_v7i4e22759_app2.docx]

Multimedia Appendix 3
Nutrient intakes of male adequate reporters from the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).
[DOCX File , 18 KB - publichealth_v7i4e22759_app3.docx]

Multimedia Appendix 4
Food group intakes (grams) of adequate reporters from the Foodbook24 web-based study (2016) and the National Adult Nutrition Survey (2011).
[DOCX File , 20 KB - publichealth_v7i4e22759_app4.docx]

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Abbreviations

24HDR: 24-hour dietary recall
ASA24: Automated Self-Administered 24 hours
BMR: basal metabolic rate
EFSA: European Food Safety Authority
EI: energy intake
FCQ: food choice questionnaire
FFQ: food frequency questionnaire
NANS: National Adult Nutrition Survey
NDNS: National Diet and Nutrition Survey

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Corrigenda and Addenda

Correction: Assessment of the Effectiveness of Identity-Based Public Health Announcements in Increasing the Likelihood of Complying With COVID-19 Guidelines: Randomized Controlled Cross-sectional Web-Based Study

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In "Assessment of the Effectiveness of Identity-Based Public Health Announcements in Increasing the Likelihood of Complying With COVID-19 Guidelines: Randomized Controlled Cross-sectional Web-Based Study" (JMIR Public Health Surveill 2021;7(4):e25762) the authors noted one error.

In the originally published manuscript, an Editorial Notice regarding the study's retrospective registration contained an incorrect quotation from the authors.

> *This randomized study was only retrospectively registered, explained by the authors with "this is a replication study". The editor granted an exception from ICMJE rules mandating prospective registration of randomized trials because the risk of bias appears low and the study was considered formative, guiding the development of the application, or specific requirements regarding preregegistration. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness, as retrospective registration does not prevent authors from changing their outcome measures retrospectively.*

The corrected version of this notice reads as follows:

> *This randomized study was only retrospectively registered as, according to the authors, their field has not adopted pre-registration as convention. The editor granted an exception from ICMJE rules mandating prospective registration of randomized trials because the risk of bias appears low. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness, as retrospective registration does not prevent authors from changing their outcome measures retrospectively.*

The correction will appear in the online version of the paper on the JMIR Publications website on April 15, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Early Detection of Dengue Fever Outbreaks Using a Surveillance App (Mozzify): Cross-sectional Mixed Methods Usability Study

Von Ralph Dane Marquez Herbuela[1,2], PhD; Tomonori Karita[3], PhD; Thaddeus Marzo Carvajal[1,4], PhD; Howell Tsai Ho[5], PhD; John Michael Olea Lorena[6], PhD; Rachele Arce Regalado[7], MA; Girly Dirilo Sobrepeña[8], MD; Kozo Watanabe[1,4], PhD

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In "Early Detection of Dengue Fever Outbreaks Using a Surveillance App (Mozzify): Cross-sectional Mixed Methods Usability Study" (JMIR Public Health Surveill 2021;7(3):e19034) two errors were noted.

In the originally published manuscript, the footnotes of Tables 1 and 3 listed incorrect currency conversions. In Table 1, footnote "b" originally read:

Philippine peso (US $48.10=[illegible]1)

In Table 3, footnote "d" originally read:

Philippine peso (US $52.16=[illegible]1)

In the corrected version of the manuscript, both of these footnotes have been changed to read:

Philippine peso (US $1=[illegible]50.5; 5-year average rate)

The correction will appear in the online version of the paper on the JMIR Publications website on April 22, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Predicting Age Groups of Reddit Users Based on Posting Behavior and Metadata: Classification Model Development and Validation

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In "Predicting Age Groups of Reddit Users Based on Posting Behavior and Metadata: Classification Model Development and Validation" (JMIR Public Health Surveill 2021;7(3):e25807) the authors noted one error.

In the originally published manuscript, one sentence under the "Principal Findings" section was incorrect. The following sentence appeared in the second paragraph of this section:

> *The adult age group tended to have shorter comments than the adult age group.*

In the corrected version of the manuscript, this sentence has been changed to:

> *The adolescent age group tended to have shorter comments than the adult age group.*

The correction will appear in the online version of the paper on the JMIR Publications website on April 30, 2021, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Original Paper

The Impact of the COVID-19 Pandemic on the Uptake of Influenza Vaccine: UK-Wide Observational Study

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Abstract

Background: In the face of the COVID-19 pandemic, the UK National Health Service (NHS) extended eligibility for influenza vaccination this season to approximately 32.4 million people (48.8% of the population). Knowing the intended uptake of the vaccine will inform supply and public health messaging to maximize vaccination.

Objective: The objective of this study was to measure the impact of the COVID-19 pandemic on the acceptance of influenza vaccination in the 2020-2021 season, specifically focusing on people who were previously eligible but routinely declined vaccination and newly eligible people.

Methods: Intention to receive the influenza vaccine in 2020-2021 was asked of all registrants of the largest electronic personal health record in the NHS by a web-based questionnaire on July 31, 2020. Of those who were either newly or previously eligible but had not previously received an influenza vaccination, multivariable logistic regression and network diagrams were used to examine their reasons to undergo or decline vaccination.

Results: Among 6641 respondents, 945 (14.2%) were previously eligible but were not vaccinated; of these, 536 (56.7%) intended to receive an influenza vaccination in 2020-2021, as did 466 (68.6%) of the newly eligible respondents. Intention to receive the influenza vaccine was associated with increased age, index of multiple deprivation quintile, and considering oneself to be at high risk from COVID-19. Among those who were eligible but not intending to be vaccinated in 2020-2021, 164/543 (30.2%) gave reasons based on misinformation. Of the previously unvaccinated health care workers, 47/96 (49%) stated they would decline vaccination in 2020-2021.

Conclusions: In this sample, COVID-19 has increased acceptance of influenza vaccination in previously eligible but unvaccinated people and has motivated substantial uptake in newly eligible people. This study is essential for informing resource planning and the need for effective messaging campaigns to address negative misconceptions, which is also necessary for COVID-19 vaccination programs.

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KEYWORDS

COVID-19; influenza; vaccination; COVID; Pandemic; National Health Service; Health Service; flu; virus; vaccine; impact; uptake; observational; United Kingdom; public health; intention; electronic health record

Introduction

To date, the COVID-19 pandemic has led to over 100,000 deaths in the United Kingdom alone. With increasing regional outbreaks [1], substantial concern has been raised about preparedness for a nationwide escalation of cases throughout winter pressures in 2020-2021 [2-4]. Seasonal influenza places the UK National Health Service (NHS) under considerable

pressure each winter, with up to 18,000 additional daily emergency admissions [5] and >4000 hospital beds occupied daily by patients with influenza in 2017-2018 [6,7].

For this reason, the NHS has extended its free seasonal influenza vaccination program for the current season to all people aged over 50 years (previously 65 years) and to include the 11-12 years age group (previously 2-10 years) [8]; thus, an estimated 32.4 million people (48.8% of the UK population) are now eligible [9]. In England in 2019, uptake of the influenza vaccine among those eligible was only 70.6% [10], below the critical 75% target for effectiveness recommended by the World Health Organization [11]. Against a background of declining numbers over the last decade (from a peak of 74.2% in 2008-2009), the uptake this season is not only unknown but is also completely unpredictable. The threat of COVID-19 and the associated publicity educating the public about viruses and vaccine development, coupled with recent evidence that coinfection with influenza and SARS-CoV-2 doubles mortality compared with infection with SARS-CoV-2 alone [12] and that the influenza vaccination may reduce incidence of life-threatening COVID-19 disease in people aged over 65 years [13], are likely to affect attitudes and the public health imperative of mass uptake. With substantial concerns that higher earlier uptake of influenza vaccination in 2020-2021 will rapidly deplete stocks (as already reported [14]), there is still a risk that a lack of informed planning will result in failure to meet the requirements of this public health initiative.

Therefore, the objective of this study was to measure the impact of the COVID-19 pandemic on the acceptance of influenza vaccination in the 2020-2021 season, specifically focusing on people who were previously eligible (aged over 65 years or having an eligible comorbidity) who routinely decline vaccination and newly eligible people (aged 50-64 years)—two groups in which the determinants of vaccine hesitancy may differ. These groups include those at highest risk from COVID-19; if the influenza vaccine confers a reduced risk of COVID-19, understanding specific covariates that relate to vaccine hesitancy can inform public health messaging to maximize uptake and help contend with potential double winter pandemics of influenza and COVID-19.

Methods

Ethical Approval

The weekly questionnaire was a direct care tool for patients to self-monitor their well-being during the COVID-19 pandemic. Participants were not paid or otherwise compensated for completing questionnaires. Upon review, the Imperial College Healthcare NHS Trust Data Protection Office advised that ethical approval for data analysis and publication was not required. Participants gave informed consent within the CIE, were free to opt out of receiving questionnaires at any time, and were informed prior to completing their responses that these would be fully anonymized and stored on secure servers before analysis toward informing local and national health policy.

Study Participants

Participants were registrants of the Care Information Exchange (CIE) of Imperial College Healthcare NHS Foundation Trust. The CIE is the largest patient-facing electronic health record in the United Kingdom; it is accessible by email registration for any patient who has had an encounter at the Trust (UK-wide population, Figure S1 in Multimedia Appendix 1). On June 5, 2020, the CIE held 57,056 registrants, of whom 34,502 were active users, defined as having one or more logins in the preceding month.

Participants in this study were CIE registrants receiving weekly web-based questionnaires through the platform, starting April 9, 2020 (week 1), as a direct care tool for self-monitoring physical, mental, and social well-being during the COVID-19 pandemic. This was the first ever such use of the CIE platform, prompted by the immediate public health priorities to provide patients with a tool to track their well-being and inform local and national health policy through this exercise in participatory epidemiology.

Questionnaire Design and Timing

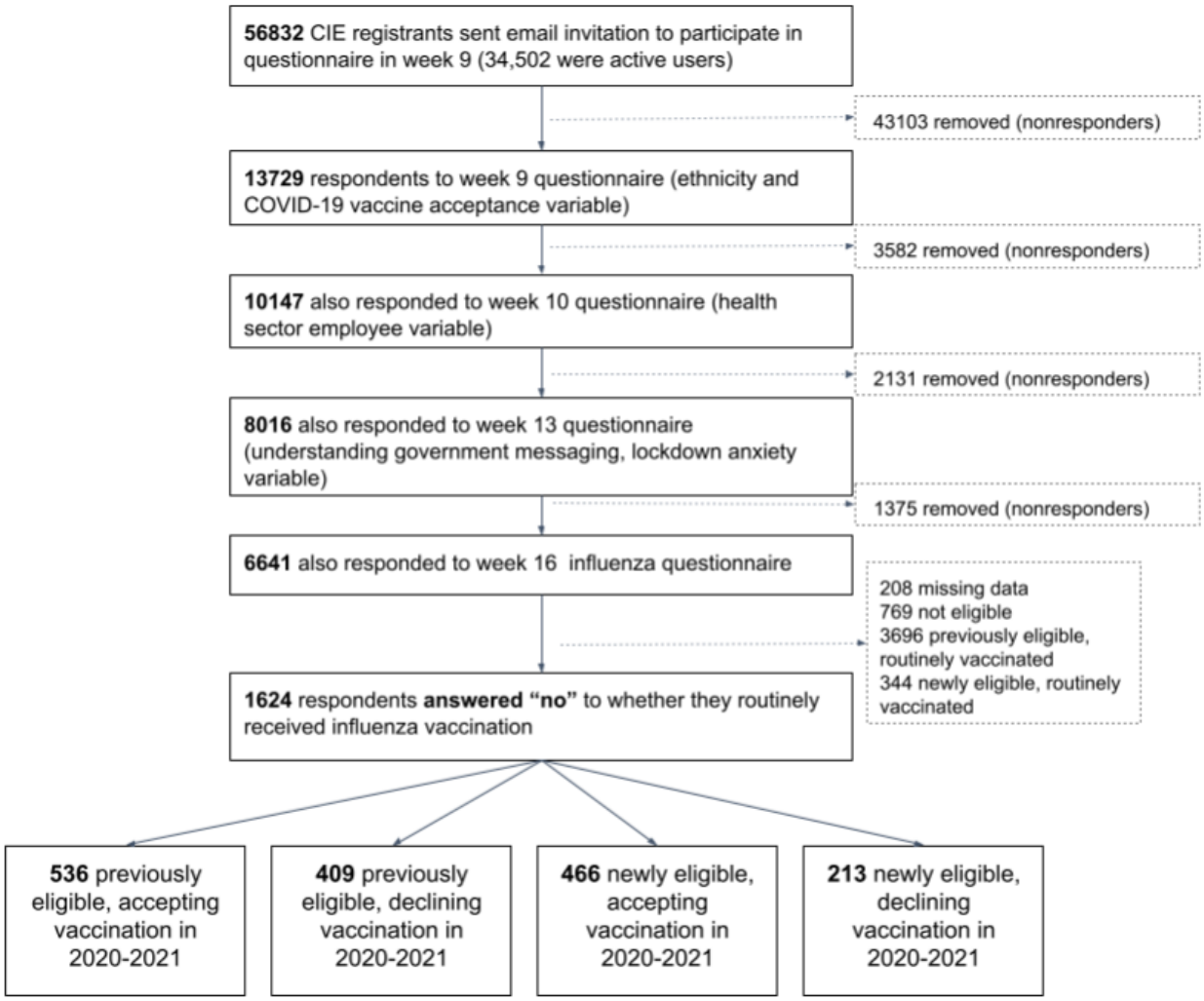
A questionnaire including items on the government's expanded influenza vaccination program was sent to participants on July 31, 2020 (week 16, Table S1 in Multimedia Appendix 1). Applying recommendations for questionnaire design [15,16], the question items were developed by a collaboration of experts in qualitative research at Imperial College London, encompassing public health, respiratory epidemiology, and digital health, and were also informed by previous studies [17,18]. Question items were externally peer-reviewed and tested on lay persons (n=5) before being included. The focus was on previous uptake of influenza vaccination, being for or against vaccination in 2020-2021 and reasons why (unrestricted free text responses), health worker status, and presence of school-age children in the household. Responses from participants regarding the presence of school-age children in their household were also recorded. Specifically, they were asked whether they would want any of these children to receive the influenza vaccination if it were offered in 2020-2021. It could not be assumed that people who were vaccinated in the previous year would continue this habit. Subsequently, a specific question was posed to also measure if any participants who were vaccinated in 2019-2020 would not be vaccinated again in 2020-2021.

Responses to items in prior questionnaires in the series were used to complete information on participant ethnicity, additional vaccine eligibility criteria (including chronic disease), index of multiple deprivation (IMD) quintile (obtained from participant postcode), health care utilization since the beginning of the lockdown, whether the participant considered themselves at high risk from COVID-19, experience of any COVID-19 symptoms, self-reported understanding of government advice, anxiety related to a return to lockdown, and whether the participant would agree to receive a COVID-19 vaccine if available.

Inclusion and Exclusion Criteria

Participants were aged 18 years or above and were required to have answered questionnaires capturing variables relevant to the analysis (see the flow diagram in Figure 1) and to have answered "no" to a question assessing whether they routinely received influenza vaccination. Respondents not eligible for influenza vaccination (ie, aged <50 years) were excluded. Participants who submitted incomplete or inconsistent responses to the questions on influenza vaccination were excluded, as were those who answered "prefer not to say" for ethnicity and who were missing responses for other variables required in the analysis, with the exception of postcode. Responses submitted later than 4 days from the time of the questionnaire launch were excluded.

Figure 1. Participant inclusion flow diagram based on responses to questionnaires capturing variables required for analysis. CIE: Care Information Exchange.



Definition of Study Groups

The analyses in this study were confined to participants who were eligible for a free NHS influenza vaccination in 2020-2021 who indicated they had previously not routinely received it (this group is the greatest unknown factor when planning resourcing and targeting public health campaigns to maximize uptake). Members of this previously unvaccinated group were either previously eligible (main criteria up to 2019-2020 were age over 65 years, eligible comorbidity, and working in the health care sector) or newly eligible for the expanded 2020-2021 program (age over 50 years).

Further stratification according to whether or not the influenza vaccine would be accepted in 2020-2021 generated four groups: (1) Previously eligible, newly responding "yes," (2) previously eligible, still responding "no," (3) newly eligible, responding "yes," and (4) newly eligible, responding "no." Owing to inherent differences in age and comorbidity status of the previously and newly eligible cohorts, their covariates for willingness to receive the influenza vaccine may be different; therefore, this stratification was maintained throughout our analyses.

Data Analysis

Age was categorized into bands of 18-29, 30-39, 40-49, 50-59, 60-69, and 70+ years to enable easier interpretation of a potential nonlinear relationship between age and responses to influenza vaccination. The 10-point scale measurements of "anxiety related to return to lockdown" and "understanding of government messaging" were regrouped into categories of 1-2,

3-4, 5-6, 7-8, and 9-10, and ethnicity was categorized into five groups due to low numbers in some categories. Descriptive statistics reported for the data set are broken down according to study group. Differences in categorical variables were assessed by chi-square test or by Fisher exact test where chi-square test assumptions were violated, and differences in continuous variables were assessed using *t* tests. *P* values <.05 were considered statistically significant.

The effects of variables of interest on the inclination to receive an influenza vaccination were calculated using univariate and multivariable logistic regression models, with presentation of both to identify if results in the univariate analysis were due to confounding by other collected variables. The relationship between age (the only continuous variable) and the log odds of receipt of influenza vaccination were plotted and visually inspected. If the effect appeared to be linear, age was included as a linear variable; otherwise, it was included as a categorical variable. All data were analyzed in R, version 3.6.2 (R Project). Variables with low numbers in categories were not included in the multivariable analyses. "Acceptance of COVID-19 vaccine if available" was deemed likely to be highly correlated with "accepting influenza vaccine in 2020-2021" and was not included in multivariable models to enable greater interpretation of other predictors. Multicollinearity was assessed by calculation of the variance inflation factor (VIF), and variables with a VIF >5 (indicating substantial multicollinearity) were removed from the model.

Each participant not routinely receiving influenza vaccination, whether previously or newly eligible, was asked to qualify their yes/no response to whether they would accept vaccination in 2020-2021 using a free text response option. Three researchers, blinded to the responses on vaccine acceptance, each independently coded the content of 100 responses according to multiple prospectively identified themes that could co-occur. A consensus was then reached to define the main themes for coding the remaining responses. For example, "I don't see the point because I've never had flu [influenza]" was coded as "unnecessary" and "not had flu before." A full list of the themes with examples is available in Table S2 in Multimedia Appendix 1.

Using this codified qualitative data, a network diagram [19,20] was generated for each of the four groups using the Networkx package in Python, version 3.7. Dimensions of centrality and overall topography of the nodes were not applicable; thus, the network was laid out in a comprehensible circular "shell" arrangement. Each diagram was limited to the 10 most represented themes within each group's responses. Nodes were color-coded to reflect positive, negative, and neutral sentiments of the themes. Separately, reasons for health care workers' continued nonvaccination in 2020-2021 were reported descriptively.

Dissemination to Participants and Related Patient and Public Communities

We plan to disseminate the findings of this study to participants in the Imperial College Healthcare NHS Trust's annual web-based newsletter.

Results

Sample Characteristics

Among respondents aged ≥18 years, 6641 completed the week 16 questionnaire on influenza vaccination in the predefined time period and the requisite previous questionnaires to complete the baseline characteristics (Figure 1). Of these, 208 (3.1%) were missing answers to one or more essential variables and were removed, leaving 6433 complete responses. The total number of previously eligible but unvaccinated (n=945) and newly eligible but unvaccinated (n=679) participants was 1624 (see Figure 1 for details).

Of the vaccinated and unvaccinated previously eligible participants, those who had previously declined vaccination were more likely to be younger (median age 61 years, IQR 51-67, vs median age 67 years, IQR 58-73, *P*<.001), female (520/945, 55.0%, vs 1727/3696, 46.7%, *P*<.001), have chronic neurological disease (102/945, 10.8%, vs 241/3696, 6.5%, *P*<.001), work in the health sector (96/945, 10.2%, vs 287/3696, 7.8%, *P*=.02), and be in a lower IMD quintile (*P*=.03), and they were less likely to have chronic respiratory disease (137/945, 14.5%, vs 757/3696, 20.5%, *P*<.001) or chronic heart disease (66/945, 7.0%, vs 757/3696, 12.2%, *P*<.001) compared to those who were previously eligible and received the vaccine. Of the newly eligible participants, when compared with those who had received the vaccine despite being ineligible by NHS criteria, those who had not received the vaccine were more likely to be younger (mean age 57 years, IQR 54-61, vs median age 59 years, IQR 55-63) and in a lower IMD quintile (Table S3, Multimedia Appendix 1). Among all respondents who indicated having received the influenza vaccine in 2019-2020, 309/6867 (4.5%) responded that they did not intend to repeat this in 2020-2021.

Change in Acceptance and Uptake of Influenza Vaccine in 2020-2021

Summary statistics for the groups broken down according to vaccine eligibility and acceptance of the influenza vaccine in 2020-2021 are shown in Table 1. Of those previously eligible but routinely not vaccinated, 536 (56.7%) intended to be vaccinated in 2020-2021, increasing the vaccination rate in the entire previously eligible cohort from 79.6% to 91.2%. Among the newly eligible, 466 (68.6%) reported they would accept vaccination in 2020-2021.

Table 1. Characteristics of the study participants (N=1624) based on UK-wide responses to web-based questionnaires administered through Care Information Exchange (influenza-related questionnaire sent July 31, 2020). Baseline demographics and questionnaire responses of all participants previously not routinely receiving influenza vaccination are grouped by previously eligible but nonvaccinated and newly eligible, further stratified by acceptance (yes/no) of influenza vaccination in 2020-2021.

Characteristic	Value			
	Previously eligible and plans to receive the influenza vaccine (n=536, 56.7%)	Previously eligible and does not plan to receive the influenza vaccine (n=409, 43.3%)	Newly eligible and plans to receive the influenza vaccine (n=466, 68.6%)	Newly eligible and does not plan to receive the influenza vaccine (n=213, 31.4%)
Age, median (IQR)	62.0 (51.0-67.0)	60.0 (49.0-68.0)	58.0 (55.0-61.8)	56.0 (53.0-60.0)
Sex, n (%)				
Male	248 (46.3)	177 (43.3)	214 (45.9)	69 (32.4)
Female	288 (53.7)	232 (56.7)	252 (54.1)	144 (67.6)
Ethnicity, n (%)				
White	453 (84.5)	320 (78.2)	415 (89.1)	181 (85.0)
Asian	36 (6.7)	39 (9.5)	19 (4.1)	13 (6.1)
Black	15 (2.8)	20 (4.9)	13 (2.8)	9 (4.2)
Mixed	8 (1.5)	6 (1.5)	6 (1.3)	2 (.9)
Other	24 (4.5)	24 (5.9)	13 (2.8)	8 (3.8)
Eligible disease, n (%)	368 (68.7)	282 (68.9)	N/A[a]	N/A
Chronic respiratory disease, n (%)	71 (13.2)	66 (16.1)	N/A	N/A
Chronic heart disease, n (%)	40 (7.5)	26 (6.4)	N/A	N/A
Chronic kidney disease, n (%)	25 (4.7)	23 (5.6)	N/A	N/A
Chronic liver disease, n (%)	15 (2.8)	11 (2.7)	N/A	N/A
Chronic neurological disease, n (%)	48 (9.0)	54 (13.2)	N/A	N/A
Immunocompromised, n (%)	196 (36.6)	137 (33.5)	N/A	N/A
Other eligible comorbidity, n (%)	103 (19.2)	93 (22.7)	N/A	N/A
Health sector employee, n (%)	47 (8.8)	49 (12.0)	N/A	N/A
Index of multiple deprivation, n (%)				
1	34 (6.3)	31 (7.6)	17 (3.6)	14 (6.6)
2	78 (14.6)	64 (15.6)	69 (14.8)	36 (16.9)
3	107 (20.0)	59 (14.4)	94 (20.2)	29 (13.6)
4	85 (15.9)	55 (13.4)	87 (18.7)	28 (13.1)
5	79 (14.7)	44 (10.8)	57 (12.2)	15 (7.0)
Missing	153 (28.5)	156 (38.1)	142 (30.5)	91 (42.7)
Health care utilization, n (%)				
None	91 (17.0)	89 (21.8)	145 (31.1)	80 (37.6)
Any	445 (83.0)	320 (78.2)	321 (68.9)	133 (62.4)
Considers self at high risk from COVID-19, n (%)	346 (64.6)	267 (65.3)	140 (30.0)	41 (19.2)
Understanding of government messaging (score from 1-10) , n (%)				
1-2	31 (5.8)	34 (8.3)	48 (10.3)	16 (7.5)
3-4	69 (12.9)	48 (11.7)	65 (13.9)	24 (11.3)
5-6	138 (25.7)	93 (22.7)	107 (23.0)	53 (24.9)
7-8	190 (35.4)	133 (32.5)	159 (34.1)	72 (33.8)

Characteristic	Value			
	Previously eligible and plans to receive the influenza vaccine (n=536, 56.7%)	Previously eligible and does not plan to receive the influenza vaccine (n=409, 43.3%)	Newly eligible and plans to receive the influenza vaccine (n=466, 68.6%)	Newly eligible and does not plan to receive the influenza vaccine (n=213, 31.4%)
9-10	108 (20.1)	101 (24.7)	87 (18.7)	48 (22.5)
Anxiety related to return to lockdown (score from 1-10) , n (%)				
1-2	87 (16.2)	85 (20.8)	76 (16.3)	50 (23.5)
3-4	90 (16.8)	59 (14.4)	85 (18.2)	35 (16.4)
5-6	149 (27.8)	111 (27.1)	127 (27.3)	48 (22.5)
7-8	150 (28.0)	105 (25.7)	130 (27.9)	50 (23.5)
9-10	60 (11.2)	49 (12.0)	48 (10.3)	30 (14.1)
Acceptance of COVID-19 vaccine if available , n (%)				
Not sure	100 (18.7)	159 (38.9)	72 (15.5)	85 (39.9)
No	35 (6.5)	117 (28.6)	25 (5.4)	38 (17.8)
Yes	401 (74.8)	133 (32.5)	369 (79.2)	90 (42.3)

[a]N/A: not applicable.

Predictors of Willingness to Receive Influenza Vaccination

In the univariate analysis (Tables 2 and 3), willingness to receive a COVID-19 vaccine was associated with willingness to receive an influenza vaccination in 2020-2021 in both groups compared to those who were unsure (odds ratio [OR] 4.79, 95% CI 3.50-6.61, vs OR 4.84, 95% CI 3.29-7.17). Among respondents who would newly accept influenza vaccination, of those who were previously eligible and newly eligible, 401/536 (74.8%) and 369/466 (79.2%), respectively, responded they would accept a COVID-19 vaccination, compared to 133/409 (32.5%) and 90/213 (42.3%) of those declining the influenza vaccine.

In respondents who were previously eligible, answering “no” in response to whether they would receive a COVID-19 vaccination if offered was associated with a lower likelihood of wanting to receive the influenza vaccination in 2020-2021 (OR 0.48, 95% CI 0.30-0.74), as was having a chronic neurological disease (OR 0.65, 95% CI 0.43-0.98). Although people aged 60-69 years were more likely to respond “yes” than those aged ≥70 years (OR 1.48, 95% CI 1.02-2.14), no clear effect of age was found in people below the age of 60 years. The multivariable analysis (Tables 2 and 3) resulted in few substantial changes to effect estimates, with the exception of age, for which all estimates shifted upward (showing a stronger association with an increased likelihood of answering “yes” after adjustment for other variables).

Table 2. Unadjusted and adjusted logistic regressions to predict a "yes" response for participants who would accept an influenza vaccine in 2020-2021 and who were previously eligible but did not routinely receive influenza vaccination.

Characteristic	Unadjusted odds ratio (95% CI)	Adjusted[a] odds ratio (95% CI)
Age (years; reference category: ≥70)		
18-29	1.99 (0.85-5.06)	2.53 (1.00-6.89)
30-39	0.83 (0.46-1.49)	1.20 (0.62-2.31)
40-49	0.86 (0.54-1.35)	1.17 (0.70-1.95)
50-59	1.11 (0.75-1.66)	1.42 (0.90-2.25)
60-69	1.48 (1.02-2.14)	1.61 (1.09-2.37)
Female sex	0.89 (0.68-1.15)	0.93 (0.70-1.23)
Ethnicity (reference category: White)		
Asian	0.65 (0.40-1.05)	0.71 (0.43-1.18)
Black	0.53 (0.26-1.05)	0.58 (0.27-1.18)
Mixed	0.94 (0.32-2.89)	1.09 (0.36-3.50)
Other	0.71 (0.39-1.27)	0.71 (0.39-1.31)
Comorbidity		
Chronic respiratory disease	0.79 (0.55-1.14)	0.78 (0.52-1.18)
Chronic heart disease	1.19 (0.72-2.00)	1.03 (0.60-1.79)
Chronic kidney disease	0.82 (0.46-1.48)	0.71 (0.38-1.33)
Chronic liver disease	1.04 (0.48-2.35)	0.94 (0.41-2.22)
Chronic neurological disease	0.65 (0.43-0.98)	0.62 (0.38-0.99)
Immunocompromised	1.14 (0.87-1.50)	0.95 (0.69-1.32)
Other comorbidity	0.81 (0.59-1.11)	0.79 (0.56-1.10)
Health sector employee	0.71 (0.46-1.08)	0.76 (0.46-1.24)
Index of multiple deprivation quintile (reference category: 1)		
2	1.11 (0.62-2.00)	1.09 (0.59-2.01)
3	1.65 (0.92-2.96)	1.54 (0.84-2.82)
4	1.41 (0.78-2.55)	1.29 (0.70 to 2.40)
5	1.64 (0.89 to 3.02)	1.59 (0.84-3.00)
Missing	0.89 (0.52-1.53)	0.91 (0.52-1.59)
Health care utilization	1.36 (0.98-1.88)	1.41 (0.99-2.01)
Considering self at high risk from COVID-19	0.97 (0.74-1.27)	1.03 (0.76-1.39)
Understanding of government messaging (score from 1-10; reference category: 5-6)		
1-2	0.61 (0.35-1.07)	0.59 (0.33-1.05)
3-4	0.97 (0.62-1.53)	0.89 (0.56-1.43)
7-8	0.96 (0.68-1.36)	0.92 (0.64-1.31)
9-10	0.72 (0.49-1.05)	0.75 (0.50-1.11)
Anxiety related to return to lockdown (score from 1-10; reference category: 5-6)		
1-2	0.76 (0.52-1.12)	0.90 (0.60-1.37)
3-4	1.14 (0.76-1.72)	1.14 (0.74-1.75)
7-8	1.06 (0.75-1.51)	1.07 (0.74-1.54)
9-10	0.91 (0.58-1.43)	1.06 (0.66-1.71)
Acceptance of COVID-19 vaccine if available (reference category: "unsure")		
No	0.48 (0.30-0.74)	N/A[b]

Characteristic	Unadjusted odds ratio (95% CI)	Adjusted[a] odds ratio (95% CI)
Yes	4.79 (3.50-6.61)	N/A

[a]Adjusted odds ratios were adjusted for every other variable in the model (age, sex, ethnicity, disease, index of multiple deprivation quintile, health care utilization, considering oneself at high risk for COVID-19, undertaking any COVID-19 test, believing oneself to have had COVID-19, understanding of government advice, anxiety related to a return to lockdown).

[b]N/A: not applicable.

Table 3. Unadjusted and adjusted logistic regressions to predict a "yes" response for participants who would accept an influenza vaccine in 2020-2021 and who were newly eligible and not routinely vaccinated.

Characteristic	Unadjusted odds ratio (95% CI)	Adjusted[a] odds ratio (95% CI)
Age	1.07 (1.03-1.12)	1.06 (1.01-1.10)
Female	0.56 (0.40-0.79)	0.54 (0.37-0.77)
Asian	0.64 (0.31-1.35)	0.57 (0.26-1.29)
Black	0.63 (0.27-1.55)	0.76 (0.30-2.01)
Mixed	1.31 (0.30-8.99)	0.89 (0.17-6.63)
Other	0.71 (0.29-1.82)	0.77 (0.29-2.17)
Other comorbidity	1.17 (0.79-1.76)	1.01 (0.66-1.59)
Index of multiple deprivation quintile		
2	1.58 (0.69-3.57)	1.60 (0.66-3.85)
3	2.67 (1.17-6.08)	2.51 (1.02-6.13)
4	2.56 (1.11-5.86)	2.63 (1.07-6.45)
5	3.13 (1.26-7.86)	2.83 (1.07-7.59)
Missing	1.29 (0.60-2.73)	1.16 (0.51-2.63)
Health care utilization	1.33 (0.95-1.87)	1.45 (1.00-2.11)
Considering self at high risk for COVID-19	1.80 (1.22-2.70)	2.00 (1.29-3.16)
Understanding government messaging (score from 1-10)		
1-2	1.49 (0.78-2.92)	1.46 (0.73-3.02)
3-4	1.34 (0.76-2.40)	1.24 (0.68-2.30)
7-8	1.09 (0.71-1.68)	0.98 (0.62-1.56)
9-10	0.90 (0.55-1.46)	1.00 (0.59-1.68)
Anxiety related to return to lockdown (score from 1-10)		
1-2	0.57 (0.35-0.93)	0.53 (0.31-0.90)
3-4	0.92 (0.55-1.54)	0.95 (0.55-1.65)
7-8	0.98 (0.62-1.57)	0.93 (0.57-1.53)
9-10	0.60 (0.34-1.07)	0.56 (0.30-1.05)
Acceptance of COVID-19 vaccine if available		
No	0.78 (0.43-1.40)	N/A
Yes	4.84 (3.29-7.17)	N/A

[a]Adjusted odds ratios were adjusted for every other variable in the model (age, sex, ethnicity, disease, index of multiple deprivation quintile, health care utilization, considering oneself at high risk for COVID-19, undertaking any COVID-19 test, believing oneself to have had COVID-19, understanding of government advice, anxiety related to a return to lockdown).

[b]N/A: not applicable.

In respondents who became newly eligible to receive the influenza vaccine, there was an association between increased age (OR for 1-year increase in age 1.07, 95% CI 1.03-1.12), IMD quintile, and considering oneself at high risk from COVID-19 (OR 1.80, 95% CI 1.22-2.70) and answering "yes" to receiving the influenza vaccine if offered. Female respondents were less likely to answer "yes" (OR 0.56, 95% CI 0.40-0.79), as were those who rated their anxiety about the lifting of

lockdown as 1-2 (low anxiety) (OR 0.57, 95% CI 0.35-0.93), compared to those who rated it 5-6. Multivariable analysis resulted in minimal changes to the estimates, demonstrating that the univariate associations found were not due to confounding by the other variables included in the model.

Subgroup Analyses of Health Care Workers and Households with School-Age Children

In the cohort of previously unvaccinated health care workers (n=96), 49 (51.0%) stated they would accept the influenza vaccine in 2020-2021, compared to 47 (49.9%) who would continue to decline it. The question items pertaining to influenza vaccination of school-age children was answered by 1419/1624 participants (87.4%). Among these, 150/1419 (10.6%) responded that they had school-age children in their household and answered "yes" or "no" to whether they would want any children to be vaccinated in 2020-2021 if offered. Among the 71 participants who were previously eligible but not routinely vaccinated, 33/40 (83%) of those who would accept vaccination in 2020-2021 would also vaccinate their children, compared to 8/31 (26%) of those who would not accept the influenza vaccine for themselves (Fisher exact test, $P<.001$). Among the 79 participants who were previously unvaccinated and newly eligible in 2020-2021, 46/56 (82%) of those who would receive an influenza vaccine this year would want their child to have it also, compared to 10/23 (44%) of those who would not get the influenza vaccine for themselves (Fisher exact test, $P=.001$).

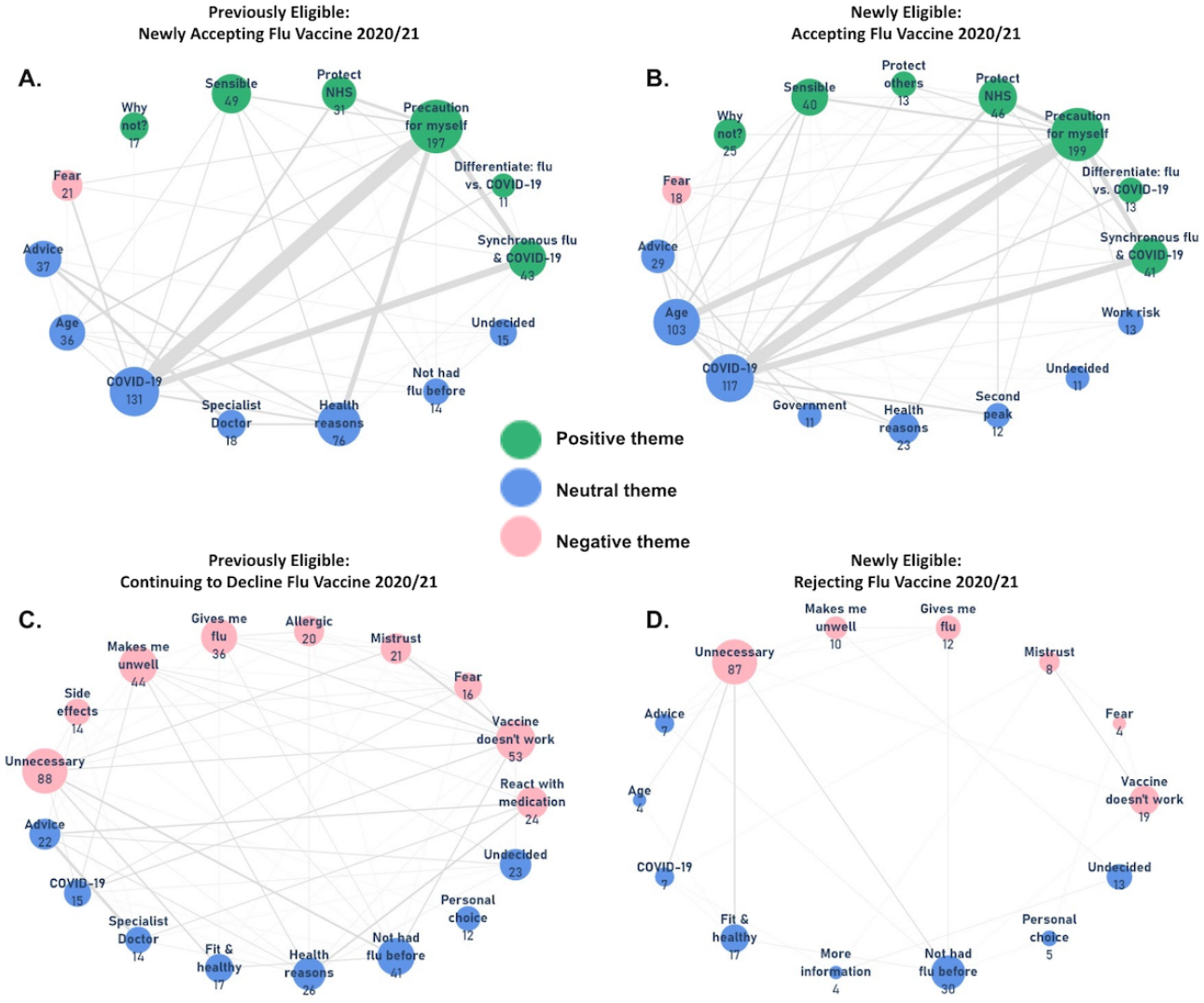
Network Diagram of Reasons For or Against Vaccination

A free text response qualifying why participants would or would not accept influenza vaccination in 2020-2021 was submitted by 834/945 (88.3%) from the previously eligible, unvaccinated group and 619/679 (91.2%) of the newly eligible group. These were coded according to 45 themes (the full list is provided in Table S2 in Multimedia Appendix 1). Figure 2 displays network diagrams for the 10 most common themes for each group.

Among the previously eligible respondents, the three most frequent themes among those newly accepting influenza vaccination in 2020-2021 were "precaution for myself" (197/478, 41.2%), "COVID-19" (131/478, 27.4%), and "health reasons" (76/478, 15.9%); among the newly eligible respondents, the three most frequent themes were "precaution for myself" (199/432, 46.1%), "COVID-19" (117/432, 27.1%) and "age" (103/432, 23.9). "Precaution for myself" was qualified by "COVID-19" in 71/197 (36.0%) and 58/199 (29.1%) participants.

For the previously and newly eligible groups declining vaccination, the three most frequent themes were "unnecessary" (88/356, 24.7%), "vaccine doesn't work" (53/356, 14.9%), and "makes me unwell" (54/356, 15.2%), and "unnecessary" (87/187, 46.5%), "not had flu before" (30/188, 16.0%) and "vaccine doesn't work" (19/186, 10.2%), respectively.

Figure 2. Study participants (N=1624) from UK-wide responses to web-based questionnaires administered through Care Information Exchange (influenza-related questionnaire sent July 31, 2020); network diagram of free-text responses (n=1453, 89.5%). Responses from previously eligible respondents who had previously not accepted the influenza vaccine but would (A) accept it in 2020-2021 (n=478) or (B) continue to decline it (n=356); responses from newly eligible participants who would (C) accept vaccination (n=432) or (D) decline it (n=187). A connecting line (edge) between nodes implies at least one response in which themes of connected nodes co-occurred; the thickness of the line corresponds to the frequency of co-occurrence. Flu: influenza; NHS: National Health Service.



Reasons for Continued Nonvaccination Among Health Care Workers

Of the health care workers reporting previous nonvaccination, 89/104 (85.6%) submitted qualifying responses, among whom 47 were from those newly accepting and 42 continuing to decline vaccination in 2020-2021. For the former, "precaution for myself" (17/47, 36.2%), "COVID-19" (16/47, 34.0%) and "health reasons" (8/47, 17.0%) were the most cited reasons. In those continuing to decline, most frequent reasons were "gives me flu" (10/42, 23.8%), "vaccine doesn't work" (8/42, 19.0%) and "unnecessary" (6/42, 14.3%).

Discussion

Principal Findings

Due to the threat of COVID-19 and the associated publicity educating the public about viruses and vaccine development, following a decade of declining numbers, uptake of the influenza vaccine this year is both unknown and unpredictable. With early reports that higher uptake of influenza vaccination will rapidly deplete stocks [14], there is yet again a threat of a lack of informed planning resulting in failure to meet the demands of a public health initiative. Our findings, including that >90% of previously and 70% of newly eligible participants want vaccination, provide strong evidence to inform planning and public health messaging to maximize vaccination.

The finding that coinfection doubles the risk of death [12] was published after collection of the data described in this study; however, our results indicate that specific avoidance of "synchronous influenza and COVID-19" and "differentiating influenza from COVID-19" were already motivators for new influenza vaccine uptake for the 2020-2021 season. This suggests that the UK public already perceived the risk from a convergence of both viruses. Indeed, in this study, increasing age, IMD quartile, and higher levels of anxiety were associated

with increased likelihood of accepting vaccination among the newly eligible; however, the strongest association was considering oneself at high risk from COVID-19, which was associated with an 80% increase in uptake. This relates to our observation in the network diagram that the common reason of "precaution for myself" was frequently qualified by "COVID-19" in both of the groups accepting vaccination. Among those not accepting vaccination, the newly eligible appear to be predominantly motivated by a belief that vaccination is "unnecessary," contrasting with previously eligible respondents, who gave substantially more misinformed reasons (eg, "gives me flu"), presumably by virtue of having more experience and exposure to vaccination and therefore having more time to develop misinformed beliefs.

Our finding that previously eligible but unvaccinated respondents in the 60-69 years age group were 50% more likely to respond "yes" to vaccination in 2021 than those aged ≥70 years is perhaps unsurprising, given that the latter are at highest risk if exposed—as in, by leaving home to receive an influenza vaccine—to COVID-19. The observation that chronic neurological disease was associated with more vaccine hesitancy may be explained by patients receiving specific therapy (such as for multiple sclerosis) contraindicating influenza vaccination.

Childhood influenza vaccination in the United Kingdom has never reached its 65% uptake target (60.8% in 2018-2019) [21], and our study suggests part of the narrative around unvaccinated children is that adults in their household may also be hesitant to receive an influenza vaccine themselves. Perhaps more concerning is that children may assume their parents' attitudes to vaccination in later life [19]. Public trust is critical for confidence in vaccination programs [20,22], which must be underpinned by clear messaging campaigns; this is particularly relevant for newly eligible people who, as shown in our study, express fewer misinformed views around the influenza vaccine. Media coverage during the current global health crisis has led to an unprecedented level of education of the general public on respiratory viruses and vaccine development and associated trust in scientific reporting [23,24]. However, social media can potentially be damaging by proliferating misinformation [25]. Collectively, misinformed themes of "makes me unwell," "gives me flu," and "vaccine doesn't work" were present across 35.1% and 20.9% of responses in previously unvaccinated and newly eligible respondents, respectively. Governmental messaging campaigns to address misconceptions such as these are doubly important because they have the potential not only to increase uptake of the influenza vaccine but also to prevent these same misconceptions from undermining the uptake of a future COVID-19 vaccine. Transparency in how a vaccine is being developed must be accompanied by assurances that safety and efficacy are critical and that problematic vaccines will be avoided, which might otherwise diminish public trust [26].

This study suggests that the UK population continues to feel a sense of duty to the NHS; 8.5% of those newly accepting vaccination cited "protect the NHS" as their reason. This messaging, which was used to encourage adherence to the government's stay-at-home policy during the height of the first wave of the pandemic [27], could also be leveraged to increase uptake of influenza and COVID-19 vaccines. It is noteworthy in the context of the general public's motivation to protect the NHS that 50% of health care professionals in this sample who previously refused the influenza vaccine still do not intend to receive it. Confirmation of this finding requires further study of larger cohorts of such professionals.

Limitations

This study has several limitations. These results are only indicative; whether the participants would maintain their responses when faced with influenza vaccination is uncertain. Intentionality may not always translate to actual vaccine uptake. Although one study of US adults aged over 18 years suggested that just over half of respondents who declared intending to receive an influenza vaccine followed through [28], follow-through in the population aged over 50 years in our study is likely to be significantly higher [29]. The advantage of this study using the CIE of the NHS to collect responses is an inherent ability to link to both primary and secondary care data, thereby enabling us to further progress this work at the end of the 2020-2021 influenza season by measuring how intentionality translated to actual uptake.

Use of the CIE, to which all participants were registered, implies both a higher disease burden and better agency over one's health, and notably, the previously eligible population had a higher baseline uptake (79.6%) than last year's national average (70.6%). This is more broadly indicative of a sample that is not fully representative of the general population, although our data do suggest that some of the lower IMD quintiles were adequately captured. Despite a representative distribution of questionnaires, ethnic minority groups were underrepresented among the respondents, limiting the generalizability of the acceptance rates and their reasons for and against new uptake. Our study could not fully consider potential mismatches between those eligible for influenza vaccination and those at highest risk of severe COVID-19. By also examining changes in vaccine hesitancy in those ineligible for influenza vaccination but nonetheless at higher risk of COVID-19, such as people who are nonmorbidly obese [30], we could inform policy for further extension of the influenza vaccine criteria to include such individuals. The time-sensitive need to accumulate these data prohibited the generation of question items using, for example, in-depth Delphi methods and full psychometric evaluation of validity; however, an expert team including patient representation designed the questionnaire.

Conclusion

In the sample in this study, the COVID-19 pandemic has influenced increased acceptance of influenza vaccination in 2020-2021 in people who were previously eligible for the vaccine but routinely unvaccinated, and it is also a major driver of acceptance among people who are newly eligible for the vaccine. This high anticipated demand requires appropriate planning but can be further increased with effective messaging campaigns to address negative misconceptions about influenza vaccination, which may also help prepare for future COVID-19 vaccination. Maximizing vaccination requires informed planning of vaccine supply and public health messaging if we are to avoid failure once again of an essential public health response to the COVID-19 pandemic this winter.

Data Availability

Imperial College Healthcare NHS Trust is the data controller. The data sets analyzed in this study are not publicly available but can be shared for scientific collaboration subject to meeting requirements of the institution's data protection policy.

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Authors' Contributions

PB contributed to the study design, data collection, literature review, data analysis, figures, and writing of the paper. AA contributed to the study design, literature review, figures, data analysis, and writing. JJC contributed to the figures, data analysis, and writing. RS contributed to the figures, data analysis, and writing. JKQ contributed to the study design, literature review, data analysis, figures, and writing. NSP contributed to the study design, data collection, literature review, data analysis, figures, and writing. NSP is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary materials.
[DOCX File , 170 KB - publichealth_v7i4e26734_app1.docx]

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Abbreviations

CIE: Care Information Exchange
IMD: index of multiple deprivation
NHS: National Health Service
OR: odds ratio
VIF: variance inflation factor

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Original Paper

Impact of Firearm Surveillance on Gun Control Policy: Regression Discontinuity Analysis

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Abstract

Background: Public mass shootings are a significant public health problem that require ongoing systematic surveillance to test and inform policies that combat gun injuries. Although there is widespread agreement that something needs to be done to stop public mass shootings, opinions on exactly which policies that entails vary, such as the prohibition of assault weapons and large-capacity magazines.

Objective: The aim of this study was to determine if the Federal Assault Weapons Ban (FAWB) (1994-2004) reduced the number of public mass shootings while it was in place.

Methods: We extracted public mass shooting surveillance data from the Violence Project that matched our inclusion criteria of 4 or more fatalities in a public space during a single event. We performed regression discontinuity analysis, taking advantage of the imposition of the FAWB, which included a prohibition on large-capacity magazines in addition to assault weapons. We estimated a regression model of the 5-year moving average number of public mass shootings per year for the period of 1966 to 2019 controlling for population growth and homicides in general, introduced regression discontinuities in the intercept and a time trend for years coincident with the federal legislation (ie, 1994-2004), and also allowed for a differential effect of the homicide rate during this period. We introduced a second set of trend and intercept discontinuities for post-FAWB years to capture the effects of termination of the policy. We used the regression results to predict what would have happened from 1995 to 2019 had there been no FAWB and also to project what would have happened from 2005 onward had it remained in place.

Results: The FAWB resulted in a significant decrease in public mass shootings, number of gun deaths, and number of gun injuries. We estimate that the FAWB prevented 11 public mass shootings during the decade the ban was in place. A continuation of the FAWB would have prevented 30 public mass shootings that killed 339 people and injured an additional 1139 people.

Conclusions: This study demonstrates the utility of public health surveillance on gun violence. Surveillance informs policy on whether a ban on assault weapons and large-capacity magazines reduces public mass shootings. As society searches for effective policies to prevent the next mass shooting, we must consider the overwhelming evidence that bans on assault weapons and/or large-capacity magazines work.

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KEYWORDS

firearm surveillance; assault weapons ban; large-capacity magazines; guns control policy; mass shootings; regression lines of discontinuity

Introduction

Background

Approximately 44,000 people are killed and an additional 100,000 people are injured by a gun each year in the United States [1,2]. Mass shooting fatalities, as a particular type of gun injury event, account for <1% of all gun deaths [3] and have largely been ignored until recently [4,5]; yet, mass shooting events occur multiple times per year [6]. This information is based on insights from firearm surveillance performed by a variety of researchers, and state and federal agencies on incidence, prevalence, risk factors, injuries, deaths, and precipitating events, similar to the surveillance of infectious diseases such as COVID-19 [7-21]. Teutch and Thacker [22] defined public health surveillance as

> *the ongoing systematic collection, analysis, and interpretation of health data, essential to the planning, implementation, and evaluation of public health practice, closely integrated to the dissemination of these data to those who need to know and linked to prevention and control.*

Not only do surveillance systems generate hypotheses to test but they also provide the data to test them.

The Federal Assault Weapons Ban (FAWB, also known as the Public Safety and Recreational Firearms Use Protection Act) included a ban on the manufacture for civilian use or sale of certain semiautomatic firearms defined as assault weapons as well as certain large-capacity magazines (LCMs). The Act was in effect for 10 years from 1994 until it sunsetted in 2004. Semiautomatic weapons (rapid fire) and assault weapons (second grip plus other features) are distinct; however, the two are often incorrectly conflated as similar [23-26]. Semiautomatic weapons are defined as weapons that automatically load another cartridge into a chamber, preparing the weapon for firing, but requiring the shooter to manually release and press the trigger for each round [23-26]. By contrast, automatic weapons are similarly self-loading, but allow for a shooter to hold the trigger for continuous fire [27]. Furthermore, the FAWB also prohibited certain ammunition magazines that were defined as "large-capacity" cartridges [28] containing more than 10 bullets [29]. These LCMs can feed ammunition to semiautomatic weapons that do not meet the criteria of being considered assault weapons. Furthermore, LCMs are considered one of the most important features of the FAWB as research has found a relationship between bans on LCMs and casualty counts at the state level [30-34]. The 10-year federal ban was signed into law by President Clinton on September 13, 1994 [28].

Firearm surveillance data have been used to test potential policy responses to prevent mass shootings, including the FAWB [32,34-39], Extreme Risk Protection Orders (also known as red flag laws) [40-45], and federal and state LCM bans [31,32,46]. In particular, it seems likely that the FAWB and LCM bans have potential to affect mass shootings because they regulate weapons and ammunition formats that are designed to enable rapid discharge, which is a key feature in mass shooting incidents [24,47]. Other types of gun deaths may not be responsive to the FAWB or LCM bans. As an example, Extreme Risk Protection Orders or "Red Flag" orders [43,48], which temporarily prohibit at-risk individuals from owning or purchasing firearms, may be effective for preventing firearm suicides or domestic violence homicides [49] but less effective for public mass shooters [50,51]. The prohibition of LCMs may have no impact on firearm suicide because suicide decedents only require one bullet to kill themselves [52].

Several studies during and after the FAWB attempted to determine if gun policy that restricts the production and sale of assault weapons and LCMs decreased gun deaths [53,54]. These initial studies make meaningful contributions to the literature because they describe what constitutes assault weapons, magazine capacity, ballistics, and loopholes in the FAWB legislation [3,53-57]. However, these studies have found little to no evidence that these policies have had any overall effect on firearm homicides, gun lethality, or overall crime [58-61]. Since deaths from public mass shootings comprise less than 1% of all homicides based on our definition, testing whether or not the FAWB/LCM ban has an impact on homicide would wash out the effect. Since the FAWB/LCM ban may be effective at specific types of gun deaths, sampling must be limited to specific types of shooters over overall gun deaths or tests for lethality [62,63]. Finally, the variation in research findings is related to differences in research design, sampling frame, and case definition of a public mass shooting [3,53-56,64,65].

Our study differs from other studies that evaluated the efficacy of the FAWB because we used economic methods and a different outcome variable. Specifically, we focused on whether the FAWB resulted in fewer public mass shooting "events," whereas other studies evaluated the number of gun injuries and deaths that occurred during the course of a mass shooting.

Objective

The aim of this study was to test whether curbing *access to certain types of guns and magazines* will decrease mass shooting *events*. We sought to empirically answer if there was a relationship between the FAWB and a reduction in mass shooting events.

Methods

Data Source

We created a firearm surveillance system based on the National Institute of Justice–funded Violence Project dataset, which culled mass shooting events from 1966 to 2019 [6]. Consistent with earlier studies, we rely on the original Federal Bureau of Investigation (FBI) definition of a massacre, specifically where 4 or more people are killed within a single timeframe. We differentiate our mass shootings from others in that our inclusion criteria require the shootings to have occurred in a public setting.

We adapted this definition to only include massacres that involved gun deaths of 4 or more victims to isolate a particular type of mass shooter [66]. Many firearm surveillance systems that include mass shootings use a lower threshold of persons shot and many do not include deaths. An FBI report on active shooters in mass shooting events identified planning and preparation behaviors that are central to prevention [67]. This more narrow definition isolates premeditation, whereas broader definitions may include shooters that are more reactive [68]. Our case definition does not include family annihilators or felony killers because *familicides are defined by the victim-offender relationship, public massacres are defined by location, and felony killings are distinguished by motive* [69]. This differentiation is consistent with other mass shooting studies [70-72].

We examined the annual number of public mass shootings occurring between 1966 and 2019 that resulted in 4 or more fatalities. The hypothesis was that the FAWB reduced the number of public mass shootings per year during the period of the ban. We used regression discontinuity analysis to test the hypothesis. Regression discontinuity analysis is a standard economist tool used in policy analysis taking advantage of quasi-experimental designs [65,73].

Analyses

Regression discontinuity analysis allows for discontinuities or shifts in both the intercept and the slope of the trend line at both the onset and sunset of the FAWB. That is, we introduced intercept shift parameters in 1995 and 2005, and trend shift parameters for the periods 1995-2004 and 2005-2019. A statistically significant shift in a parameter indicates a discontinuity (ie, a finding that the FAWB had a statistically significant effect on the number of public mass shootings). We tested for statistical significance of the intercept and trend shift parameters both independently and jointly. All statistical inference was based on a significance level set at .05. We used the Huber-White robust residuals, which attenuate problems of autocorrelation, heteroscedasticity, and some types of model misspecification [74].

We then used the estimated model for two types of counterfactual analysis. First, we used the model to predict the number of public mass shootings that would have occurred had the FAWB not been in place. The difference between this counterfactual prediction and the modeled number of incidents with the FAWB in place provided an estimate of the number of public mass shootings that the FAWB prevented.

Second, we projected forward the number of public mass shootings that would have occurred had the FAWB been permanent (ie, continued from 2004 through to the end of the sample period). We note that in some sense, this is an “out of sample” exercise because even though the sample extends to 2019, the FAWB ended in 2004; thus, this exercise would not pick up events in the past 15 years that would have augmented or compromised the effects of the FAWB. The difference between the modeled number of public mass shootings and the projected counterfactual number of public mass shootings could provide an estimate of the number of public mass shootings that the FAWB prevented.

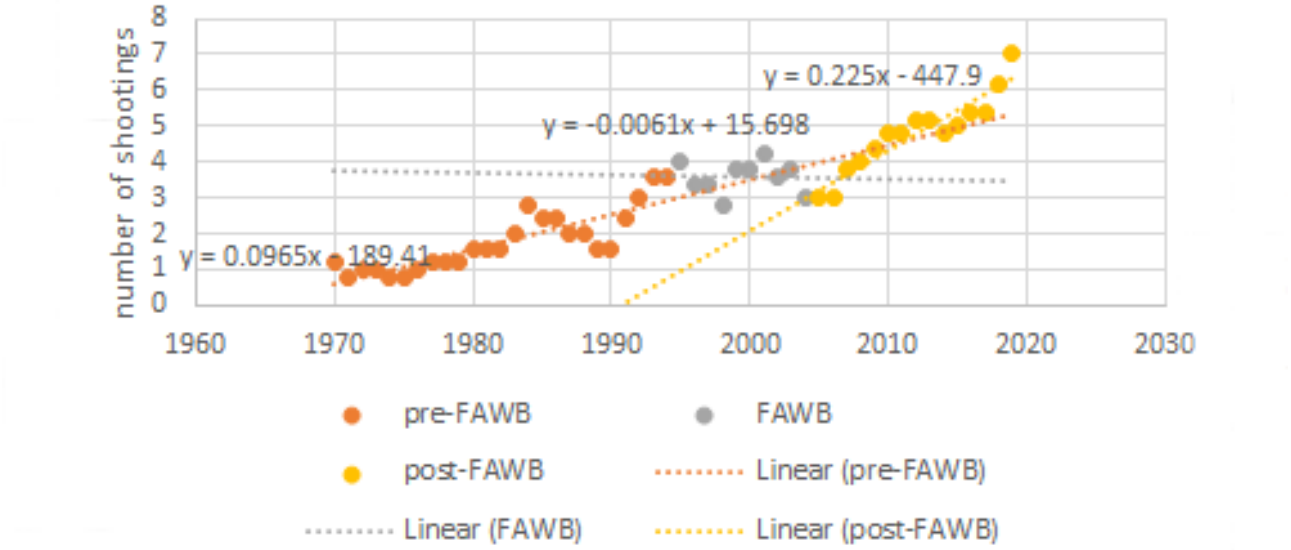
We performed a regression of the 5-year moving average of public mass shootings on the US population in millions, the homicide rate, and discontinuity variables to capture both the effects of the FAWB and its discontinuation. We did not introduce a trend line for the entire sample period because it is highly collinear with the population variable. For the period of the FAWB’s implementation, we originally introduced an intercept shift, time trend, and shift in the homicide rate; for the post-FAWB period, we introduced an intercept shift and a time trend. Due to collinearity, we retained only the trend shift in the final model for the FAWB period; for the post-FAWB period, we retained both the intercept and the trend shift.

Results

We identified a total of 170 public mass shooting events, the primary outcome variable, with 4 or more fatalities between 1966 and 2019. The 5-year cumulative number of public mass shootings is shown in Figure 1, providing a visualization of the impacts of the FAWB on the number of shootings. The first mass shooting occurred in 1966; hence, the first data point for the cumulative number of shootings over the previous 5 years occurs in 1970. For 1966 and 1967, the cumulative number of public mass shootings was 3. This number then increased to 12 in 1993 and declined to 3 in 2004. After 2004, the cumulative number of public mass shootings increased to 81 in 2019. The last year of the ban, 2004, experienced the fewest public mass shootings through 2019.

The regression results showed excellent explanatory power (R^2=0.94). The coefficient on population was positive and statistically significant (.044, P<.001). This coefficient means that for every increase in population of 1 million people, there are an additional .044 public mass shooting events per year. The coefficient on the homicide rate was negative and statistically significant (–.249, P=.01). The coefficient on the time trend for the FAWB period captures the effect of the FAWB; this coefficient was negative and statistically significant (–.187, P=.001). Using prediction models in combination with regression slopes, we estimate that 11 public mass shootings were avoided due to the FAWB. The intercept discontinuity for 2005-2019 was negative and statistically significant (–2.232, P=.001), and the trend coefficient was positive and statistically significant (.081, P=.001).

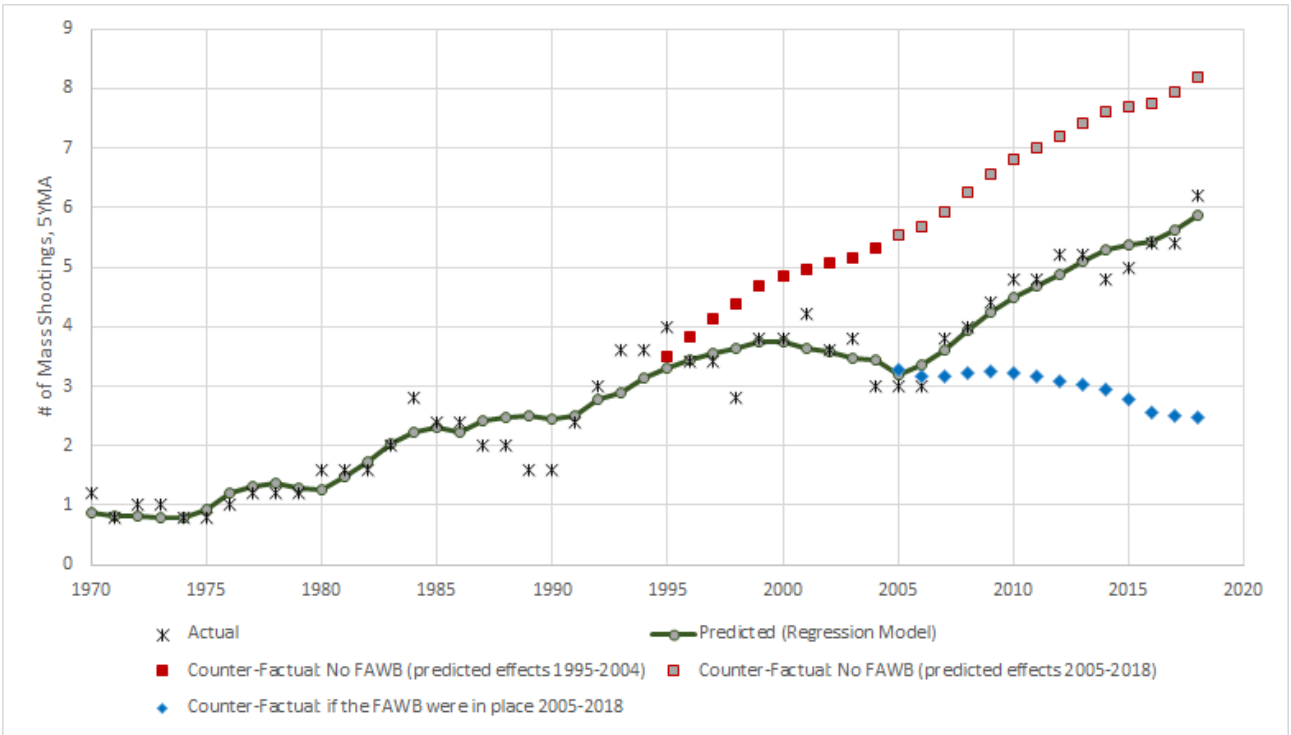
Figure 1. Public mass shooting trend line using five year moving averages (1966-2019).



These results are graphed in Figure 2 in which the black stars represent the actual data and the green line represents the predicted numbers of public mass shootings from the regression discontinuity model. A bending of the trend during the FAWB period to become downward sloping at the end of the period is apparent, as is the return of the upward trajectory upon expiration of the FAWB. The red squares represent the projected numbers of public mass shootings during the FAWB period had there been no FAWB. The difference between the red squares and the green lines represents the predicted number of public mass shootings averted by the FAWB. The model predicts that 11 public mass shootings were averted over the period of 1995-2004.

The blue diamonds represent the projected effects of a continuation of the FAWB through 2019 based on the observed trend from 1995 to 2004. This projection indicates that 30 public mass shootings would have been prevented from 2005 to 2019 had the FAWB been left in place.

Figure 2. Regression lines from discontinuity analysis of the federal assault weapons ban (1994-2004).



Discussion

Principal Findings

In total, 1225 people were killed in a mass shooting over the past 53 years with more than half occurring in the last decade, a function of increases in mass shootings and weapon lethality [62,63,75]. Public mass shooting fatalities and injuries far outpace population growth [75]. Between 1966 and 2019, the US population increased by 67% [76], whereas public mass shooting deaths increased by over 5-fold. The rise in public mass shootings throughout the sample period is in fact partially a function of population growth and homicide rate, along with the effects of the FAWB and its removal. An increase in the US population of 1 million people was associated with an increase of .040 (P<.005) public mass shootings per year. During the post-FAWB period, the increase in population from approximately 300 million in 2005 to 330 million in 2019 should be associated with an increase of 1.2 public mass shootings per year, compared to the actual increase of 4 public mass shootings per year in the data (5-year moving average). After controlling for population growth and homicide rate, a positive and statistically significant coefficient (.081, P=.001) on the 2005-2018 trend was seen. This further indicates a separate, nonpopulation trend of increasing violence operating during the post-FAWB period. The negative coefficient on the homicide rate invalidates the hypothesis that decreases in the numbers of public mass shootings are simply reflections of an overall decreasing homicide rate. The negative intercept discontinuity is consistent with an effect of the FAWB that persists somewhat beyond the immediate end of the ban. The positive trend coefficient is consistent with the hypothesis that the FAWB was associated with a decrease in the number of public mass shootings, as the expiration of the FAWB was associated with a shift from a downward trend to an upward trend in the number of public mass shootings per year.

The most striking finding from this study is that there was a reduction in the number of public mass shooting events while the FAWB was in place. Using prediction models in combination with regression slopes, we estimate that 11 public mass shootings were avoided due to the FAWB. By projecting what would have happened if the FAWB remained in place, we found that there would have been significantly fewer public mass shootings if the FAWB had remained in place to 2019. Remarkably, although it is intuitive that the removal of assault weapons and magazine clips will reduce the lethality of a mass shooting, we observed an inverse relationship between weapons/ammunition and mass shooting events, meaning that mass shooters may be less likely to perpetrate a mass shooting without rapid fire military-style weapons. This is an independent effect, which indirectly leads to fewer injuries and deaths. DiMaggio et al [64] also found evidence of a decrease in public mass shootings during the ban; however, their study period was shorter and was restricted to 51 public mass shootings. Unlike our study, they implicitly modeled public mass shootings as a random instance of general gun homicides that had a high death count [64]. In contrast, our findings suggest that public mass shootings are a unique type of premeditated gun violence. We found that prior to enactment of the FAWB, the rate of public mass shootings was increasing. During enactment of the FAWB, there was a downward trend of mass shooting events. After the FAWB was lifted, public mass shootings increased dramatically. Firearm homicides in general follow no such patterns.

This effect was not found in the work of Koper, Roth, and colleagues [53-55]; however, their inclusion of all gun homicides masks the ban's effect on mass shootings. Even though Peterson and Densley's [77] work focused on perpetrator histories and not the FAWB, their findings that ease of gun access is characteristic of public mass shooters further supports our study. We restricted the inclusion criteria to public mass shootings to specifically test the effectiveness of the FAWB on public mass shooting events.

Regardless of the FAWB, bringing a semiautomatic rifle with high magazine capacity to a massacre significantly increases the number of fatalities and injuries. The increase in deaths is a function of rapid fire and increased ballistic energy. The increase in injuries is also a function of rapid fire and high-capacity magazines, enabling the shooter to shoot more people in crowded venues quickly before the crowd can disperse or hide. When controlling for the FAWB, the use of assault rifles decreased by half during implementation of the ban and tripled after the ban was lifted. This is a particularly important finding given that the FAWB had loopholes and that overall violent crime is decreasing [78]. First, all people with an assault weapon prior to the FAWB were allowed to retain their semiautomatic weapons [54,64]. Second, without a buyback program, semiautomatic weapons remained in the community [54,64]. Third, the ban did not target some military assault-like weapons [54,64]. Finally, a major loophole found in gun control legislation is that buyers can bypass background checks by purchasing their weapons and ammunition from gun shows, through illegal purchasing, or legally purchasing their guns and ammunition from another gun owner [57,63,79-87]. Even with these loopholes and issues, there was still a significant reduction in public mass shootings during the FAWB. These loopholes indicate that most people who purchase assault weapons do not become mass shooters; however, mass shooters require assault weapons and LCMs to carry out a mass shooting. Ban effectiveness might have improved if all assault weapons were included in the FAWB.

Some recent studies have specifically analyzed the effects of LCM bans on the incidence of public mass shootings. In a review of state legislation, Webster et al [88] found that bans of LCMs were associated with a significant reduction in the incidence of fatal public mass shootings. This study shows that the FAWB, which included a ban on LCMs, was associated with fewer fatalities and injuries during mass shootings in addition to fewer public mass shooting events. Koper et al [27] previously reported that 19% of public mass shootings resulting in 4 or more fatalities included the use of LCMs, while only 10% involved an assault weapon. Klarevas et al [29] found a similar pattern in shootings of 6 or more people, in which 67% of shooters utilized LCMs, whereas only 26% utilized an assault weapon. Because our study only looked at effects of the FAWB, which included an LCM ban, we were only able to determine the combined effects of limiting assault weapons and LCMs. To be clear, the reduction in the number of public mass

shootings, and resulting fatalities and injuries, may be a function of the ban on assault weapons, assault weapons plus LCMs, or only LCMs. We cannot separate out their independent effects at the national level.

Unlike our study, Webster et al [88] did not evaluate the incidence of assault weapons used in public mass shootings. Rather, they focused on fatalities from public mass shootings vs public mass shooting events. Although Webster et al [88] utilized the FBI Supplemental Homicide Report as their dataset, which is a voluntary reporting measurement system prone to errors in reporting, their findings are applicable to our analysis.

Limitations

Although we found statistically significant decreases during the FAWB, we cannot isolate aspects of the policy that are attributed to the decline. Most notably, the FAWB also included LCMs during the ban. It may be that the type of gun and/or the type of magazine resulted in a decline. Indeed, assault weapons and LCMs provide the means to carry out a mass shooting; however, there are likely other factors beyond this study that partially explain the radical increase in public mass shootings in the post-FAWB period. For example, the FAWB was in place from 1994 to 2004, which is the same time period that the US population largely adopted the internet, along with associated social communication software and websites. This may have resulted in better tracking of public mass shootings or increased media coverage. Because our study specifically targeted the federal legislation, we omitted state-level gun policies such as state-level prohibitions on certain types of guns, LCMs, or more lethal types of bullets. It is likely that the internet serves as a contagion and as a guide to potential mass shooters, allowing them to access weapons and multiple stories about other mass shooters [62,67,89,90].

Conclusions

In summary, public mass shootings are a unique and specific type of homicide by a gun. We found evidence that public mass shootings are qualitatively different from general homicides because after the FAWB expired, mass shooting events increased while general homicides decreased. The increase in public mass shootings was more dramatic in the final 10 years of the study period following the end of the FAWB. We suspect that these outcomes may be improved by removing existing semiautomatic weapons with large bullet capacity by creating a buyback program for all rapid-firing weapons. Moreover, the legislation would be strengthened if it closed loopholes that allow gun buyers to get around the background check legislation and other purchase prohibitions by exempting gun shows and internet or person-to-person purchases, which were exempted from the FAWB and LCM ban [87].

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Conflicts of Interest

None declared.

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Abbreviations

FAWB: Federal Assault Weapons Ban
FBI: Federal Bureau of Investigation
LCM: large-capacity magazine

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Original Paper

Public Discourse Against Masks in the COVID-19 Era: Infodemiology Study of Twitter Data

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Abstract

Background: Despite scientific evidence supporting the importance of wearing masks to curtail the spread of COVID-19, wearing masks has stirred up a significant debate particularly on social media.

Objective: This study aimed to investigate the topics associated with the public discourse against wearing masks in the United States. We also studied the relationship between the anti-mask discourse on social media and the number of new COVID-19 cases.

Methods: We collected a total of 51,170 English tweets between January 1, 2020, and October 27, 2020, by searching for hashtags against wearing masks. We used machine learning techniques to analyze the data collected. We investigated the relationship between the volume of tweets against mask-wearing and the daily volume of new COVID-19 cases using a Pearson correlation analysis between the two-time series.

Results: The results and analysis showed that social media could help identify important insights related to wearing masks. The results of topic mining identified 10 categories or themes of user concerns dominated by (1) constitutional rights and freedom of choice; (2) conspiracy theory, population control, and big pharma; and (3) fake news, fake numbers, and fake pandemic. Altogether, these three categories represent almost 65% of the volume of tweets against wearing masks. The relationship between the volume of tweets against wearing masks and newly reported COVID-19 cases depicted a strong correlation wherein the rise in the volume of negative tweets led the rise in the number of new cases by 9 days.

Conclusions: These findings demonstrated the potential of mining social media for understanding the public discourse about public health issues such as wearing masks during the COVID-19 pandemic. The results emphasized the relationship between the discourse on social media and the potential impact on real events such as changing the course of the pandemic. Policy makers are advised to proactively address public perception and work on shaping this perception through raising awareness, debunking negative sentiments, and prioritizing early policy intervention toward the most prevalent topics.

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KEYWORDS

pandemic; coronavirus; masks; social medial, opinion analysis; COVID-19

Introduction

COVID-19 is an infection caused by the novel coronavirus SARS-CoV-2 that is known to cause severe acute respiratory syndrome [1]. As of December 26, 2020, COVID-19 had affected 192 countries around the word, with a total of 80,416,535 reported cases and 1,757,888 resulting deaths [2]. The World Health Organization, the Center for Disease Control and Prevention, and other leading public health organizations have outlined several guidelines to mitigate the COVID-19 pandemic. These guidelines have also been reported in recent scientific studies regarding the spread of COVID-19. The success of initiatives aimed at reopening the national and regional (state) economies ultimately relies on public awareness and acceptance of these guidelines for limiting the transmission of COVID-19. Among these guidelines is the importance of wearing masks.

Existing studies have shown that masks could have a substantial impact on virus transmission and wearing masks might significantly decrease the number of new COVID-19 cases [3,4]. Wearing a mask was found to be more effective than just handwashing [5]. Studies have also shown that mask-wearing diminishes disease spread by reducing the transmission probability per contact. Wearing masks in the public is most effective in stopping the spread of the virus when compliance is high [6] and presents a rational way to implement as a nonpharmaceutical intervention to fight COVID-19 [7]. Wearing a face mask can be effectively combined with social distancing to flatten the epidemic curve [7]; it is also an effective method of adequate isolation for individuals [8]. Ma et al [9] found that N95 masks, medical masks, and even homemade masks could block at least 90% of the virus in aerosols. Wang et al [10] found that the necessity of wearing masks during the COVID-19 pandemic has been underemphasized by the public. Despite its importance, as supported by scientific evidence, wearing masks has stirred up a significant debate, particularly in the United States.

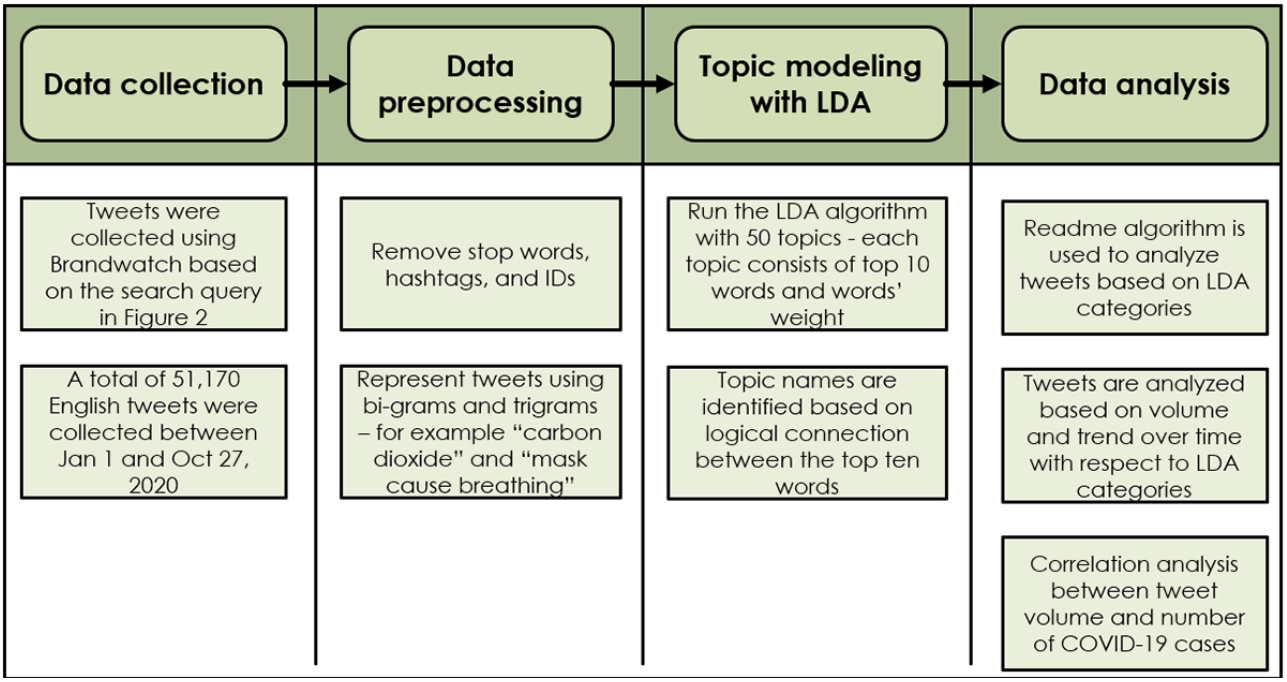
With millions of people forced out of public spaces, many conversations about wearing masks take place on social media [11]. Popular social media platforms, including Twitter, have enabled new channels for users to share information and their experiences [12]. These platforms provide efficient methods of information access for health surveillance and social intelligence [13-15], and they have a growing popularity for sharing and debating scientific information [16-18]. Several studies have used Twitter as a data source to demonstrate the potential to identify the public's reactions to a variety of public health concerns, including the opioid crisis [19], marijuana [20-22], and vaping [23]. However, there are limited studies that have examined the public discourse against wearing masks on social media and its potential relation to the rise of COVID-19 cases.

With plenty of evidence supporting the effectiveness of masks in mitigating the spread of COVID-19, the vigorous public debate about masks is still ongoing [24]. Accordingly, in this study, we aim to provide insights into factors and topics encompassing the ongoing (and sometimes contentious) debate surrounding mask-wearing. Specifically, our research objective is to investigate the topics associated with the public discourse against wearing masks. The study also analyzed trends over time for each topic, with a particular emphasis on the relative volume for each topic, and the spikes in volume. Further, we studied the relationship between the anti-mask discourse on social media and the number of new COVID-19 cases. The time-lagged cross-correlation (TLCC) is used to identify directionality between two signals—volume of tweets and COVID-19 cases—to determine which signal occurs first by analyzing cross-correlations, wherein a peak correlation may have a different offset if one signal leads another. The analysis provided insights into the potential relationship between the cyber world represented by activities on social media and the physical world represented by individuals' actions and possibly reflected in increased infection rates. Such an understanding is needed as governments and public health officials grapple with reopening the economies, and keeping them open, in a manner that does not aggravate the COVID-19 pandemic as a public health crisis of epic proportions.

Methods

Figure 1 shows the methodology adopted in this study for mining social media. The first stage involved data collection. The researchers agreed on a time period of interest to collect data and keywords (ie, hashtags) to search for relevant tweets. Second, the tweets collected were preprocessed by removing stop words, keywords with IDs, and hashtags; these were then represented using bi- and trigrams. Third, a topic modeling technique, the latent Dirichlet allocation (LDA) algorithm [25], was used to analyze the preprocessed tweets to identify the prominent topics or categories in the posts. Finally, a social media analytics tool by Brandwatch was used to analyze the frequency and track the volume of the predefined categories over time. Brandwatch employs unsupervised and supervised machine learning techniques and a text analysis model developed by Hopkins and King [26].

Figure 1. Methodology for mining social media. LDA: latent Dirichlet allocation.



Data Collection

Our target social media platform for data collection was the microblogging platform Twitter. Initially, we identified all hashtags against wearing masks that were being actively used on Twitter. Next, using Brandwatch with the search query shown in Figure 2, we extracted all tweets for the identified hashtags between January 1, 2020, and October 27, 2020. A total of 51,170 English tweets were collected. The hashtags were identified by reviewing the literature [27] as well as by exploring similar trending hashtags used against wearing masks on websites such as hashtags.org [28] and hashtagify.me [29]. A key advantage of using a social media analytics platform such as Brandwatch is that it provides access to the "Twitter firehose" (ie, every public tweet ever posted on Twitter in any language and from any geographic location that meets the search criteria).

Figure 2. Hashtags and search query used for data collection.

```
(#maskoffamerica  OR #NoMask* OR #takeoffthemask OR #maskburning OR #BurnYourMask OR
#burnyourmaskchallenge OR #masksdontwork OR #nomaskonme OR #NoMasksOnMe OR #nomaskselfie OR
#maskhoax OR #maskshoax OR #NoMasksEVER  OR #NoMoreMasks OR #IWillNotWearAMask OR #MaskOff*
OR #MasksOff* OR #facefreedom  OR #masksmakemesweaty OR #MasksAreDangerous OR #TakeTheMaskOff
OR #Stopforcingmasksonme OR #takeoffyourmask* OR #refusemask* OR  #NeverMasker OR
#StopWearingMask* OR #StopWearingTheDamnMasks OR #MasksdontMatter OR #stopmasking OR
#stopthestupidmask OR #maskingchildrenischildabuse OR #MomsAgainstMasks OR #MasksRUnhealthy OR
#SheepWearMasks OR #MasksAreForSheep OR  #RefuseToWearMasks OR #MasksAreMurderingMe)
AND - (RT OR http OR https)
```

For comparing the volume of tweets against wearing masks and the number of COVID-19 cases, we collected a time series of the daily number of newly reported COVID-19 cases in the United States from January to October 2020 by using data from John Hopkins University [30]. We also collected data on new COVID-19 cases reported daily in the USA from January 22 to October 27, 2020.

In acquiring data from Twitter, we considered all the common regulatory concerns that arise with social media research. Specifically, the study conforms with federal regulations on research about human subjects by using only public information that requires no interaction with the poster [31]. Moreover, the use of Brandwatch ensured that the study conformed with all the common ethical questions raised when performing web mining [32].

Data Preprocessing

We excluded retweets and addresses to focus solely on personal opinions or statements. First, the collected tweets were preprocessed by removing stop words as well as keywords with IDs and hashtags. Second, tweets were represented using unigrams, bigrams, and trigrams, such as "results," "lab results," and "check test results." Word-level n-grams features were selected to represent tweets instead of the bag-of-words (ie, single words) feature because the latter has two major drawbacks: (1) they lose the ordering of the words and (2) they ignore semantics of the words [33,34].

Data Analysis Using the LDA Algorithm (Unsupervised Learning)

To discover the abstract "topics" that occur in the collected posts, we ran a topic mining model, specifically the LDA

algorithm, with 50 topics. Given a set of documents, $D = \{d_1, d_2, \ldots, d_n\}$; a number of topics, $T = \{t_1, t_2, \ldots, t_m\}$; and a number of words in each topic, $W = \{w_1, w_2, \ldots, w_k\}$; the LDA algorithm generates the following:

- A $D \times T$ matrix with $n \times m$ size, where the weight $w_{i,j}$ is the association between a document d_i and a topic t_j [35].
- A $T \times W$ matrix with$m \times k$ size, where the weight $w_{i,j}$ is the association between the topic t_i and a word w_j[35].

The corresponding reproductive process is shown below [35,36]:

1. For each topic $t \in \{1, \ldots, m\}$,
   i. generate a probability distribution over words $\beta t \sim$ Dirichlet (η)
2. For each document d,
   i. generate a vector of the topic probability distribution $\theta d \sim$ Dirichlet (α)
   ii. For each word w_i in document d,
      a. generate a topic assignment $z_i \sim$ Multinomial (θd);
      b. generate a word $w_i \sim$ *Multinomial* (βzi)

βt is the word distribution for topic t, and θd is the topic distribution for document d. The notations η and α are model parameters.

Topic models are statistical based models for uncovering the main themes (ie, set of topics) that depict a large and unstructured collection of documents. Topic models make it possible to summarize textual data at a scale that cannot possibly be tackled by human annotation. In this study, we chose the LDA algorithm [25] owing to its conceptual advantage over other latent topic models [35-38].

The 50 topics from the LDA were labeled by first author and validated by second author. The identified topics were further analyzed and grouped into 10 representative categories. The grouping was done based on semantic similarities between the topics identified. For example, the topics "build herd immunity," "herd Immunity," and "build immune system" could be grouped into in one main topic, namely, "herd immunity and dependency on the immune system." Overall, we discovered and collected 10 different categories.

Analysis of Tweets Using Categories Obtained (Supervised Learning)

Brandwatch employs ReadMe, a supervised algorithm developed by Hopkins and King [26]. The algorithm is particularly suited when the objective is to know the proportion of all posts that fit in specific categories. Rather than calculating these proportions based on the categorization of individual posts, ReadMe gives approximately unbiased estimates of category proportions even when the optimal classifier performs poorly [26].

The ReadMe algorithm requires the researcher to hand-code a "training set" of documents into a set of predefined categories. In this study, the tweets represent the set of documents and the predefined categories are obtained using the LDA algorithms. The authors hand-coded 20 tweets into each predefined category obtained from the LDA and then ran the ReadMe algorithm iteratively on the remaining posts, ensuring that the examples clearly outline each category. Then, based on the training phase, the algorithm builds a model that can automatically assign the remaining tweets into categories and obtain the total number of tweets in each category. Brandwatch automatically generates the trends of tweet volumes over time.

Analyzing the Relationship Between the Tweet Volume and the Number of COVID-19 Cases

To analyze the relationship between the volume of tweets against mask-wearing and the daily volume of new COVID-19 cases, we plotted two time-series over the time span from January to October 2020 and calculated the Pearson correlation coefficient, which measures how two continuous waves co-vary over time and indicate the linear relationship as a number ranging from –1 (negatively correlated) to 0 (not correlated) to 1 (perfectly correlated) [39]. The correlation is a snapshot measure of global synchrony. Although the Pearson correlation coefficient provides a very simple way to compute both global and local synchrony, it does not provide insights into signal dynamics such as which signal occurs first or which can be measured via cross-correlations. A TLCC can identify directionality between two signals such as a leader-follower relationship. We can get a sense of which signal occurs first by looking at cross-correlations. A TLCC is measured by incrementally shifting one time-series vector and repeatedly calculating the correlation between two signals. If the peak correlation is at the center (offset=0), this indicates that the two time-series are perfectly synchronized at that time. However, the peak correlation may have a different offset if one signal leads another [40]. To analyze the relationship between the two time-series, the volume of tweets against mask-wearing, and the daily volume of new COVID-19 cases, we calculated the Pearson correlation coefficient and TLCC in Python using the SciPy package.

Results

Tweet Distribution and Categories

Overview

A total of 51,170 tweets were analyzed with respect to categories identified from the LDA model. These categories were mainly related to (ordered per their frequency in posts) (1) constitutional rights and freedom of choice; (2) conspiracy theory, population control, and big pharma; (3) fake news, fake numbers, fake pandemic, and lies; (4) unhealthy, low oxygen, carbon dioxide, lung infections, and weakened immune system; (5) political, fear, and control people; (6) masks ineffective and cannot block tiny particles; (7) mental health and suicide; (8) herd immunity and dependency on the immune system; (9) child abuse and dehumanization; and (10) virus-related statistics (high recovery rates and low mortality rates). Figure 3 shows the word clouds for the first three categories. The distribution of the tweets over the categories identified is shown in Figure 4.

Figure 3. Word cloud for the most common categories identified: (1) constitutional rights and freedom of choice; (2) conspiracy theory, population control and big pharma; AND (3) fake news, fake numbers, fake pandemic, and lies.

Figure 4. Distribution of 51,170 tweets across the top 10 categories obtained using the latent Dirichlet allocation model.

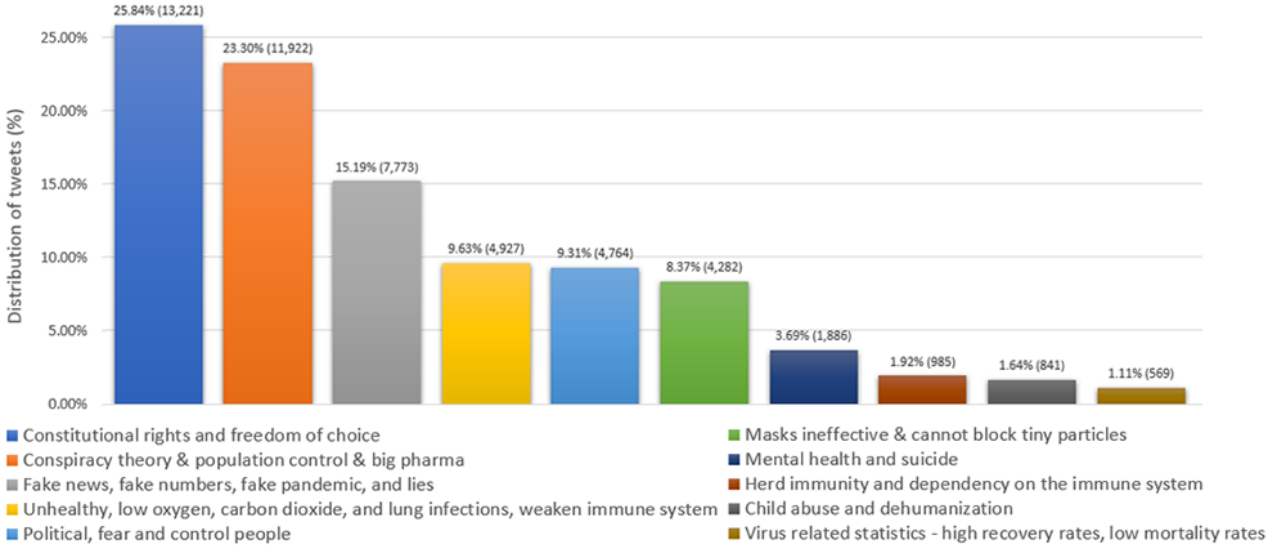
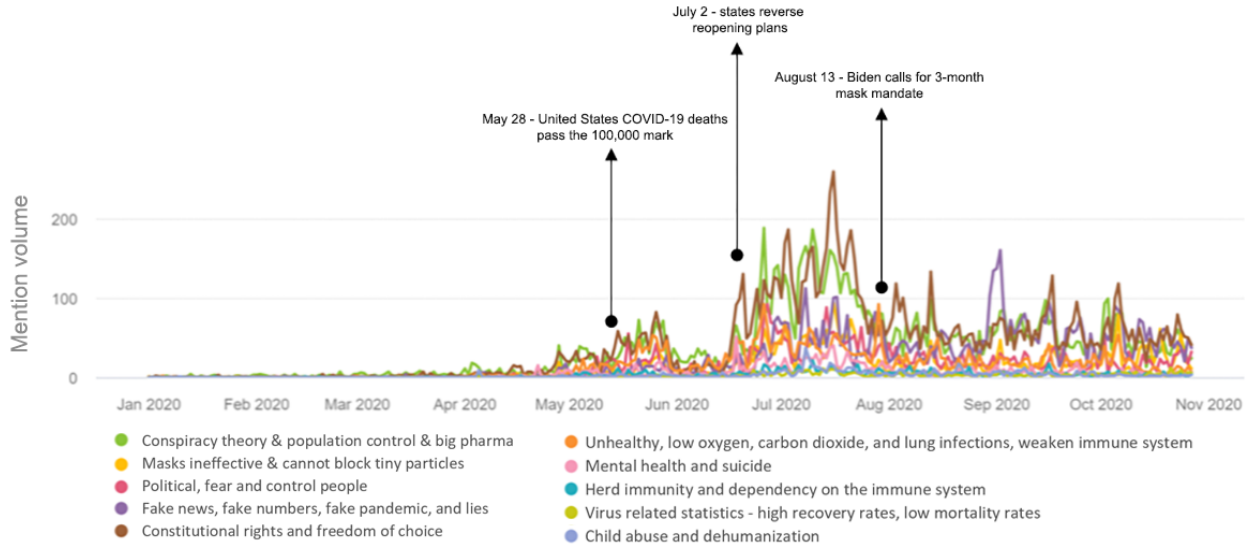


Figure 5 shows the volume of tweets over time by category. Overall, the number of tweets posted increased with time, with the highest volume of tweets recorded in July 2020. Between April 8, 2020, and May 29, 2020, a total of 15 states issued a mask mandate, which could be related to the spike in tweets posted on masks between April and the beginning of July 2020. Furthermore, between June 18 and August 11, 2020, another 20 states issued mask mandates [41]; this could explain the increase in tweets posted about masks between late-June and mid-August. Figure 5 also shows three relevant milestones between May and August 2020 [42]. These three milestones are related to the number of deaths reported in late-May, states reversing reopening plans, and the call for 3-month mask mandates. These milestones could also relate to the increasing number of Twitter posts on masks. Furthermore, after August 13, 2020, we noted consistent debates on masks across all post categories.

Figure 5 also shows that more tweets were posted as governments and public health officials relaxed the lockdown restrictions but requested people to continue wearing masks. The number of tweets posted about constitutional rights and freedom of choice increased noticeably, followed by tweets about conspiracy theory, population control, and big pharma. The following paragraphs provide a synopsis of each of the categories of tweets posted.

Figure 5. Volume of tweets and trend analysis over 10 categories based on the latent Dirichlet allocation model as well as three significant milestones during the pandemic between January 1, 2020 and October 27, 2020.



Constitutional Rights and Freedom of Choice

Our results revealed several reasons why some Americans refuse to wear face masks despite the overwhelming evidence that wearing masks saves lives. One important reason discussed during the study period was constitutional rights and freedom of choice. Many say mandatory masks violate their constitutional right and freedom of choice. An example tweet is shown below:

> *Dear #****, I am an American citizen with constitutional rights. I have the right & freedom to choose #NoMask. If u try to enforce this ridiculous order, I will sue your ass 2 hell & back. Kentucky is a #redstate & you don't belong. GTFO. Signed a pissed of Kentucky girl*

Conspiracy Theory, Population Control, and Big Pharma

Americans also discussed concerns related to conspiracy theory, population control, and big pharma. They believed that COVID-19 was human-engineered. Example tweets are shown below:

> *Won't have to listen to people blabbering on about their latest favourite conspiracy theory*
>
> *You can have a ridiculous opinion. Democrats follow blindly, I do not. **** IS Big Pharma. Masks = Control = Submission that will lead to mandatory inoculation of a genetically modifying vaccine. If dems win, we all lose. #MasksOffAmerica*

Fake News, Fake Numbers, Fake Pandemic, and Lies

Many also believed the pandemic is fake and there was fake news, misinformation, and lies spread about COVID-19. Example tweets are shown below:

> *@**** Seasonal flu kills more people EVERY year. You and the fake news media are losing credibility FAST. #nomasks #nonewnormal*
>
> *@**** So how many other false positives are out there...this makes the numbers even more questionable*

Unhealthy, Low Oxygen, Carbon Dioxide, Lung Infections, and Weakened Immune System

Tweets posted also discussed the health impact of wearing masks. Many believed masks limit oxygen intake and cause rebreathing of carbon dioxide, which can lead to lung disease and weaken the immune system. Example tweets are shown below:

> *Wearing it blocks oxygen and recycles carbon dioxide and carries the bacteria to your respiratory system. #nomasks*
>
> *Masks weaken the immune system. Masks allow oral bacteria to affect gums, throat & lungs. Masks limit oxygen intake. Masks cause rebreathing of carbon dioxide*
>
> *#COVID-19 #NoMasks Hypercapnia is generally caused by hypoventilation, lung disease, or diminished consciousness*

Political, Fear, and Control People

Another topic discussed by Americans on Twitter was fearmongering. Many users believed that politicians and media have only focused on the numbers that present a negative picture of the COVID-19 pandemic rather than a more balanced and honest overview of the case numbers. Example tweets are shown below:

> *@**** Nor do they speak about the low death rate. They want us living in fear. Fear controls the masses! #SheepNoMore #MaskOff*
>
> *FEAR MONGERING!!! THIS IS WHAT IT LEADS TO! ENOUGH! NO MORE MASKS!!*

Masks Ineffective and Cannot Block Tiny Particles

Many users also had an opinion that masks are ineffective and cannot block tiny particles. Example tweets are shown below:

> *People wearing #masks and shaming others for NOT wearing them though all #science deems them almost*

totally ineffective in protecting against the nano particles of the coronavirus. #DumbPandemicDecisions #Masks4All #MasksOff

*@**** says masks are ineffective to stop the virus. Why is there a state execution/executive order now to mandate masks? #NoMasks #ControlRemedy*

Mental Health and Suicide

Many users thought that wearing mask could also have impact on the mental health of people and could lead to suicidal thoughts. Example tweets are shown below:

they are causing a severe mental health issue. #NoMasks #MasksOff

Masks are causing horrible harm with the mental health of children. Stop wearing them before these damages are irreversible! #NoMasks #MasksOffArizona

Masks are causing serious mental health issues in children. Stop with the masks before it's too late! #MasksOff

*Where is the **** physician saying that this lockdown needs to end b/c suicide is up? Mental health has been ignored completely*

Herd Immunity and Dependency on the Immune System

People should not be forced to wear masks in order to build herd immunity and maintain a healthy and strong immune system. Example tweets are shown below:

*It's time we focus on REAL solutions like herd immunity. #NOMASK for me. @****

You need INTERACTION with people and #NoMasks to maintain a healthy immune system #OpenAmericaNOW #OPenHawaiiNow

I will NOT wear a damn mask!! It is my right to come in to contact with germs that strengthen my immune system!

Child Abuse and Dehumanization

Asking children to wear masks was considered child abuse according to many Twitter users in USA. Example tweets are shown below:

Masking children is child abuse! Kids are not at risk and not carriers of the virus! Kids need to see and communicate clearly. They need to see facial expressions. A mask desensitizes kids! #maskingchildrenischildabuse

Mandating our young children to wear a mask for 7hrs per day while attending school is tantamount to child abuse. #OpenTheSchools #NoMasks

Masks in this case are a tool for soft torture and dehumanization #NoMasks

Virus-Related Statistics (High Recovery Rates and Low Mortality Rates)

Twitter users also discussed that the high recovery and low mortality rate of the virus that make wearing mask not necessary. Example tweets are shown below:

I will not comply and wear a useless mask that has potential health risks to me for a virus that has a 98% recovery rate. #NoMask

COVID-19 Mortality Rate in CA is .00006925% that means 99.999932% are forced 2 destroy R lives 4the weakest virus on the planet! Stop Quarentining the Healthy, Open up Businesses & only Quarantine the Sick! #UnMaskAmerica

Tweets Versus New COVID-19 Cases

Figure 6 depicts the volume of tweets against wearing masks and the number of newly reported COVID-19 cases over the study period. The two time-series exhibit a high positive Pearson correlation (r=0.77). Since information about directionality between the two waves—leading and following—cannot be interpreted solely from this data, we further studied the relationship between both waves (Figure 7). Overall, the results show a 9-day lead for tweet volume over the number of new COVID-19 cases. This 9-day lag is considered comparable to the number of days after which people can develop COVID-19 symptoms. According to a previous study, approximately, 97% of people infected with COVID-19 developed symptoms within 12 days after exposure [43].

Figure 6. Pearson correlation of tweets against wearing masks and newly confirmed COVID-19 cases over time (days) between January 2020 and October 2020.

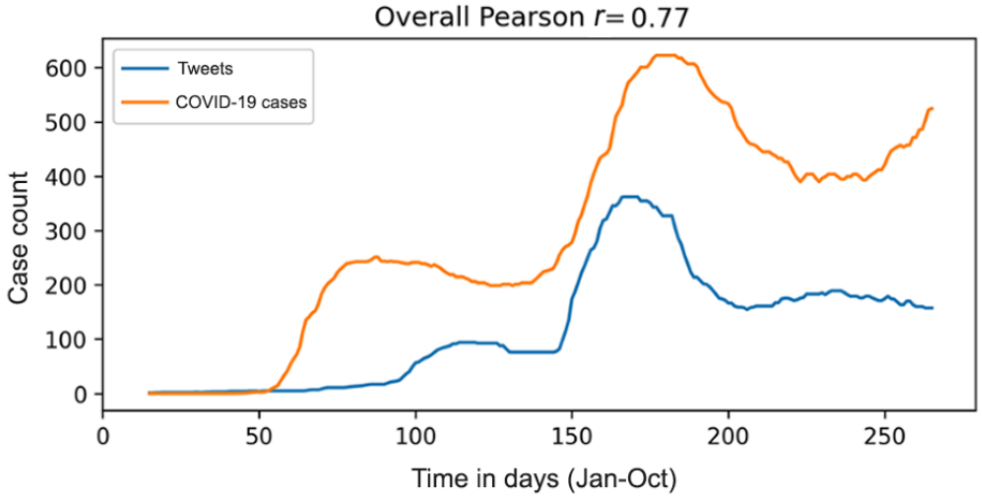
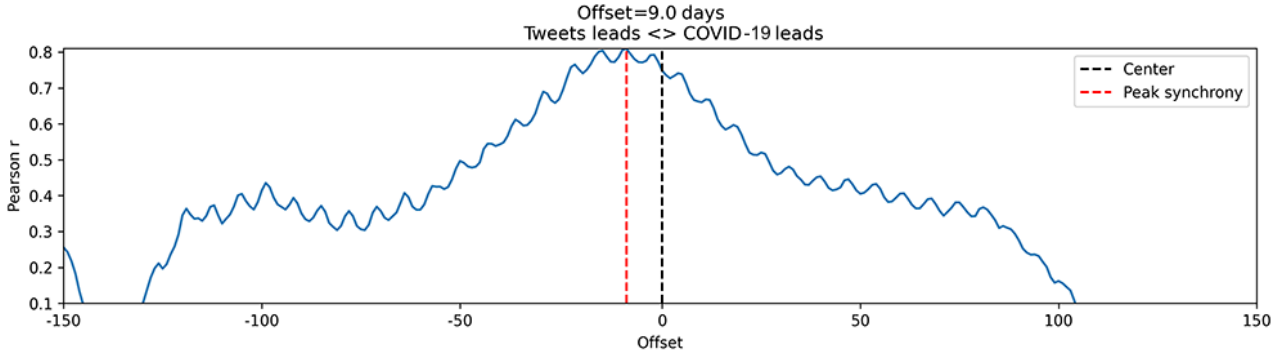


Figure 7. Graph illustrating the 9-day lead in the volume of tweets against mask-wearing compared with new COVID-19 cases by 9 days (study period: January to October 2020).



Discussion

Principal Findings

This study analyzed the negative stance regarding masks on social media, the specific themes within this discourse, and how this discourse could be associated with the prevalence of new COVID-19 cases. The study reported Twitter users' concerns related to constitutional rights and freedom of choice, conspiracy theory, misinformation, health issues, fearmongering, and other concerns related to the use of face masks during the COVID-19 pandemic. Furthermore, the time-series analysis demonstrated a strong correlation between the number of tweets posted against mask-wearing and the actual number of COVID-19 new cases, with the volume of negative tweets leading the number of newly reported COVID-19 cases by 9 days.

The study findings emphasize the potential relationship between social media behavior and its manifestation in the physical world. Such findings highlight the importance of listening to social media and proactively reacting to public perception in fighting COVID-19. Lyu and Wehby [44] showed that mask mandates in a number of states were associated with lowering infection rates by 0.9%-2% after wearing masks for 1-21 days. However, when the government mandates mask-wearing in public, many people feel their constitutional rights and freedom of choice are being violated [45]. As a result, there is a need to increase awareness about the fact that wearing masks can protect others from contracting COVID-19 even though they do not fully protect the person wearing the mask from the infection [46]. The government should also address the challenges faced by implementing a balanced mask-wearing mandate that considers protecting people's lives while also protecting their freedom of choice [47].

Social media platforms have been used to spread fake news, lies, and conspiracy theories, all of which have a strong impact on people and society [48]. As a result of such an impact, the public is less likely view actions like wearing masks as a necessity to mitigate the spread of the virus during a pandemic [49]. Therefore, it is crucial that, as we seek to control the spread of COVID-19 and future viruses, we develop policies to fight against misleading and damaging conspiracy rhetoric. Similarly, there should be policies in place to combat fake news, lies, and misinformation, especially on social media, which could negatively affect the public's trust in science [49].

Health care professionals should actively engage in the conversation with the public in order to discuss scientific evidence supporting the importance of wearing a mask and debunk rumors on social media that promotes discussions related to masks causing low oxygen levels or lung infections. They should also discuss evidence and guidelines such as "wearing a mask does not raise the carbon dioxide (CO_2) level in the air

you breathe" [50] and "people aged 2 and older should wear masks in public settings and when around people who don't live in their household" [50] to increase awareness regarding the effectiveness of masks in protecting the wearer from inhaling and spreading airborne particles.

Children of specific age groups should be encouraged to wear masks to protect them from COVID-19. However, protecting these age groups only by using a mask could prove very difficult [51]. To overcome these challenges, there is a need to advocate for parental involvement and support for the initiatives aimed at increasing mask-wearing among children [51]. Children should be encouraged to "take off their masks to breathe in fresh air after wearing masks for a certain amount of time," and they should not wear masks in certain cases, such as while exercising [51]. In the case of noncompliance, it would be a better option for children to not wear masks and follow other measures to reduce infection risk and remain at home [51].

Following an empathetic approach to motivate people to wear masks and adhere to physical distancing could be an effective alternative [52] for fearmongering that focuses only on presenting a negative picture of the COVID-19 pandemic [53]. In addition, policy makers could use positive messaging to curb the spread of fear while still maintaining a transparent and accurate depiction of the situation [53].

With physical, mental, social, and economic burdens imposed by the pandemic, many populations may experience increased suicide risk [54]. Furthermore, the prevalence of anxiety, depression, posttraumatic stress disorder, and stress was reported to have increased in a number of countries during the COVID-19 pandemic [55]. Data analysis and event surveillance conducted during the first 6 months of the pandemic have shown impacts on suicide risk [54]. As a result, knowing the facts about masks and containing the spread of rumors can reduce stress and the adverse impacts on people's mental health [56]. Finally, since many people believe that herd immunity is the best solution to this public health crisis and to strengthen their immune systems, a scientific and fact-driven view should be shared with the public explaining why herd immunity is not an ideal solution as has been reported by many researchers [57].

By carefully analyzing social media posts, policy and decision makers are in a better position to tailor public health awareness campaigns to respond to specific themes and thereby improve their effectiveness in a crisis situation such as the COVID-19 pandemic. Thus, exploring the categories of tweets surrounding the topic of mask-wearing during the COVID-19 pandemic may help reveal a number of insights that could help better design and implement awareness campaigns.

Limitations and Future Work

This study has some limitations that could be addressed in future research. First, although we identified a very strong correlation between the increase in the volume of tweets against wearing masks and the rise in the number of COVID-19 cases, we cannot claim causality, as the rise in COVID-19 cases could be attributed to population density, government-enforced lockdown restrictions, and other factors that are beyond the scope of this study. Second, the study focused on analyzing English tweets in the United States. Future studies need to address and compare the public discourse on masks across different social media platforms and in different countries. Third, given the number of tweets collected and the focus on Twitter as a data source, the public discourse might not reflect the actual public opinion against masks. According to Wojcik and Hughes [58], Twitter has been found to have much younger audiences, with the most prolific 10% of users creating 80% of all tweets published. Finally, we did not separately analyze the opinions of Twitter users against masks in the early and later stages of the pandemic. Such analysis could unmask other important trends that are not discussed in this paper.

Conclusions

In this study, we analyzed tweets against wearing masks on social media to understand topics, insights, and information about user-reported issues. We used data analytics to identify trending themes and topics of concern by the public about wearing face masks. The most discussed issues were related to the constitutional rights and the freedom of choice, conspiracy theory, misinformation, health issues, fearmongering, and the ineffectiveness of masks, followed by issues related to mental health, herd immunity, child abuse, and virus-related statistics. Another key finding of this study is that it highlights the strong correlation between the increase in the volume of tweets against wearing masks and new COVID-19 cases and the lead of negative tweets published in comparison with the rise in new COVID-19 cases in the time-series analysis. In effect, these findings demonstrated the impact of social media not only on people's opinion or perceptions about public topics but also the potential impact on real events such as changing the course of the pandemic. The significance and implication of this research transcends the COVID-19 pandemic, as it demonstrates the importance of social media mining and its potential to support public health–related policies and decisions. Government officials and decision makers could tailor and fine-tune public awareness campaigns and prioritize policy interventions toward the most discussed topics. In case of a future massive-scale health crisis such as the COVID-19 pandemic, government officials and policy makers could leverage social media analytics and surveillance as important tools in proactively responding to the impending crisis. Policy makers need to proactively address public perception and work on shaping this perception through raising awareness, debunking negative sentiments, and adopting early policy intervention to steer the wheel towards public acceptance of more precautionary measures and thereby containing the situation.

Conflicts of Interest

None declared.

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Abbreviations

LDA: latent Dirichlet allocation
TLCC: time-lagged cross-correlation

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Original Paper

Reporting and Availability of COVID-19 Demographic Data by US Health Departments (April to October 2020): Observational Study

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Abstract

Background: There is an urgent need for consistent collection of demographic data on COVID-19 morbidity and mortality and sharing it with the public in open and accessible ways. Due to the lack of consistency in data reporting during the initial spread of COVID-19, the Equitable Data Collection and Disclosure on COVID-19 Act was introduced into the Congress that mandates collection and reporting of demographic COVID-19 data on testing, treatments, and deaths by age, sex, race and ethnicity, primary language, socioeconomic status, disability, and county. To our knowledge, no studies have evaluated how COVID-19 demographic data have been collected before and after the introduction of this legislation.

Objective: This study aimed to evaluate differences in reporting and public availability of COVID-19 demographic data by US state health departments and Washington, District of Columbia (DC) before (pre-Act), immediately after (post-Act), and 6 months after (6-month follow-up) the introduction of the Equitable Data Collection and Disclosure on COVID-19 Act in the Congress on April 21, 2020.

Methods: We reviewed health department websites of all 50 US states and Washington, DC (N=51). We evaluated how each state reported age, sex, and race and ethnicity data for all confirmed COVID-19 cases and deaths and how they made this data available (ie, charts and tables only or combined with dashboards and machine-actionable downloadable formats) at the three timepoints.

Results: We found statistically significant increases in the number of health departments reporting age-specific data for COVID-19 cases (P=.045) and resulting deaths (P=.002), sex-specific data for COVID-19 deaths (P=.003), and race- and ethnicity-specific data for confirmed cases (P=.003) and deaths (P=.005) post-Act and at the 6-month follow-up (P<.05 for all). The largest increases were race and ethnicity state data for confirmed cases (pre-Act: 18/51, 35%; post-Act: 31/51, 61%; 6-month follow-up: 46/51, 90%) and deaths due to COVID-19 (pre-Act: 13/51, 25%; post-Act: 25/51, 49%; and 6-month follow-up: 39/51, 76%). Although more health departments reported race and ethnicity data based on federal requirements (P<.001), over half (29/51, 56.9%) still did not report all racial and ethnic groups as per the Office of Management and Budget guidelines (pre-Act: 5/51, 10%; post-Act: 21/51, 41%; and 6-month follow-up: 27/51, 53%). The number of health departments that made COVID-19 data available for download significantly increased from 7 to 23 (P<.001) from our initial data collection (April 2020) to the 6-month follow-up, (October 2020).

Conclusions: Although the increased demand for disaggregation has improved public reporting of demographics across health departments, an urgent need persists for the introduced legislation to be passed by the Congress for the US states to consistently collect and make characteristics of COVID-19 cases, deaths, and vaccinations available in order to allocate resources to mitigate disease spread.

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KEYWORDS

coronavirus disease 2019; COVID-19; SARS-CoV-2; race; ethnicity; age; sex; health equity; open data; dashboards

Introduction

The COVID-19 outbreak originated in December 2019 in China. On January 20, 2020, the Centers for Disease Control and Prevention (CDC) reported the first confirmed COVID-19 case in the United States in Snohomish County, Washington [1]. By March 2020, the USA had the highest number of reported cases and one of the highest test-positive rates globally. The USA was initially presented with a series of time-bound public health challenges during and immediately after that 3-month timespan, including implementing testing processes, engaging in timely data collection and reporting, and maintaining trust while educating the public. As of our last data collection period (October 24, 2020), there have been 8,469,976 confirmed cases and 223,393 deaths in the USA, with the highest number of newly confirmed cases reported on October 23, 2020 [2].

Since a national emergency was declared on March 13, 2020 [3], state and local health departments have not been provided the funding or resources to collect and make surveillance data on patient demographics, testing, hospitalizations, confirmed cases (morbidity), and mortality available for the general public, institutions and academic organizations to use for developing targeted risk communication efforts and prevention policies. The quick nature of the outbreak, in combination with a lack of clear guidelines as to what could or should be made publicly available led to staff at health departments working extended hours to determine what information can be shared while building the structure for regularly reporting COVID-19 data.

Meanwhile, interest in COVID-19 information resources skyrocketed. Major US news websites saw 50% growth in webpage visits, with coronavirus stories making up 10%-25% of pageviews [4,5]. In March 2020, English Wikipedia pageviews rose from 1.6 million to 146 million, primarily on pages about (1) COVID-19 and SARS-CoV-2 virus, (2) outbreak data related to particular regions, (3) celebrities and public figures who tested positive for COVID-19, and (4) other relevant pages discussing topics such as lockdowns and the socioeconomic impact of the pandemic [6].

Because the prevention of COVID-19 requires global participation in prevention efforts, with one infected person having the ability to lead to large clusters of infection, it is likely that confusing, missing, or otherwise inaccessible COVID-19 data acts as a *data void* [7,8] and contributes to the broader COVID-19 infodemic—or an increased spread of a disease due to growing misinformation on the internet that either fills in the gaps or outpaces trustworthy and reliable sources. A 17-year old launched an online COVID-19 tracker called ncov2019.live [9] in December 2019, while the available data were still scarce; the website garnered millions of visits internationally [10]. Citizens tend to lose confidence in public response due to gaps in how democracies communicate with the public, particularly when social distancing becomes voluntary and does not rely on state orders.

In response to this need, agencies and institutions have built dashboards based on official government reports and various newspapers sources. For instance, the COVID Tracking Project at The Atlantic [11] was built using official governmental reports, and the Johns Hopkins University COVID-19 Dashboard [12] was built using estimates based on various news and official reports. At their peaks, these dashboards saw over a billion visitors daily [11,12]. However, inconsistent reporting makes it difficult to accurately track and compare surveillance data on the pandemic across US states. For example, several popular sites (Google, Twitter, and Facebook) provide real-time information from the CDC or from data aggregate websites when users explore COVID-19–related topics. However, due to differences in reporting, data are typically limited to statewide or national case counts and rates [11,12]. Global comparisons are also difficult owing to challenges in reporting and making data publicly available. The World Health Organization (WHO) reports cumulative and newly reported confirmed COVID-19 cases and deaths by region on a weekly basis [13]. However, the definitions for confirmed cases or deaths differ by country, and the WHO does not publicly report or make available any additional data on sociodemographic characteristics to make between-country comparisons [14,15].

Barriers to data availability are numerous and include time and effort toward data synchronization and sharing; the need for sufficient platforms that facilitate sharing in ways that promote awareness but do not risk identification; and accuracy of metadata in addition to ethical, political, and legal boundaries (S. C. Clarke, MLIS, unpublished data, August 2019). Although case surveillance data collection and reporting internally to health departments tend to be executed in a well-structured format, these standards should be extended and translated into public reporting [16]. Having data available during disease outbreaks builds trust [17] and invokes the four ethical principles of social value, respect, justice, and transparency (S.C. Clarke, MLIS, unpublished data, August 2019). Data can be made available at individual-level, population-level, and exposure-level, each of which, if shared in measured ways with appropriate groups, is crucial for the prevention of sluggish response times and unnecessary suffering and death.

Throughout the initial spread of COVID-19 in the USA, reporting at the population-level (and exposure-level) was inconsistent, with many data points unreliable or unavailable [18]. Those that were provided were presented on health department websites in portable document format (PDF) files with file names that did not clearly express that the files contained incidence data. Moreover, there were issues with data being conflated as were the results of serology and virology tests on the websites of the CDC and various state health departments [19,20]. Demographic data were largely unavailable at all reporting levels, and, when present, incongruent reporting

of age, sex, race, and ethnicity of cases and deaths contributed to the COVID-19 infodemic.

Therefore, not only is there an urgent need for a unified collection of demographic data on COVID-19 morbidity and mortality statistics, but data also need to be shared in open and accessible ways. Open and accessible data sharing allows for health educators, researchers, and lawmakers to calculate accurate statistics for implementing targeted interventions for specific states and develop policies to mitigate the spread and impact of the virus [21]. Integrating open and accessible data sharing also prevents issues of access that often come with charts and dashboards for those with visual impairment or cognitive disabilities (eg, dyslexia). The open data movement is a global attempt to make data freely available in a format that can be reused in machine-actionable downloadable formats by others [22]. Those opposed to providing open data highlight the significant number of resources needed to develop and maintain databases and concerns about legal and ethical issues with data sharing. However, there are several benefits to providing open data for public health that can directly improve data reporting and availability for the COVID-19 pandemic. For example, providing open data will allow for increased opportunity for early detection, improve real-time response, inform interventions and policy decisions, improve accountability, and enable transparency [22].

Due to mounting demands for transparency, on April 21, 2020, House of Representatives (HR) 6585, the Equitable Data Collection and Disclosure on COVID-19 Act was introduced into the Congress, with support from the American Public Health Association, to mandate the collection and reporting of demographic COVID-19 data on testing, treatment, and deaths by race, ethnicity, sex, age, disability, primary language, socioeconomic status, and county [23]. The bill states that the secretary of the US Department of Health and Human Services and the director of the CDC must make data publicly available on the CDC website. The bill recommends collecting data on race and ethnicity in line with other federal standards, including the Office of Management and Budget's (OMB) guidelines for collecting data pertaining to race (White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander) and ethnicity (Hispanic or Latino, not Hispanic or Latino) [24]. Although this bill has not been passed as of the latest writing of this manuscript (January 20, 2021), its introduction laid the groundwork for greater exposure on the need for consistent demographic data linked with COVID-19 morbidity and mortality to be reported at the state level and be made openly accessible for the public research institutions, academic organizations, and the general public. There is a need to determine how its initial introduction into the Congress has impacted how data have been reported and made available by health departments during this rapidly changing pandemic.

To address this need, this study aimed to determine the consequence of a lack of standard reporting guidelines for US health departments. Our specific aims were to evaluate immediate and 6-month statewide differences in (1) reporting of demographic data for confirmed COVID-19 cases and deaths and (2) public availability of data by charts or tables only, dashboards, and machine-actionable datasets due to increasing public pressure for greater transparency.

Methods

Data Collection

We reviewed the websites of local health departments from all 50 states and Washington, District of Columbia (DC), to determine how COVID-19 data were made available to the general public, health educators, and researchers and to identify which demographic data were reported. In order to determine the immediate actions being taken in reporting and to determine changes in reporting over time, data were collected and reviewed before (April 13-20, 2020), immediately after (April 27-28, 2020), and 6 months after (October 23, 2020) the introduction of the Equitable Data Collection and Disclosure on COVID-19 Act on April 21, 2020.

Data Reporting

We evaluated how each US state reported demographic characteristics of laboratory-confirmed COVID-19 cases and deaths. Variables were created to determine whether each state or municipality reported data on age (varying age groups), sex (including male and female), and race or ethnicity (none, race and ethnicity separated, or race and ethnicity as a combined measure) for confirmed COVID-19 cases and deaths. We also evaluated whether race and ethnicity data were reported based on federal reporting standards set for by the OMB, which includes the identification of White, Black or African American, Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander race and Hispanic or Latino ethnicity [24].

Data Availability

Data availability is described as "the degree of convenience for users to obtain data and related information….[and] includes the difficulty level that users may experience when accessing data" and its timeliness [25]. A data quality indicator should incorporate existence of a specific data component, data availability at a specific geographical scale, relevance to the users' needs and "data quality components that are used to build a composite index in which indicator quality is assessed under a scoring system" [25]. As a result, we created a data availability score to compare how each US state made data available to the public, to researchers, journalists, and public health professionals. The frequency of reporting was not analyzed, as states were reporting new data daily despite technical difficulties. A Likert scale of 1 to 4 was developed, with the following options: 1=totals only (COVID-19 cases and deaths); 2=charts and figures showing disaggregation of any kind; 3= interactive dashboards; and 4=machine-actionable data (ie, data downloadable in a format readable by data analytics software).

Statistical Analysis

Descriptive statistics (frequencies and percentages) were used to present data reporting characteristics by each state in tabular and visual formats. McNemar tests were used to determine significant (P<.05) changes in COVID-19 morbidity and mortality data reporting and availability by health departments

before and immediately after as well as before and six months after the introduction of the Equitable Data Collection and Disclosure on COVID-19 Act on April 21, 2020. Analyses were conducted using STATA 14.0 (StataCorp LLC) [26].

This secondary study did not involve human subjects; therefore, institutional review board approval was not required.

Results

The data availability scores for each state and how data were reported before and immediately after the Equitable Data Collection and Disclosure on COVID-19 Act was introduced into the Congress are illustrated in Figure 1.

Statistical comparisons of how data were reported for confirmed COVID-19 cases and deaths and made available to the public before, immediately after, and 6 months after the introduction of the Equitable Data Collection and Disclosure on COVID-19 Act are presented in Table 1. From April 13 to 20, 2020, 46 of 51 (90.2%) health departments reported age-specific data for confirmed COVID-19 cases but only 25 of 51 (49%) health departments reported age-specific data for patients who died due to COVID-19. There was a statistically significant increase in the number of health departments that reported confirmed COVID-19 cases immediately after and 6 months after the act was introduced (50/51, 98%, *P*=.045) and COVID-19 deaths by age immediately after the act was introduced (35/51, 69%, *P*=.002) and 6 months later (39/51, 76%, *P*=<.001). Despite these significant increases, differences still remained between states in the ways that age was reported. For example, the health department of California reports the following age groups for confirmed cases and deaths: 0-17 years, 18-49 years, 50-64 years, and 65 years and older [27]. The health department of Texas reports the age groups for COVID-19 cases and resulting deaths across multiple categories: <1 year, 1-9 years, 10-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-64 years, 65-69 years, 70-74 years, 75-79 years, and 80 years and older [28]. From April 13 to 20, 2020, only 21 of 51 (41%) health departments reported the sex of COVID-19 deaths. This number rose after the introduction of the legislation (30/51, 59%, *P*=.003) and 6 months later (36/51, 71%, *P*<.001). Significant increases were found in the number of health departments reporting the race or ethnicity for confirmed cases and deaths (*P*<.001) immediately after (*P*<.001 confirmed cases; *P*<.001 deaths) and 6 months after (both *P*<.001) the introduction of the legislation on April 21, 2020. Moreover, the number of health departments that reported race or ethnicity data using federal standards more than quadrupled over the 6-month data collection period, that is, from 10% (5/51) to 53% (27/51; *P*<.001). Prior to the introduction of the legislation, a majority (35/51, 69%) of state health departments provided COVID-19 surveillance data using dashboards, but only 7 (14%) of 51 health departments provided machine-actionable data that could be downloaded and used for additional reporting and analyses by public health researchers. Six months later, 23 (45%) of 51 health departments made their data available to the public for download (*P*<.001).

Figure 1. Demographic COVID-19 data reported by state public health departments of the Unites States (A) before, (B) immediately after, and (C) 6 months after the introduction of the Equitable Data Collection and Disclosure on COVID-19 Act. Data availability scores: 1=totals only (confirmed cases and deaths in the state); 2=figures or web tables showing disaggregation of any kind; 3=interactive dashboards; and 4=machine-actionable data. Disaggregation types available: A=ASR (age, sex, race), B=AS (age and sex), C=A (age), D=R (race).

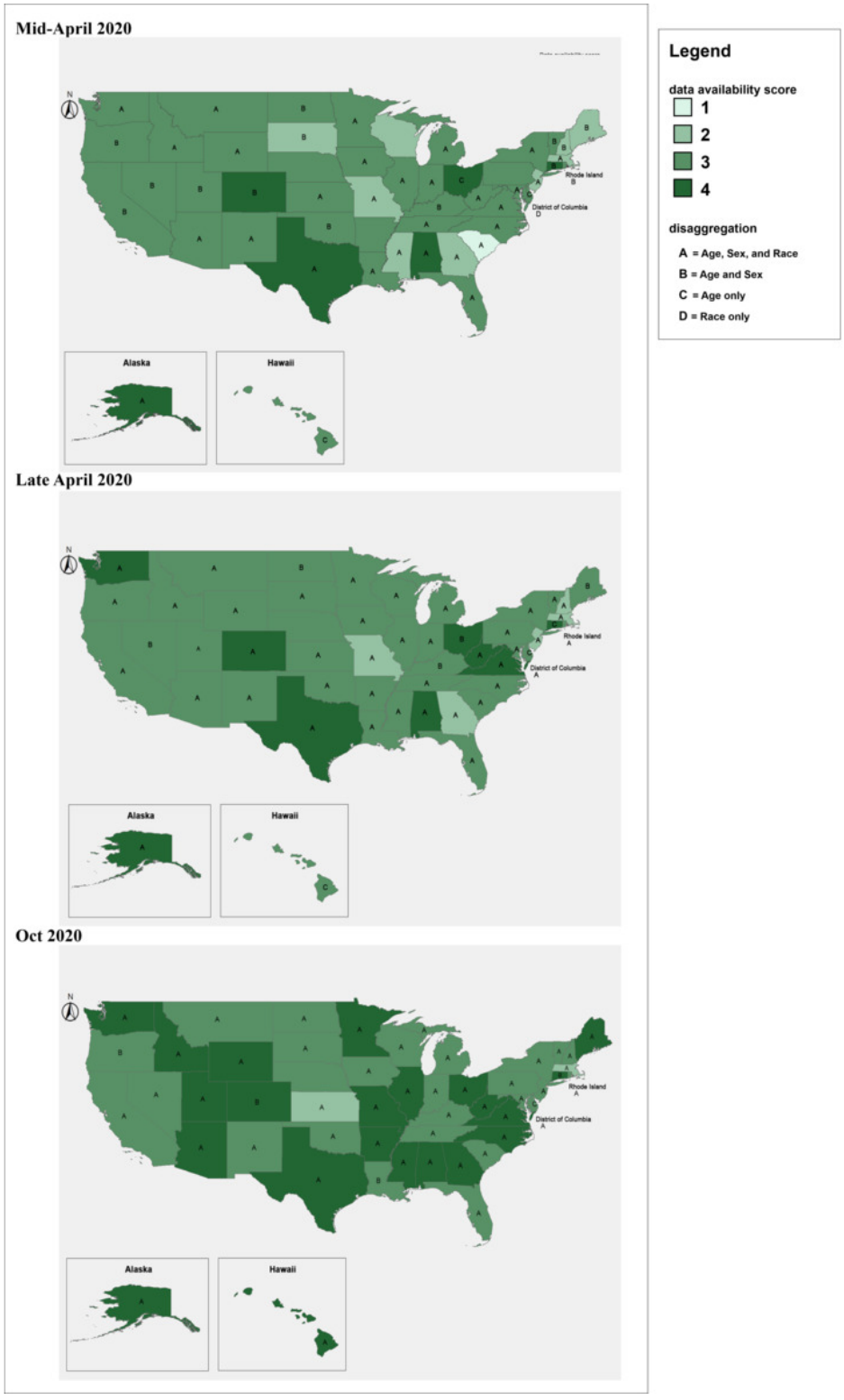

Table 1. Statistical comparisons of data reported before (pre-Act), immediately after (post-Act), and 6 months after (6-month follow-up) the introduction of the Equitable Data Collection and Disclosure on COVID-19 Act (N=51).

Data reported	Value, n (%)			*P* value[b]
	Pre-Act	Post-Act	6-month follow-up	
Age[a]				
Confirmed cases	46 (90)	50 (98)	50 (98)	.045
Deaths	25 (49)	35 (69)	39 (77)	<.001
Sex[a]				
Confirmed cases	45 (88)	48 (94)	49 (96)	.045
Deaths	21 (41)	30 (57)	36 (71)	<.001
Race and ethnicity[a]				
Confirmed cases	18 (35)	31 (61)	46 (90)	<.001
Deaths	13 (24)	25 (49)	39 (77)	<.001
OMB[c] standards	5 (10)	22 (43)	27 (53)	<.001
Data availability				
Charts or tables only	9 (18)	9 (18)	2 (4)	<.001
Dashboards[d]	35 (69)	31 (61)	26 (51)	<.001
Machine-actionable[e]	7 (14)	11 (22)	23 (45)	<.001

[a]Data collection for age, sex, and race and ethnicity for confirmed COVID-19 cases and deaths took place during April 13-20, April 23-27, and October 23, 2020.

[b]McNemar test results reported for pre-Act and 6 months post-Act comparisons.

[c]OMB: Office of Management and Budget.

[d]Dashboards in addition to charts and tables.

[e]Machine-actionable data in addition to charts and tables.

Discussion

Principal Findings

The purpose of our study was to describe and compare how US state and Washington, DC, health departments reported COVID-19 confirmed cases and deaths and made data available to the public. Demographic characteristics and data availability were analyzed and compared before, immediately after, and 6 months after the legislation (Equitable Data Collection and Disclosure on COVID-19 Act on April 21, 2020) was proposed, urging consistent collection and reporting of certain COVID-19 data [24]. Reporting of data based on race and ethnicity showed the greatest increase over the given time period. Three main findings were observed.

First, we found a significant increase in the number of states reporting COVID-19 surveillance data disaggregated by race and ethnicity during our study period. In addition to the presentation of a new legislation, this is likely due to the growing media coverage spotlighting this gap in reporting [29]. Illinois became one of the first US states to report race and ethnicity data on confirmed COVID-19 cases on March 26, 2020 [30]. Comparable data from the state of Connecticut are the only estimates published in the medical literature thus far [31]. Although we found that a significantly higher number of states reported racial and ethnic breakdowns based on federal standards, only half of them (27/51, 53%) reported it using the OMB guidelines. The racial and ethnic composition of the US population has significantly changed since the federal standards were implemented in 1997, and within-group differences (eg, West African Black, Southeast Asian, or Arab White) were not available using these categorizations. Nonetheless, there is a need for consistent reporting and availability of racial and ethnic data across states to use as a baseline that can be expanded to identify disparities in racial and ethnic subgroups. Although states have made progress in the collection of racial and ethnic data for confirmed COVID-19 cases, hospitalizations, and deaths among populations that are non-Hispanic Black or African American, Hispanic or Latino, and Asian, smaller groups such as Native Hawaiian and Pacific Islander populations are often neglected or categorized as “other” despite the OMB guidelines [32]. As of August 13, 2020, only 20 (39%) of 51 health departments reported Native Hawaiian and Pacific Islander estimates based on federal regulations. There is an urgent need for US states to collect and report fully representative COVID-19 morbidity and mortality data by race and ethnicity so that resources can be allocated and policy decisions can be improved for minority groups disproportionately affected by COVID-19.

Second, we found a significant increase in the number of states reporting COVID-19 surveillance data based on age. With age being one of the first identified risk factors for COVID-19

complications, it is surprising that this has not been reported consistently for confirmed cases and deaths since the start of the COVID-19 pandemic. Despite the need for reporting this data, researchers have cautioned that emphasizing on chronological age can be detrimental to older adults. In a recent editorial, Ayalon and colleagues [33] highlighted that the focus on reporting COVID-19 case data by chronological age only can lead to a parallel epidemic of discrimination, increasing societal age divisions between the young and old, and ethical challenges among overburdened health care systems. Nonetheless, media reports have consistently focused on the need for older adults to stay at home and for younger individuals to contribute to social distancing in order to protect older adults [33]. Studies are underway to determine the beneficial and detrimental effects of social distancing by measuring changes in loneliness, communication, and physical contact among close family and friends before and after social distancing measures were established [34]. As states move to report more accurate data on age, researchers on aging caution against reporting chronological age as a risk factor using arbitrary cutoffs, but in conjunction with other factors such as chronic illness and comorbidities. In this study, we did not systematically collect data on the number of states that reported pre-existing conditions of confirmed COVID-19 cases and deaths in, and this data has been rarely collected and reported in the context of age of patients. If the Equitable Data Collection and Disclosure on COVID-19 Act is passed by the Congress, the CDC will be required to report this information [23]. If this data is made openly available and accessible, further clarification of risks among individuals of all ages can be more accurately explained.

Third, we found a significant increase in the number of states that provided machine-actionable data immediately after and 6 months after the introduction of the legislation. Most states (49/51, 96%) had interactive dashboards available, whereas only 23 states and Washington, DC, (45%) had machine-readable morbidity and mortality data available (in addition to their dashboards). Dashboards were created through data visualization tools and geographic information system software and have become a modern way to present basic epidemiologic data that tracks disease by location, which has been used for centuries. The most well-known dashboard that presents US COVID-19 data is not from a public health department, but from Johns Hopkins University [35]. The dashboard was developed and first made available to the public on January 22, 2020; it has since received billions of views and shares on social media platforms and has been recognized by several media outlets. In March 2020, with 4.56 billion feature requests, the Johns Hopkins University COVID-19 Dashboard outpaced Pokémon Go, the mapping software by Esri's formerly most popular map [36]. An initial limitation of this data source was its inability to provide this information at the local level in combination with national and international surveillance. However, county-level data are now available [37]. Despite the value that dashboards provide to the public for tracking and mitigating the spread of disease, there is a need to go beyond visualizations and provide open data for researchers and policy makers to fully capture health disparities in real time. As previously mentioned, if the Equitable Data Collection and Disclosure on COVID-19 Act is passed, the CDC will be required to collect and provide this information [23]. If the infrastructure is not put in place for the CDC to collect this information in a unified manner, there will be a need for other national surveys such as the National Health Interview Survey collected by the National Center Health Statistics to be revised to include variables to identify these health indicators.

In addition to the three main findings described above, this study revealed other areas that are currently lacking in reporting of data. The majority of data reported are still being provided as *counts*. In addition to the need for disaggregation, states are far from data reporting using key epidemiological concepts such as population attack rate, case fatality rate, and models of COVID-19 incidence that include estimates of untested cases; these data points are necessary to enable policy decisions [21]. More advanced methods of reporting are also needed to make more meaningful comparisons between states and at the international scale. Differences in reporting data on COVID-19 confirmed cases and deaths across countries have made standard epidemiological comparisons more difficult. For example, Belgium includes all deaths that have COVID-19 suspected as a contributing cause, translating to considerably higher mortality rates than those reported by other countries [14]. Countries without widespread testing for COVID-19 may also report higher mortality rates due to smaller denominators of total confirmed cases, yet lower overall case fatality rates. Differences in case fatality rates may also be due to national differences in public health infrastructure, policy interventions, comorbidities, and sociodemographic factors [15]. Calculating excess all-cause mortality during the COVID-19 pandemic may be a more comprehensive way of making comparisons of the impact of COVID-19 on deaths both within and between countries [38].

At the end of our data collection period, only Hawaii, Indiana, Kansas, North Carolina, and Utah reported race or ethnicity rates to population (5/51, 10%), and only the state health department of California reported race and ethnicity data on confirmed COVID-19 cases and deaths in comparison with the corresponding percentages of the population [39]. A recent report by Resolve to Save Lives, an initiative endorsed by Trust for America's Health, the American Public Health Association, Association of Schools & Programs of Public Health, and Johns Hopkins Bloomberg School of Public Health, developed 15 essential indicators representing 780 data points stratified by sex, age, and race and ethnicity as best practices for collecting and presenting data on COVID-19 surveillance dashboards. As of July 2020, at least 60% of the recommended data points were not reported by dashboards in some way [40].

Limitations

Although our pre-post analysis showed significant improvements in state-level data reporting before and after the introduction of the Equitable Data Collection and Disclosure on COVID-19 Act, our results do not account for other factors, such as media coverage and improved knowledge of the disease. Therefore, we recognize the significant improvements may not directly represent causality. The biggest limitation of this study was information bias due to the rapid changes in reporting of surveillance data on a daily basis. States reported different case and death counts for each day, but case counts often increased,

sometimes dramatically, and decreased at times, due to new count standards, data maintenance, and weekends and holidays. There was also variability in the ways the states reported demographics. For example, although several states reported age, sex, and race and ethnicity data from April 13-20, 2020, the way the data were reported varied between cases and deaths. The Equitable Data Collection and Disclosure on COVID-19 Act calls for morbidity and mortality surveillance data to be collected by sex, age, race and ethnicity, primary language, socioeconomic status, disability, and county [23]. Our study was limited to differences by sex, age, and race and ethnicity. However, we hope to explore how other data on primary language, socioeconomic status, chronic disease, and disability are reported and made available in future studies.

Conclusions

The variation in reporting practices at both state and local levels indicate a need for standardized reporting across the US and for a national infrastructure for monitoring, auditing, and evaluating the quality of data reporting by states and subregions. The improvement in data reporting can be attributed to several factors, including increased clarity and capability of sharing data along with public demand for improved reporting; however, the need continues and includes additional stratification to provide more data points, including hospitalizations and hospital availability as well as COVID-19 vaccine availability and rates of vaccination among populations.

Despite numerous barriers to data sharing—which include technical, motivational, political, economic, legal, and ethical barriers (S. C. Clarke, MLIS, unpublished data, August 2019), policy makers must set reporting requirements for local public health agencies to determine what data should be made publicly available and how the data should be communicated to the public. Furthermore, in line with the open data movement, if at all possible, data should be shared in machine-actionable formats, allowing others to explore the data for spotting new trends and early detection, informing decision-making, and ensuring transparency and accountability.

Having standardized methods of counting, calculating, and reporting incidence can prevent future disagreements about data accuracy [41]. Two areas of particular importance are rates, rather than solely raw numbers, of confirmed cases and deaths provided by complete and consistent age, race, and ethnicity desegregation, as this can guide public response and resource allocation, especially as vaccinations become available for an increasing number of people. As vaccines are distributed and administered using different criteria and with differing uptake in various populations, websites reporting COVID-19 data and progress continue to be exceedingly useful as a primary source for the public to continually stay informed. Moreover, there is an urgent need for the legislation to be passed for all US states to consistently collect and make characteristic data of confirmed COVID-19 cases and deaths publicly available in order to allocate resources to mitigate the spread of the disease.

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Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
DC: District of Columbia
HR: House of Representatives
OMB: Office of Management and Budget
PDF: portable document format

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Original Paper

The Causality Inference of Public Interest in Restaurants and Bars on Daily COVID-19 Cases in the United States: Google Trends Analysis

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Abstract

Background: The COVID-19 pandemic has affected virtually every region in the world. At the time of this study, the number of daily new cases in the United States was greater than that in any other country, and the trend was increasing in most states. Google Trends provides data regarding public interest in various topics during different periods. Analyzing these trends using data mining methods may provide useful insights and observations regarding the COVID-19 outbreak.

Objective: The objective of this study is to consider the predictive ability of different search terms not directly related to COVID-19 with regard to the increase of daily cases in the United States. In particular, we are concerned with searches related to dine-in restaurants and bars. Data were obtained from the Google Trends application programming interface and the COVID-19 Tracking Project.

Methods: To test the causation of one time series on another, we used the Granger causality test. We considered the causation of two different search query trends related to dine-in restaurants and bars on daily positive cases in the US states and territories with the 10 highest and 10 lowest numbers of daily new cases of COVID-19. In addition, we used Pearson correlations to measure the linear relationships between different trends.

Results: Our results showed that for states and territories with higher numbers of daily cases, the historical trends in search queries related to bars and restaurants, which mainly occurred after reopening, significantly affected the number of daily new cases on average. California, for example, showed the most searches for restaurants on June 7, 2020; this affected the number of new cases within two weeks after the peak, with a *P* value of .004 for the Granger causality test.

Conclusions: Although a limited number of search queries were considered, Google search trends for restaurants and bars showed a significant effect on daily new cases in US states and territories with higher numbers of daily new cases. We showed that these influential search trends can be used to provide additional information for prediction tasks regarding new cases in each region. These predictions can help health care leaders manage and control the impact of the COVID-19 outbreak on society and prepare for its outcomes.

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KEYWORDS

bars; coronavirus; COVID-19; deep learning; infodemiology; infoveillance; Google Trends; LSTM; machine learning; restaurants

Introduction

The entire world is currently being significantly affected by a global virus pandemic. The first case of this virus, SARS-CoV-2, was reported in China in December 2019, and the first case outside China was discovered in January 2020 [1]. In February, the World Health Organization named the disease caused by this virus COVID-19 [2].

Worldwide, as of July 19, 2020, there had been approximately 14,400,000 confirmed cases of COVID-19, with 604,000 deaths [3]. The United States of America, with 3,830,000 confirmed cases and 143,000 deaths, was the most affected country in the world. In some states, such as California, the numbers are still increasing, while in some other states, such as New York, the peak has passed and the average number of daily new cases is decreasing.

Due to the rapid spread of SARS-CoV-2, finding effective reasons for its spread can play a significant role in prevention policies. Using data mining and time series analysis methods, it is possible to investigate the impact of different phenomena on time series data. For example, in economics, different studies have modeled the temporal relationships of two or more time series (eg, the relationship between oil and gold prices) using these methods [4]. Wang et al [5] used the same causality inference methods to determine whether a relationship exists between the main air pollutants and the mortality rate of respiratory diseases.

Through the study of infodemiology, which was first introduced by Eysenbach [6], it is now possible to extract knowledge from real-time and inexpensive data from web-based sources. These sources reflect the status of public health and answer the question of "what people are doing [7]." Conventionally, the collection of such information has been based on data collected by public health agencies and personnel [8]. However, it is now possible to extract global health information using web-based data mining [9]. Google search trends, for instance, can be a useful tool for reflecting public interests and concerns during different periods [10-12]. Morsy et al [13] considered the searches related to Zika virus to predict confirmed cases in Brazil. During the COVID-19 outbreak, different studies have investigated the correlation of web-based data and cases of SARS-CoV-2. Kutlu et al [14] investigated the correlation of dermatological diseases obtained by specific Google search trends with the COVID-19 outbreak. In addition, Google Trends has been used to predict and monitor COVID-19 cases worldwide [10,15-20]. Multiple studies have involved analysis of data related to the United States to correlate search trends and COVID-19 cases [21-26]. Although these studies consider the predictive ability of search trends on future confirmed cases, their search queries were limited to the symptoms and keywords related to the virus. For example, Ayyoubzadeh et al [10] investigated concepts related to COVID-19, such as hand washing, hand sanitizer, and antiseptic, as input features to predict the incidence of COVID-19 in Iran. However, these studies only considered the correlation of search trends with the spread of SARS-CoV-2, and no causality analysis has been performed.

In this paper, we were interested to investigate the effect of the reopening of in-store shopping on COVID-19 cases rather than searches directly related to the virus. Therefore, we considered the causality effect and predictive ability of search terms related to bars and restaurants on the number of daily new cases in different US states and territories. We analyzed the states and territories with the highest and lowest numbers of daily new cases to investigate the effect of Google searches with higher confidence.

In addition to linear correlation analysis between the search trends and COVID-19 cases, we used statistical causality methods to investigate the influential confidence of these methods on daily new COVID-19 cases.

Methods

Data Sets

For our analysis, we obtained the numbers of daily cases of COVID-19 in the United States using the COVID Tracking Project [27], which is publicly available. This project compiles daily statistics, including the numbers of positive and negative tests, hospitalization, available ventilators, and the number of deaths, in each US state and territory. For this study, we considered the data from a period of approximately three months, from April 9 to July 7, 2020, which contains 5040 data points for 56 states and territories.

For infodemiology studies, multiple sources can provide information regarding health informatics. Twitter and Google Trends are among the most popular data sources that have been used to track outbreaks [18]. Although in some studies, social media posts (eg, Twitter) have been leveraged for time series forecasting (eg, the stock market [28]), in this research, we selected Google Trends for the following reasons. First, for our analysis, we required access to location (ie, state) information; however, location is not available by default in social media platforms. More precisely, social media users must opt in to the use of location features (eg, tweeting with location), which limits the amount of available data. Second, search engines (eg, Google Trends) represent a wider scope of participants (eg, age, ethnicity, socioeconomic status) and are more universal than social media platforms (eg, Twitter) requiring memberships. In other words, Google Trends is a better proxy for the entire population in this case [29]. Lastly, social media is often used for idea and news sharing, whereas search engines are more informative with respect to searches for venues such as bars and restaurants.

For these reasons, we decided to use Google Trends to determine the public interest in bars and restaurants with daily resolution. We followed the methodology presented in [30] to obtain the results. We used queries for each state or territory from April 9 to July 7, 2020, for 45 available states and territories in the Google Trends application programming interface. For restaurants and bars, we chose *dine-in restaurants that are open near me* and *bars near me* as our queries, respectively. Throughout the remainder of this paper, we refer to "bar searches" and "restaurant searches" as the Google Trends data

for the queries used to retrieve data related to bars and dine-in restaurants, respectively.

We did not narrow the category, as the keywords were specific [30]. Google Trends does not provide the number of queries per day. Instead, it provides a normalized number between 0 and 100, where 0 refers to a low volume of data for the query while 100 refers to the highest popularity for the query [31]. To be consistent with Google Trends values, we normalized the number of daily new cases in the United States between 0 and 100 in our analysis.

Aggregating data from the Google Trends results and COVID-19 daily cases and removing missing values resulted in available data for 45 US states and territories. Although all the results for all the states and territories are provided in Multimedia Appendices 1-4, we categorized our analysis into two different groups. The first group included the 10 states or territories with the highest numbers of daily new cases as of July 7, 2020, which consisted of Texas, Florida, California, Arizona, Georgia, Louisiana, Tennessee, North Carolina, Washington, and Pennsylvania. The second group included the 10 states or territories with the lowest numbers of daily new cases as of July 7, 2020: Kansas, Hawaii, New Hampshire, Maine, West Virginia, Rhode Island, Connecticut, Montana, Nebraska, and Delaware.

All the data used in this study are publicly available and are therefore exempted from the requirements of the Federal Policy for the Protection of Human Subjects under Category 4.

Statistical Analysis

Correlation and Causation

To analyze the linear correlation of two time series, the Pearson correlation was used. The value of this correlation ranges from –1 to 1; these values show negative and positive correlations, respectively. Our analysis measured the Pearson correlation between the trends of search queries (ie, restaurants and bars) and the daily new cases of COVID-19 in each state.

In addition, we used Granger causality [32] to model the influence of past values of a time series on new values of another time series. Cross-correlation (lag correlation) is not an appropriate method in this context because due to its symmetrical measurement, it does not explain the causation. However, Granger causality tests whether the past values of a time series X cause the current values of another time series Y. Hence, in this study, the null hypothesis is that the past values of X do not affect the current values of Y. If the *P* value is less than the marginal value (.05), we can reject the null hypothesis. In our analysis, we reported *P* values for the influence of each aforementioned search query on the number of daily new cases. One of the main assumptions of modeling the influence of time series on each other is their stationarity. To test this characteristic, we used the augmented Dickey-Fuller (ADF) test [33] as our unit root test (Multimedia Appendix 4). This test determines the effect of a trend in the creation of the time series. In other words, it determines how strongly a trend defines a time series. The alternative hypothesis in the ADF test is the stationarity of the time series.

In this study, because the time series were not stationary, we applied first differencing on search trends and second differencing on daily new cases to ensure that all three series were stationary. For the statistical analysis, we used the Python statsmodels package [34].

Vector Autoregression

In our study, we leveraged the fact that search trends may impact the number of daily new cases in the future; hence, a vector autoregression (VAR) [35] model for each region was fitted to the data. A VAR model takes into account the influence of the past values of time series X and Y on the current values of time series Y with a given lag order. The lag order with the lowest Akaike information criterion was chosen in this study. Because symptoms may appear within 2-14 days after exposure to SARS-CoV-2 [36], a maximum of 14 lags was used. The equation for the VAR model with two lags is summarized below:

$$Y_t = \alpha + \beta_1 X_{t-1} + \beta'_1 X_{t-2} + \beta'_2 Y_{t-1} + \beta'_2 X_{t-2} + \in_t \textbf{ (1)}$$

In equation 1, Y_t represents the value of time series Y at time t, which consists of a combination of previous lag values from Y and X with different weights β, β′ and random white noise, $\in_t$. In other words, this equation models the importance of past values of the considered time series, as well as a secondary time series, for the estimation of the current value. We fitted a VAR model with different lag orders to perform the Granger causality test. Although the VAR model was used to compute the Granger causality, we did not use this model for the prediction task. Instead, we used a deep learning architecture for our prediction task.

Long Short-Term Memory

A long short-term memory (LSTM) [37] model is a type of recurrent neural network that is useful for time series prediction. LSTM models capture the long-term effect of a time series as well as its most recent values. In this study, we used LSTMs to predict the daily new cases using two sets of features: (1) the historical values of the new cases time series and (2) additional information from the search query time series. We used 70% of the data for training, and the remaining data were used for evaluation of the model. Root mean square error (RMSE) was selected as the performance metric. RMSE can be calculated as follows:

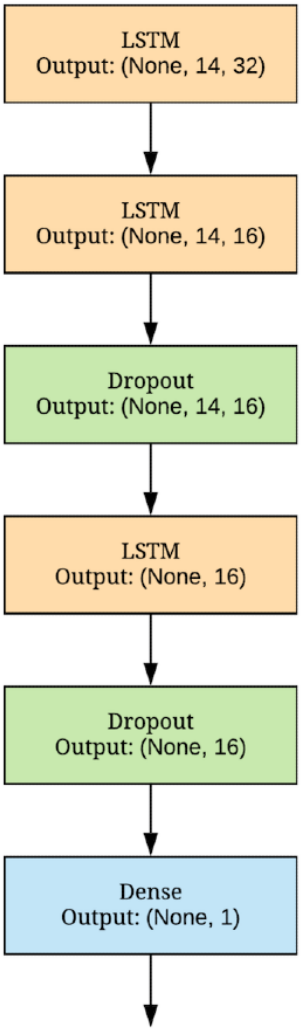
In equation 2, N is the number of samples, $Y_{predict}$ is the predicted value, and Y_{actual} is the actual value of the time series.

We calculated RMSEs for three models: (1) the baseline model, which uses only the past values of the new cases time series for the prediction, (2) the model that uses the past values of restaurant searches along with the past values of the new cases time series, and (3) the model that combines the information from the time series of daily cases and the bar searches.

The architecture of the model used in the study is illustrated in Figure 1. It consists of three LSTM layers along with dropout layers and a fully connected layer at the end. Dropout layers were used to avoid overfitting, which is a typical problem in

machine learning tasks. To train this model, we used the TensorFlow package in Python.

Figure 1. The proposed model architecture. LSTM: long short-term memory.

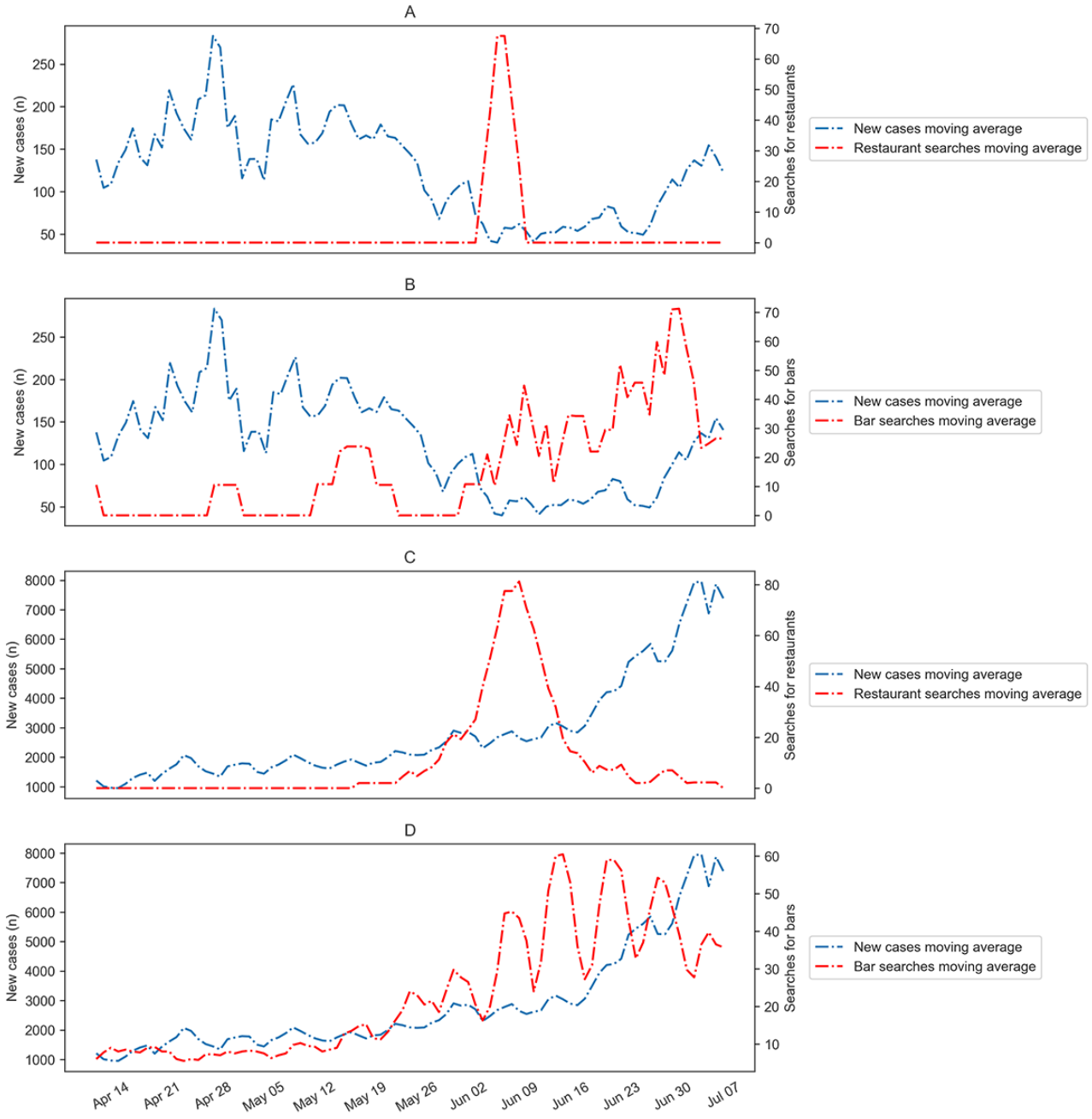


Results

Observations

Investigation of daily new cases and historical trends in search queries related to bars and restaurants showed correlations in some of the states and territories in the United States. For some states and territories, such as California, there was a steep rise in restaurant searches, peaking on June 7. The number of daily new cases showed a drastic increase within 2 weeks of this peak. Considering the bar searches in California, the plot shows an increasing trend, with the peak value appearing on June 13. However, in Delaware, the daily new cases were not profoundly affected by these search trends (Figure 2).

Figure 2. Effects of restaurant and bar search trends on daily cases of COVID-19 in Delaware (A, B) and California (C, D) from April 9 to July 7, 2020.



Granger Causality

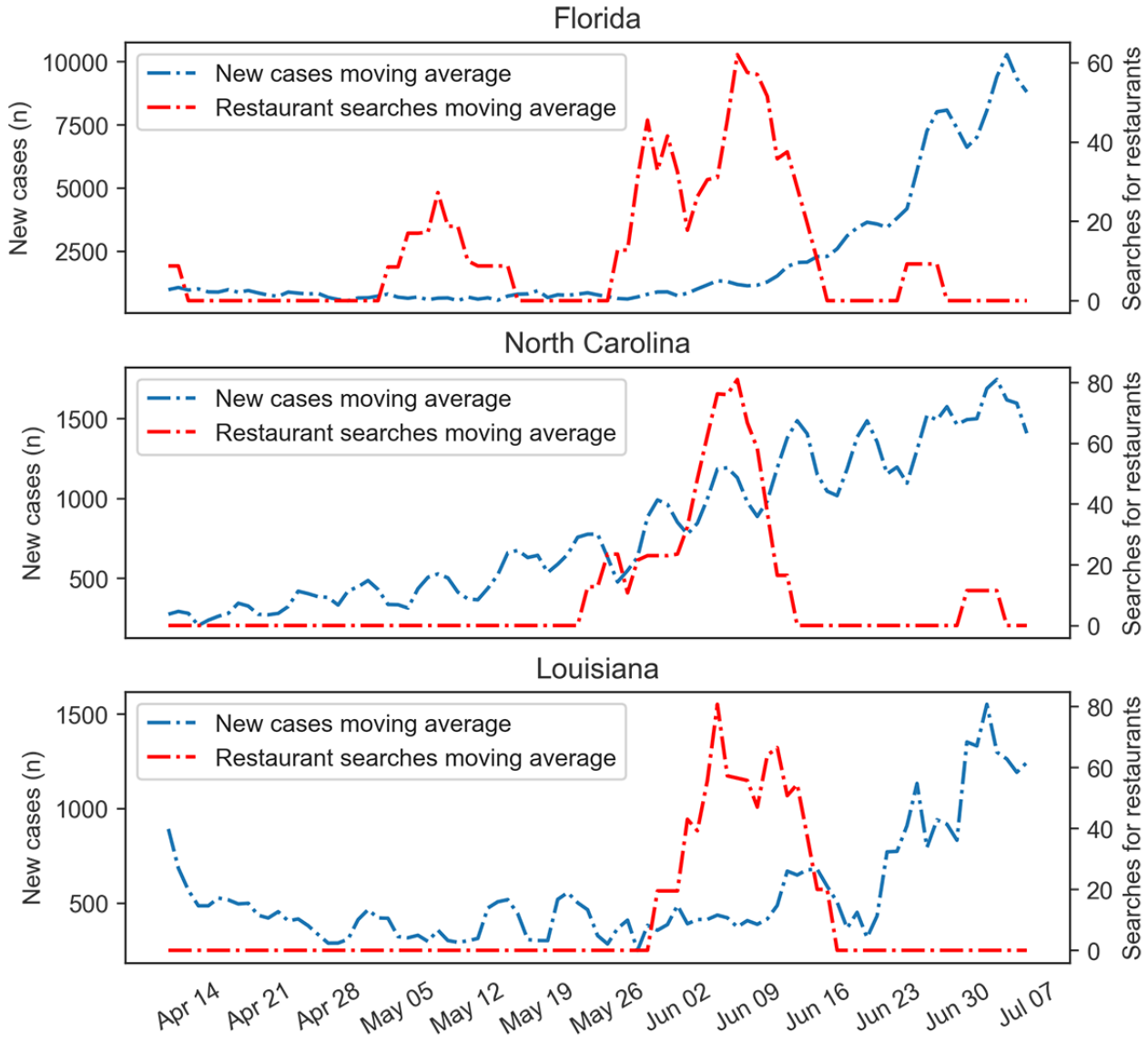
In this section, we provide the results of the Granger causality tests for the 10 US states and territories with the highest and lowest numbers of daily new cases as of July 7, 2020.

The *P* values for California are small, indicating that the effect of the search queries is significant; hence, these searches can be used to predict daily new cases. Florida and North Carolina are two examples of states in which the effect of restaurant searches is rejected based on the Granger causality test; however, new cases in Louisiana were significantly affected by restaurant searches (Table 1). Figure 3 illustrates the moving average of daily new cases and restaurant search trends for these three states. The high *P* value for Florida is because of the first peak in the restaurant search, which did not change the daily new cases trend. North Carolina has an overall increasing trend; therefore, the effect of the searches was marginal. However, Louisiana was influenced by the sudden changes in restaurant search trends, which affected the number of daily new cases (Figure 3).

Table 1. *P* values of the Granger causality tests on daily new cases of COVID-19 for the 10 US states and territories with the most daily new cases from April 9 to July 7, 2020.

Cause → caused	*P* value									
	Texas	Florida	California	Arizona	Georgia	Louisiana	Tennessee	North Carolina	Washington	Pennsylvania
Restaurant searches → new cases	.11	.35	.004	.003	.30	<.001	.09	.53	<.001	.11
Bar searches → new cases	.02	.16	<.001	.04	.001	<.001	.08	.20	.02	.01

Figure 3. Comparison of restaurant search effects on daily new cases of COVID-19 in Florida, North Carolina, and Louisiana from April 9 to July 7, 2020.



Similarly, Table 2 summarizes the *P* values for the Granger causality test for the second group (ie, the 10 states and territories with the fewest daily new cases). Most of the *P* values for these states and territories are not significant.

Table 2. *P* values of the Granger causality tests on daily new cases of COVID-19 for the 10 US states and territories with the fewest daily new cases from April 9, 2020, to July 7, 2020.

Cause → caused	*P* value									
	Kansas	Hawaii	New Hampshire	Maine	West Virginia	Rhode Island	Connecticut	Montana	Nebraska	Delaware
Restaurant searches → new cases	.99	<.001	.88	.08	.08	.54	.99	<.001	.99	>.99
Bar searches → new cases	.01	.001	.50	.11	.45	.28	.008	.07	.08	<.001

Pearson Correlation

In this section, we provide the Pearson correlation results. Tables 3 and 4 summarize these correlations with the corresponding *P* values for each group. Based on these two tables, the linear correlation between the search trends related to bars and restaurants and daily new cases in states and territories with a higher number of daily new cases is more substantial, on average, compared to that for states and territories with fewer daily new cases.

Table 3. Pearson correlations between search trends and daily new cases of COVID-19 for the 10 US states and territories with the most daily new cases from April 9 to July 7, 2020.

Variable	Texas	Florida	California	Arizona	Georgia	Louisiana	Tennessee	North Carolina	Washington	Pennsylvania
Restaurant searches versus new cases										
Correlation	–0.17	–0.19	0.0	–0.11	–0.2	–0.13	–0.18	0.17	–0.11	–0.23
P value	.11	.07	.96	.30	.07	.23	.08	.10	.29	.03
Bar searches versus new cases										
Correlation	0.11	0.41	0.47	0.31	0.31	0.12	0.39	0.73	0.13	–0.52
P value	.28	<.001	<.001	.003	.003	.26	<.001	<.001	.20	<.001

Table 4. Pearson correlations between search trends and daily new cases of COVID-19 for the 10 US states and territories with the fewest daily new cases from April 9 to July 07, 2020.

Variable	Kansas	Hawaii	New Hampshire	Maine	West Virginia	Rhode Island	Connecticut	Montana	Nebraska	Delaware
Restaurant searches versus new cases										
Correlation	–0.05	–0.08	–0.08	–0.08	0.09	–0.08	–0.06	–0.01	–0.05	–0.17
P value	.62	.43	.45	.42	.35	.42	.55	.85	.61	.10
Bar searches versus new cases										
Correlation	–0.20	0.22	–0.11	0.13	0.11	–0.61	–0.22	0.19	0.007	–0.18
P value	.06	.03	.27	.21	.28	<.001	.04	.07	.94	.09

Prediction of New Cases

The prediction results of daily new cases using our deep neural network architecture are provided in this section. The RMSE scores for test data for the US states and territories with the 10 highest and lowest numbers of daily new cases are summarized in Tables 5 and 6 for each model.

Table 5. Root mean square error scores for the time series of new COVID-19 cases (baseline), the baseline + restaurant searches time series, and the baseline + bar searches time series for the 10 US states and territories with the most daily new cases from April 9 to July 7, 2020.

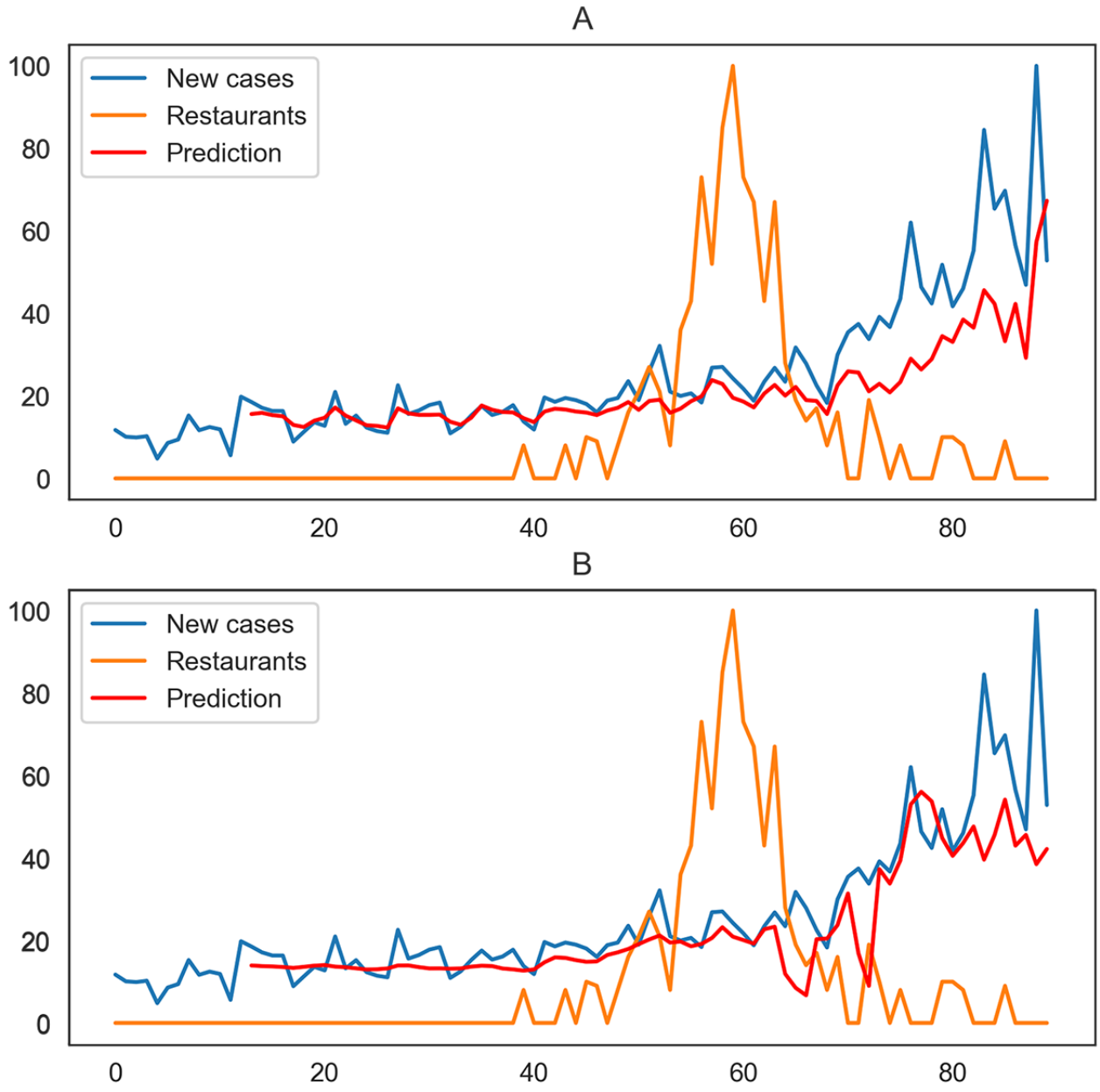
Model	Root mean square error									
	Texas	Florida	California	Arizona	Georgia	Louisiana	Tennessee	North Carolina	Washington	Pennsylvania
Baseline	18.00	48.21	24.19	31.35	29.90	39.84	35.88	19.74	26.44	18.70
Baseline + restaurant searches	32.44	43.84	21.86	45.32	33.46	29.36	32.51	22.91	23.92	18.10
Baseline + bars	44.50	32.55	19.89	26.20	36.39	43.51	38.09	26.68	22.75	24.68

Table 6. Root mean square error scores for the time series of new COVID-19 cases (baseline), the baseline + restaurants time series, and the baseline + bars time series for the 10 US states and territories with the fewest daily new cases from April 9 to July 7, 2020.

Model	Root mean square error									
	Kansas	Hawaii	New Hampshire	Maine	West Virginia	Rhode Island	Connecticut	Montana	Nebraska	Delaware
Baseline	28.41	51.49	12.09	20.92	26.18	5.37	3.47	29.58	5.49	20.73
Baseline + restaurant searches	25.56	43.64	8.10	14.57	22.55	8.88	3.91	43.34	8.22	20.42
Baseline + bars	34.43	49.01	15.30	21.96	24.15	6.01	4.68	43.27	8.67	12.81

For the states and territories with significant causality effects, the RMSE improves on average. California is an example of a state that shows this improvement (Table 5). Similarly, Figure 4 illustrates the prediction performance with and without considering the restaurant search trends. The predicted values are closer to the actual values when the effect of restaurant searches is taken into consideration in the prediction model.

Figure 4. Prediction values for daily new cases of COVID-19 without (A) and with (B) restaurant search trends for California from April 9 to July 7, 2020.



For some states, although there was no causality effect for restaurant searches, the RMSE value improved. On the other hand, for states such as Montana, in which the Granger causality test shows a significant effect, the RMSE increased (Table 6). By investigating the time series for these two states (Figures 5 and 6), we can interpret these inconsistencies as arising for two reasons. First, for states such as Kansas, the value improves because of the fluctuation in the new cases time series, which makes the prediction unreliable. Second, as Figures 5 and 6 show, the impulses in restaurant searches for Kansas and Montana are point impulses. These unit jumps cannot significantly improve the prediction of the time series, although they appear in the causality tests.

Figure 5. Prediction values for daily new cases of COVID-19 without (A) and with (B) restaurant search trends for Kansas from April 9 to July 7, 2020.

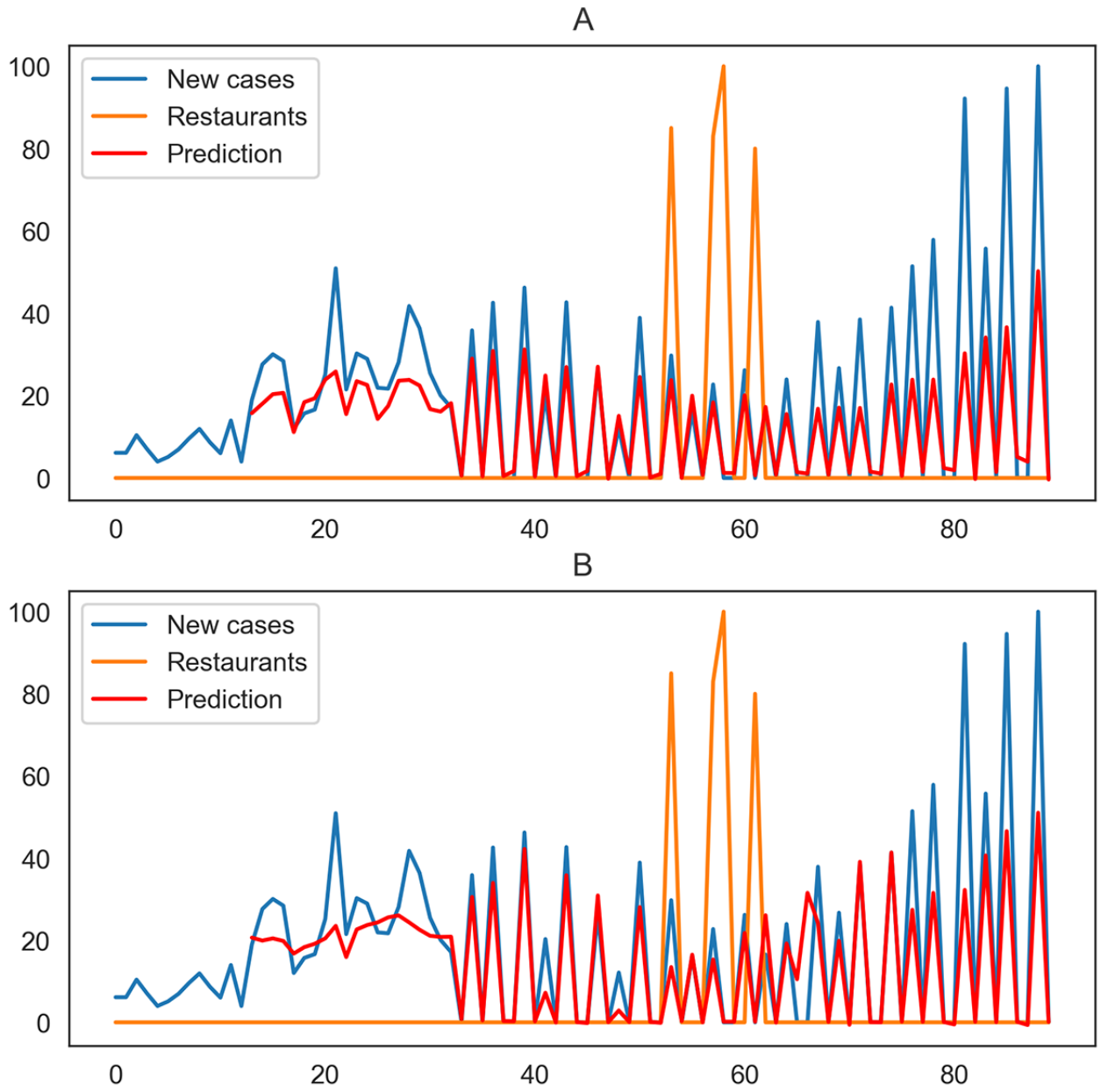
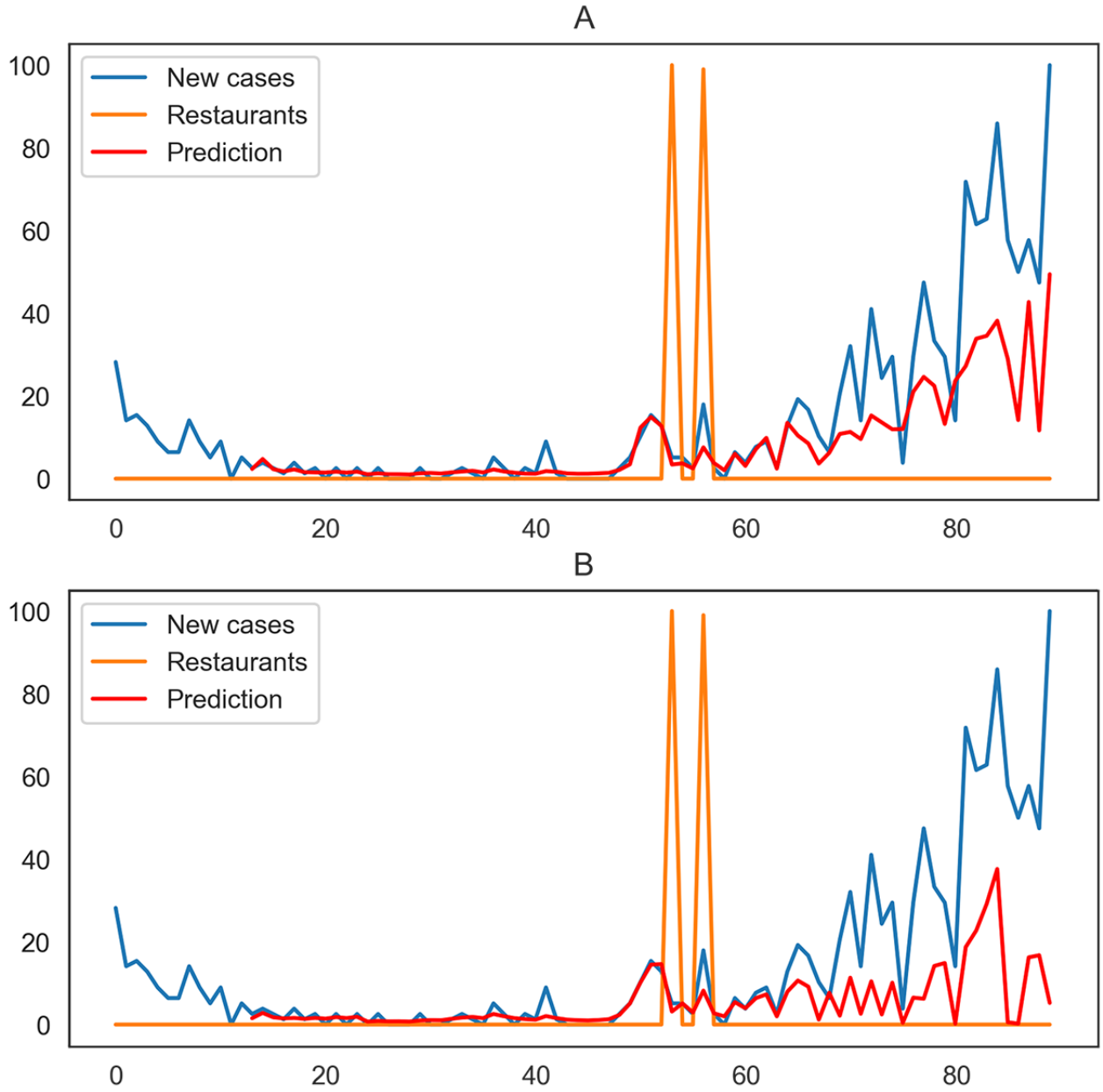


Figure 6. Prediction values for daily new cases of COVID-19 without (A) and with (B) restaurant search trends for Montana from April 9 to July 7, 2020.



Discussion

Principal Results

To the best of our knowledge, this study is the first analysis that considers the ability of Google search trends related to dine-in restaurants and bars to predict daily new cases of COVID-19 in the United States. Our main findings show that in states and territories with higher numbers of daily cases, the historical trends in search queries related to bars and restaurants (queries related to dine-in venues), which occurred primarily after reopening, significantly correlate with the number of daily new cases on average. In this study, we used statistical methods to validate this effect on the number of daily new cases. One potential reason for this effect could be a smaller population, as this is reflected in the number of daily new cases. The other reason may be the high number of new daily cases, in California for instance, at the time of reopening of restaurants and bars (+2000).

The Granger causality tests show that in some states and territories, the effect of restaurant searches on daily new cases is significant. California is an example of such a state. On May 18, the governor of California announced the easing of criteria for counties to reopen, enabling them to reopen faster than the state, and on May 25, he announced plans for the reopening of in-store shopping [38]. Consequently, there was an increase in restaurant searches, and the peak of the searches occurred on June 7. The number of daily new cases drastically increased within two weeks of the escalation in dine-in restaurant searches.

A similar trend in bar searches was observed in California. Irrespective of the seasonal effect of the time series, which shows a higher number of searches related to bars during weekends, the average trend in bar searches increased. However,

North Carolina was not influenced by restaurant searches. This is because this state showed an increasing average trend irrespective of the other time series. Therefore, the *P* value for the Granger causality is high (.53). In summary, Granger causality showed significant results for states and territories with higher numbers of daily new cases on average.

This study suggests that the effect of restaurant and bar searches is greater in states and territories with higher numbers of daily new cases compared to states and territories that report lower numbers of positive cases every day. On average, in the states and territories with higher numbers of daily new cases, the more significant Granger casualties and higher Pearson correlation values support this fact. Additionally, by taking restaurants and bar searches into account, we can improve the underestimation of the prediction task. We used artificial intelligence models to improve the prediction results of new cases using additional information, namely Google Trends. These Google Trends for searches for restaurants and bars can be useful depending on the time series structure.

According to infodemiology, capturing real-time information and public attitudes can help decision makers to be prepared based on the feedback loop on public data and disease spread [7] and can provide a better estimation of a deadly disease such as COVID-19 in each state to distribute health care–related utilities such as ventilators. In addition, this information can be used to model and analyze food- and lifestyle-related behaviors at the global level based on real-time events [39-41].

Limitations

There are several limitations to this study. We only used specific search queries for each category. People use different search terms to find the information they are looking for. Moreover, we only considered the effect of restaurants and bar searches on the number of daily cases. Further research could aim to consider the effects of other public places, such as gymnasiums and adventure parks. Another limitation of our study is the limited number of data points for each region (88 samples on average). This limitation, which is a consequence of the daily report data structure, affects the prediction results to a certain degree.

Conclusions

We investigated the causality effect and correlation of search queries related to dine-in restaurants and bars on the daily numbers of new cases of COVID-19 in the US states and territories with the highest and lowest numbers of daily cases from April 9 to July 7, 2020. We showed that for most of the states and territories with high numbers of daily new cases, the effect of search queries related to bars and restaurants is greater; hence, these searches can be used as additional information for prediction tasks.

Acknowledgments

No funding was received for this project.

Conflicts of Interest

None declared.

Multimedia Appendix 1
P values for the Granger causality tests on daily new cases of COVID-19 for the remaining US states and territories from April 9 to July 07, 2020.
[DOCX File , 13 KB - publichealth_v7i4e22880_app1.docx]

Multimedia Appendix 2
Pearson correlations between search trends and daily new cases of COVID-19 for the remaining US states and territories from April 9 to July 07, 2020.
[DOCX File , 13 KB - publichealth_v7i4e22880_app2.docx]

Multimedia Appendix 3
Root mean square error scores for the new cases time series of COVID-19 (baseline), baseline + restaurant searches time series, and baseline + bar searches time series for the remaining US states and territories from April 9 to July 7, 2020.
[DOCX File , 13 KB - publichealth_v7i4e22880_app3.docx]

Multimedia Appendix 4
P values of the augmented Dickey-Fuller statistics for the stationarity tests for the US states and territories.
[DOCX File , 13 KB - publichealth_v7i4e22880_app4.docx]

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Abbreviations

ADF: augmented Dickey-Fuller
LSTM: long short-term memory
RMSE: root mean square error
VAR: vector autoregression

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Viewpoint

Test, Trace, and Put on the Blockchain?: A Viewpoint Evaluating the Use of Decentralized Systems for Algorithmic Contact Tracing to Combat a Global Pandemic

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Abstract

The enormous pressure of the increasing case numbers experienced during the COVID-19 pandemic has given rise to a variety of novel digital systems designed to provide solutions to unprecedented challenges in public health. The field of algorithmic contact tracing, in particular, an area of research that had previously received limited attention, has moved into the spotlight as a crucial factor in containing the pandemic. The use of digital tools to enable more robust and expedited contact tracing and notification, while maintaining privacy and trust in the data generated, is viewed as key to identifying chains of transmission and close contacts, and, consequently, to enabling effective case investigations. Scaling these tools has never been more critical, as global case numbers have exceeded 100 million, as many asymptomatic patients remain undetected, and as COVID-19 variants begin to emerge around the world. In this context, there is increasing attention on blockchain technology as a part of systems for enhanced digital algorithmic contact tracing and reporting. By analyzing the literature that has emerged from this trend, the common characteristics of the designs proposed become apparent. An archetypal system architecture can be derived, taking these characteristics into consideration. However, assessing the utility of this architecture using a recognized evaluation framework shows that the added benefits and features of blockchain technology do not provide significant advantages over conventional centralized systems for algorithmic contact tracing and reporting. From our study, it, therefore, seems that blockchain technology may provide a more significant benefit in other areas of public health beyond contact tracing.

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KEYWORDS

COVID-19; public health; blockchain; distributed ledger technology; mobile apps; pandemic mitigation; contact tracing; epidemiological monitoring

Introduction

Background

To many global health professionals, the emergence of the COVID-19 pandemic has not come as a complete surprise. The outbreak of SARS that occurred in the autumn of 2002 in Guangdong Province, China—characterized as the first near-pandemic in the era of globalization [1]—marked the beginning of a new century in which global health security events would become more frequent and escalate rapidly across the globe. Following SARS came the global pandemic of H1N1, outbreaks of Middle East Respiratory Syndrome, the Zika virus, and new Ebola outbreaks. These served as early warning signs of what would become the most significant human health emergency since the 1918 influenza pandemic: the current COVID-19 global pandemic that has, as of February 2021, resulted in at least 100 million cases and 2 million deaths worldwide [2].

Throughout this period of accelerated outbreaks of novel, emerging, and re-emerging infectious diseases, calls for sound public health policy and further expansion of public health surveillance capacity to prevent future pandemics have become more frequent and urgent [3]. However, investment in public health infrastructure, such as strengthening state capabilities under the World Health Organization International Health Regulations, did not heed these warnings: experts have painted a bleak picture of outbreak preparedness by characterizing the global pandemic response as cycles of panic succeeded by neglect [4]. Consequently, various systems for disease surveillance, including electronic public health reporting modalities, were challenged by the complex requirements associated with COVID-19-related data. Some of these challenges stemmed from the inability of the relevant public health agencies to receive and share electronic data at a pandemic scale [5], some from the use of inappropriate or outdated tools lacking interoperability [6], and some from failing to meet security and privacy requirements [7].

As COVID-19 cases continue to surge, national governments have attempted to invest in and deploy more robust digital disease surveillance systems. These encompass different forms of technology (eg, digital epidemiology, big data, machine learning, mobile apps, and distributed computing), which are now viewed as critical tools to explore in order to modernize the pandemic response [8]. While a rapid increase in innovation and investment in this area of technology has occurred, many of these technology-centric initiatives have encountered implementation barriers due to nontechnical challenges associated with data governance, user adoption, concerns about accountability and oversight, and patient privacy and social acceptance concerns [7,8]. An emerging technology that has been suggested in this context is blockchain, a form of distributed ledger technology that is maturing in several industries, including in areas of digital cryptocurrencies, financial transaction technology, and growing attention in industrial sectors, such as energy, transportation, supply chain, auditing, and health care [9].

Blockchain Uses in Health Care

The adoption of blockchain, which can be characterized as an append-only distributed database that is coordinated via a peer-to-peer protocol [10], removes the need for central operators and can offer potential improvements over traditional health care information management systems (eg, client-server systems) [9]. Blockchain allows for tamper-proof replication of data in an adversarial environment [11]. The technology is resilient to fault scenarios in which adversaries send conflicting information to different parts of the system [12], even if those adversaries present large numbers of pseudonymous identities with malicious intent [13]. Participants on a blockchain form consensus on whether a proposed record is admissible by adjudicating it using a consensus mechanism [14], thus ensuring only valid records agreed upon by network members are replicated.

Consensus on a blockchain network can be proof based (eg, proof-of-work consensus as used by the Bitcoin blockchain) or voting based (eg, proof-of-authority consensus) [15], with different hybrid forms being an emerging field of research [16]. Regarding access control, blockchain protocol taxonomies differentiate between public or private and permissionless or permissioned networks [17]. Public blockchains are open to participation by anyone, whereas private, or *enterprise*, blockchains employ access control mechanisms. In a permissionless system, all members have the same responsibilities in the consensus protocol, while permissioned networks assign different responsibilities in consensus to participants, depending on their role and authority.

Several use cases have emerged evidencing the potential utility of blockchain in health care data management. These include electronic health record (EHR) management and aggregation, privacy-preserving algorithms for health systems data, integration of blockchain systems with the Internet of Medical Things, enabling distributed patient-provider directories across multiple payers and providers, and enhancing management and security of health supply chains [18-21]. Accompanying this potential, blockchain also faces real-world implementation challenges, including storing and transferring data on- and off-chain, interoperability with other health information systems, managing permission structures, and ensuring scalability [22].

Blockchain has also been suggested as a potential solution in the context of COVID-19 algorithmic contact tracing by promising protection from cyberattacks [23], allowing for global monitoring of social encounters to inform health policies [24], enabling privacy [25,26], preventing the falsification of diagnoses [27], allowing users to retain ownership of personal data [28], and ensuring the trustworthiness of that data [29], while maintaining a record of its provenance [26]. While none of the popular algorithmic contact tracing frameworks on the

market today [30] uses blockchain, the growing number of academic works [23,25,27,31-38] suggests significant interest. Hence, this viewpoint aims to critically examine the potential utility and technical feasibility of blockchain technology for pandemic algorithmic contact tracing. This is accomplished by applying a blockchain evaluation framework that assesses the suitability of using the technology for specific use cases based on seven key questions. The viewpoint concludes with some recommendations of whether blockchain is a viable application for this critical public health use case and other observations about how to leverage this technology in the ongoing fight against COVID-19.

Algorithmic Contact Tracing

Overview of Conventional and Algorithmic Contact Tracing Approaches

Contact tracing is an epidemiological control measure aimed at identifying all the people with whom an individual who contracted an infectious disease has been in contact, and who are, in turn, at risk of being infected with and transmitting that disease to other close contacts [39]. It has pronounced benefits in controlling infections that remain undetected in the population [40], such as the transmission of COVID-19, in which a large proportion of cases could be asymptomatic [41]. Quick, reliable, and accurate tests to confirm cases are a prerequisite for successful contact tracing [42,43], as, without them, infectious individuals can remain unidentified and continue to serve as human vectors sustaining community transmission. Insufficient testing can lead to underreporting of the true prevalence of the disease and its attack rate, as well as limit the effectiveness of nonpharmaceutical interventions, such as masking, social distancing, and other crucial public health interventions [44]. Contact tracing, however, represents only one single stage in the process of effective outbreak control and response, which is only effective when combined with quarantine and isolation procedures [45].

Contact tracing has a rich history dating back to the late nineteenth century, when UK medical officers responded to infectious disease outbreaks such as smallpox with surveillance systems involving notification, isolation, disinfection, and case finding [46]. The information age brought digital case management systems and other innovations (eg, digital epidemiology via mobile apps, internet surveillance, and disease modeling and forecasting using artificial intelligence) that are now being leveraged by health authorities. Yet, traditional interview-based approaches remain a mainstay [8,47,48]. Here, contact information is collected by health care professionals or volunteers who discover the contact history of individuals affected by an infectious disease through interviews with patients, families, or health care professionals or by analyzing medical records, tracking data, or surveillance data [49].

Where an interview-based contact tracing technique is used, its success relies on the ability of those affected to recollect their contact history. The reliability of such self-reported data is, however, questionable [50]. Moreover, contact with unknown persons cannot be discovered through this approach. Furthermore, conventional contact tracing regimens are labor intensive, are associated with high costs per case, and yield diminishing disease prevalence reductions under incremental investments [51]. Consequently, doubts have been raised about whether these traditional methods alone can be effective in the context of a large-scale pandemic. As a reaction, digital epidemiology methods, including algorithmic contact tracing, have been proposed to reduce virus transmission more effectively [8]. Digital epidemiology, or "the use of data generated outside the public health system for disease surveillance" [8], has been discussed since the 1990s [52]. Most of the early approaches to digital epidemiology use *passive* methods by repurposing data from "a range of sources most of which do not relate to healthcare utilization" [supplementary material, 8]. In contrast, most modalities of algorithmic contact tracing can be considered *active* methods, as users have to enable data monitoring and sharing consciously.

Algorithmic contact tracing automates the conventional contact tracing process by allowing for the collection, aggregation, and analysis of automatically generated data about a case's contacts by a public health agency, thus eliminating the need for laborious interviews. The large volume and multimodal nature of the clinical informatics systems and epidemiological data that go along with this approach constitute a challenge that new technologies can help address [53]. This applies particularly to algorithms that can quickly assess potential exposure and risk patterns while enabling faster notification to suspected contacts [54]. Countries that have applied algorithmic contact tracing aggressively, by making the use of mobile phone tracing apps compulsory (eg, China and South Korea), were able to reduce daily positive cases more effectively than those that used approaches where participation was voluntary [55]. While it is unclear whether the containment of case numbers can be directly attributed to algorithmic contact tracing, the use of big data to trace individuals is a commonality of the pandemic containment strategies applied by these countries [56]. Further, real-world experiences with the deployment of algorithmic contact tracing illustrate the complexity of the ethical issues associated with these technologies, including the need to balance individual privacy and autonomy concerns with the utility of such data to prevent disease spread during a public health emergency [8,56].

To reiterate, the goal of contact tracing is to identify people that *had contact* with each other, thereby identifying a potential path of exposure and infection. While a definition of what can be considered *contact* in the context of COVID-19 is still evolving [57], active algorithmic contact tracing commonly uses physical proximity and duration of exposure [58] as an approximation. Data gathered for algorithmic contact tracing commonly takes one of three forms: (1) proactively reported data (ie, manual digital check-ins that require participants' compliance [59]), (2) active sensor data (ie, information about an encounter with a different device utilizing the same tracing app), and (3) passive sensor data (ie, information about the geographic position of the device). These are commonly generated by devices using Bluetooth, including Bluetooth Low Energy; GPS; and Wi-Fi signal strength information [60]. Bluetooth allows for active sensing, delivering information about the proximity of two sensors with submeter accuracy [61,62]. Passive sensing through GPS and Wi-Fi uses

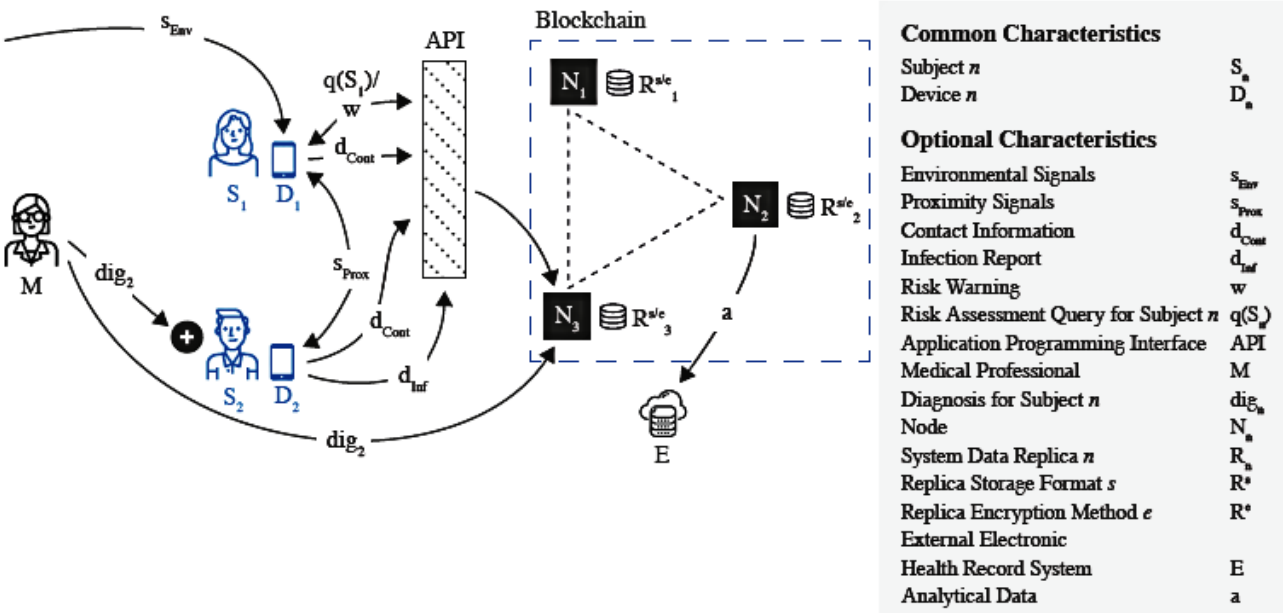
environmental data to approximate the geographic position of a device with relatively high precision under good conditions [63,64], but insufficient precision under suboptimal conditions [65-67]. Based on this information, an algorithmic contact tracing system can reconstruct when individual devices have been close, thereby allowing it to proactively alert those who are identified as being at risk of infection once confirmation of a positive case is made known to the system.

Existing Literature on Blockchain Technology for Algorithmic Contact Tracing

As previously discussed, algorithmic contact tracing is now an emerging use case for blockchain technology. However, little had been published on this topic and its application to infectious disease control before the COVID-19 pandemic, despite prior outbreaks of other diseases. One of the first contributions in this space is by Kangbai et al [68], who proposed a "Blockchain platform to conduct real-time Ebola contact tracing" in the context of the 2018 outbreak of this highly virulent virus in the Democratic Republic of Congo. Subsequently, the COVID-19 pandemic has led to increased interest in the topic and several publications and preprints in the medical and engineering literature. From a systemic perspective, the dominant function of blockchains in algorithmic contact tracing is that of tamper-proof, distributed data stores for managing contact data [23,25,27,31-38]. A less pronounced function is that of a data integration layer that allows for the exchange of medical and public health information from different sources among different actors in health care settings [23,25,27,32]. Data that are exchanged in this way take the shape of certified COVID-19 diagnostic data [23,25,32] or immunization data [27].

Proposed algorithmic contact tracing blockchain systems appear as distributed architectures consisting of varying numbers of nodes in a network (see Figure 1). Commonly, these systems do not employ access control but, instead, grant read and write access to the public [23,25,31,33-36,38]. Less commonly, read access is provided to the public but write access is restricted [37], yet other architectures operate as private systems [27,32]. In most public systems, each node stores a replica of all data network-wide. Here, data are potentially encrypted and stored according to a format specific to the protocol used. In some architectures, external entities like hospitals or laboratories access the blockchain to obtain data for analysis [37], potentially correlating them with data held by external EHR systems. The consensus mechanisms used for data replication between nodes are rarely discussed. Where they are, mechanisms are selected either for their performance characteristics [25] or to implement authority-based forms of consensus [23,35,37]. While some proposals do not discuss the role of smart contracts [31,37,38], many employ smart contracts to validate data on the chain [23,32,34-36], mostly to prevent malicious users from inserting fabricated records of positive diagnoses into the system [23,32].

Figure 1. An archetype of a blockchain-based contact tracing environment derived from architectures described in the published literature. EHR: electronic health record.



Proposed blockchain-based algorithmic contact tracing systems (see Figure 1) also generally cater to two types of actors: subjects that use contact tracing apps and, except for cases in which only self-reported data are used [34,36], medical professionals that digitally attest to positive cases [23,25,32]. Through their mobile devices, subjects obtain environmental signals from passive sensors [33], proximity signals from active sensors [23,31,32,34,36-38], or a combination of both [25,27,35,36]. The data received are converted into a target format to be stored on the blockchain, the particulars of which are a key differentiator between protocols. While some protocols disregard information privacy [33], more commonly, the confidential nature of tracing data is recognized and addressed by proposing formats that are deemed to prevent a subject's privacy from being compromised.

The goals of privacy-focused blockchain architectures are as follows: preventing manipulation of diagnostic data [23], preventing impersonation of health authorities [31], protecting the identity of infected persons [25,36], or, most commonly,

precluding mass surveillance through the derivation of movement or contact profiles from stored data [25,31,32,34,35,37,38]. To approach these goals, various models to capture data relevant to contact tracing are proposed. Contact data commonly come in the form of contact lists using one-time pseudonyms [23], pseudonymized user data combined with encrypted location information [25], pseudonymized or encrypted diagnoses [31,32], or encrypted epidemiological data [37].

Irrespective of the format, after being generated on the user's device, contact data are sent to the blockchain. This can happen via submission of a transaction to a public network [23,25,31,33-36,38] or, specifically in the case of private systems where subjects do not have direct access to the blockchain [27,32,37], by passing through an upstream application programming interface that can be operated by government bodies [27,37] or by a consortium of otherwise trustworthy entities [32]. The data are then replicated between nodes. In the case of a positive diagnosis for a subject, there are two alternative patterns. First, subjects can reveal their positive status on the chain proactively, oftentimes by providing some form of proof [23,32]. Second, a pseudonymized diagnosis can be uploaded to the chain [31,33] or endorsed on-chain by an authorized diagnostician [25]. Subjects can then query the blockchain at intervals to obtain a risk assessment based on their previous contacts [32,38] or to receive notifications [23,36,37]. The overall purpose of these proposed systems is to enable decentralized networks that can share trusted data relevant to contact tracing efforts, including self-reported data and environmental signals. Nevertheless, parameters around data storage, computation, and measures to ensure privacy-preserving processing vary and can be further modulated by developers should these be implemented.

Evaluation of Applicability of Blockchain to Algorithmic Contact Tracing

Overview

Based on our review of proposed blockchain system designs for algorithmic contact tracing, we now conduct an in-depth assessment of the potential suitability and technological feasibility for their application to COVID-19 based on a technical evaluation framework. We used the Lo et al [69] framework, which assesses the suitability of applying blockchain for the requirements of general use cases by posing a set of seven questions and associated decision gates to answer the question of whether blockchain or conventional databases are more suitable for a particular technology use case. These questions include the following:

1. Are multiple parties required?
2. Is a trusted authority required?
3. Are operations centralized?
4. Is data transparency or confidentiality required?
5. Is the integrity of transaction history required?
6. Is data immutability required?
7. Is high performance required?

Below, we assess core blockchain features, such as decentralization, information privacy, immutability, data integration, transaction verification, and network performance, aligned with the suitability assessment and applied to the use case of algorithmic contact tracing (see Table 1).

Table 1. Suitability evaluation of the applicability of blockchain technology to algorithmic contact tracing, with comparison to conventional database applications (CDAs).

Consideration for blockchain use cases	Evaluation	Indicated system architecture
Are multiple parties required?[a]	Yes	Blockchain is preferred, but CDA is also applicable
Is a trusted authority required?[a]	Yes	Either blockchain or CDA
Is the operation centralized?[a]	Inconclusive	Possibly CDA, as it inherently supports centralized operations
Is transparency required?[a]	No	CDA
Is transaction history required?[a]	No	CDA
Is immutability required?[a]	No	CDA
Is high performance required?[a]	Inconclusive	Possibly CDA, as it can generally achieve higher throughput
Is integration with other systems required?	Yes	Either blockchain or CDA
Is decentralized data validation required?	No	CDA
Is high data reliability required?	Yes	CDA, as it can generally provide higher reliability of data without need for on-chain and off-chain approaches needed for blockchain

[a]This consideration is based on the framework proposed by Lo et al [69].

Multi-Party Decentralization

The first question Lo et al [69] raise in their framework is whether a use case requires multiple parties to be involved and, if so, whether a trusted authority is required and whether that trusted authority is decentralizable. In this context, assessing whether there is a need to operate a multi-party decentralized

authority on a public or private blockchain is the first topic that needs to be addressed. Public blockchains were conceived as a design paradigm that is effective in an adversarial environment in which no central trusted party exists, and where potential malicious writers operate on the same hierarchical level as honest ones [11]. In this sense, public blockchains constitute fully decentralized networks that do not require a single trusted authority to validate transactions. Private blockchains introduce some variation to this paradigm by limiting who can access a network and, in the case of private permissioned blockchains, by limiting who can participate in the consensus protocol on the network. Hence, private blockchains, and iterations of consortium blockchains—where a single entity or group controls access to the blockchain—inherently exhibit a lower degree of decentralization. Still, either paradigm can only exploit its respective strengths where there is distrust between those who write the data and where trusted third parties are absent [70].

The environment in which algorithmic contact tracing is conducted, however, is very different. Even though it is a multi-party environment, it requires a trusted authority (Question 2) to be involved in the validation of critical public health data, particularly in the context of addressing a pandemic. Decentralizing the role of the trusted authority may not bring with it any added benefit. For example, a multi-party public blockchain network, where patients have the same rights and responsibilities—including access to and validation of data—as medical practitioners and health authorities, is not optimal for case detection and investigation, as other potential nodes participating in the blockchain may inherently be less trustworthy. Specifically, contact tracing is generally carried out in an environment with clear hierarchies, expertise, and legal mandates that national authorities lead [56]. Authorities also supervise the reporting of case numbers to other local, national, and international organizations and develop necessary calculations based on the epidemiology of the disease to assess the risk of transmission associated with the date and duration of contact with an infected individual. The hierarchical nature of this public health use case becomes particularly evident when considering the possibility of intervention by law enforcement against individuals who do not comply with public health measures [71]. Health authorities are, therefore, in control of virtually all of the factors contributing to the technical success of an algorithmic contact tracing regimen, fundamentally making it a centralized problem requiring a trusted authority and centralized operation (Question 3), which may make it more suitable for conventional information management systems. Those systems commonly consist of infrastructure built around relational database management systems and application settings [72] that employ access control mechanisms as mandated by legislation and regulations [73].

Information Privacy

Algorithmic contact tracing, while having the potential to be an effective tool for controlling disease transmission [74], has also been characterized, fairly or unfairly, as a potent mass surveillance tool, leading to the fear of the normalization of state-run electronic surveillance [32,75-78]. This can be explained by the nature of the data needed for algorithmic contact tracing, which, as discussed earlier, can manifest as location or contact data. Clarke and Wigan [79] discuss why location data are particularly vulnerable by identifying specific dangers that arise from their collection. Among other factors, they discuss psychological harm through embarrassment, the danger of profiling and suspicion generation through the discovery of behavior patterns, as well as social, cultural, scientific, and economic harm arising from the knowledge or suspicion of being watched [79]. While an in-depth debate of these issues is beyond the scope of this viewpoint, we discuss the influence of blockchain on information privacy by comparison to conventional, centrally managed contact tracing systems. This topic aligns with the blockchain suitability framework's question that is focused on the tension between weighing the benefits of enhanced transparency against the needs of such systems to maintain confidentiality (Question 4) and the impact of these decisions on data governance and network performance.

When operated on a public network, blockchain poses significant challenges for engaging with privacy-sensitive data, including protected health information. While proposed blockchain-based systems for contact tracing commonly address the privacy of tracing data through cryptographic protocols [25,31,32,34,35,37,38], their effectiveness in an adversarial environment has to be approached with concern for three reasons:

1. Cryptanalysis can bring to light deficiencies in cryptographic protocols previously believed to be secure, potentially revealing data that were believed to be protected from attackers [80].
2. Even protocols that apply data hygiene diligently by "minimizing or eliminating personally identifiable data of...subjects" [81] and appear unproblematic with regard to privacy might be vulnerable to abuse by methods not yet known, potentially through correlation with data from other sources not yet considered [82].
3. The cryptographic integrity of today's blockchain protocols is threatened by methods of quantum computing [83].

It is, therefore, inadvisable to make any data related to contact tracing, even if considered harmless or undecryptable by today's methods, available beyond completely trustworthy parties that have a legitimate *need to know*, irrespective of whether data are stored in a conventional or decentralized system.

When operated as a private network, blockchain systems generally have a weak negative effect on information privacy: while more finely grained controls of data access in blockchain are possible through permission structures [84], typically, all nodes in a private blockchain network have visibility of network-wide data. Storing only a hash or a similarly obfuscated datum on-chain and keeping sensitive health-related or individually identifiable data off-chain, including approaches that use off-chain blockchain storage and computation, can improve confidentiality. However, this requires the application of appropriate hash algorithms and randomization techniques [85]. Moreover, obfuscation can diminish the utility of said data and can inhibit network performance, including when data are encrypted [9,69]. Though privacy-preserving approaches to managing health care data leveraging different

combinations of off-chain and on-chain storage are possible, their application requires careful design and mapping to appropriate legal and privacy frameworks specific to particular health care use cases and types of data [9]. Given the highly sensitive nature of contact tracing data, confidentiality considerations appear to outweigh the benefits of blockchain-mediated distributed trust and transparency.

Data Integrity and Immutability

An original principle and key value proposition of blockchain systems is their ability to provide data integrity and immutability through creating provenance by linking of transaction blocks [11], which means that data appended to the blockchain cannot be deleted or changed trivially and can, therefore, be considered final in most circumstances [86]. While alternative designs providing mutability have been proposed [87], the applications discussed here consider blockchain as a near-immutable technology and emphasize this quality. This aligns with key decision points in the assessment of suitability for use cases (Questions 5 and 6). Immutability has practical disadvantages in an algorithmic contact tracing context since data cannot be expunged after the incubation period. This means that contact records that no longer serve the purpose of enabling contact tracing may still be present in such systems, potentially threatening the privacy of those that reported them or negatively impacting blockchain system performance (Question 7).

Further, proposed applications commonly embrace the *tamper-proof* nature of contact tracing data on the blockchain. This is largely due to the abstract threat of an attacker tampering with tracing data or the risk of having a trusted authority as a single point of failure. However, in the context of digital contact tracing, data integrity and immutability are of less concern than accuracy and correctness, which are decisive factors for predicting chains of transmission. By their nature, data on confirmed cases should come from trusted centralized sources (eg, health authorities). Therefore, the need to establish data provenance by ensuring the integrity of the transaction history through establishing consensus system-wide is rendered of low importance. Unlike other health care use cases, such as enabling enhanced track and trace of pharmaceuticals in the global supply chain, contact tracing data are not a physical asset that requires tracking changes to its access, ownership, and transfer [88].

As discussed, common blockchain protocols aim to achieve immutability of data recorded [89] and, should the need for correcting existing records arise, address it by appending updated records to the blockchain. This stands in contrast to centralized data storage systems in which records can simply be deleted or corrected. Consequently, data hygiene is hard to achieve in blockchain-based algorithmic contact tracing systems, as those might retain tracing data for longer than medically necessary, simply because the technical capabilities to delete them are not given. Incorrect or inconsistent testing results, or duplicates occurring during integration and consolidation of contact tracing data from different jurisdictions and agencies, are equally harder to correct in an immutable setting [69].

Performance

Performance (Question 7) is recognized as one of the major challenges for real-world implementation of blockchain systems [90]. This can be attributed to challenges associated with their scalability [91], particularly in the context of modulating between on-chain and off-chain storage and computation [9]. Although scale has been achieved in some blockchain applications in the financial sector by applying partitioning [92] or second-level protocols like *side chains* [93], performance may be negatively impacted by the need to achieve consensus among network members during record creation. Achieving consensus is a complex problem to which different blockchain protocols offer different solutions with varying performance characteristics [94]. In the context of algorithmic contact tracing, throughput (ie, the number of transactions that can be executed per unit of time) can be considered the most relevant approximation of overall performance. What all consensus protocols have in common is that coordination among nodes or members is required, which imposes penalties on throughput in exchange for distributed networks of shared trust. Penalties are particularly severe on major public permissionless blockchains, where data validation and replication are subject to *proof-of-work* or *chain-based proof-of-stake* consensus protocols that are characterized by allowing a throughput of only tens of transactions per second [95].

For example, while permissioned blockchains can provide significant performance benefits over their permissionless counterparts [96], achieving around 1000 transactions per second in some common configurations [97], they are still inferior to traditional replicated databases, particularly when multi-leader strategies with low consistency levels are applied, as these can support throughputs above 15,000 operations per second even under challenging workloads [98]. Therefore, traditional database systems can more effectively address the use case of contact tracing in which data validation, where necessary, can be performed centrally by the appropriate authority. Throughput is critical in the context of algorithmic contact tracing infrastructures, especially where vast populations generate large volumes of contact data rapidly and where privacy requirements will inevitably require off-chain storage and computation. Despite the lack of a standardized workload that would be necessary to conclusively answer this question, it can be speculated that private blockchains may have the capability of handling contact tracing data volumes, at least on a regional scale. Nevertheless, the fact that they do not provide a throughput benefit over traditional database systems minimizes their suitability from a performance perspective.

Other Evaluation Considerations

In addition to the evaluation based on the framework proposed by Lo et al [69], further aspects are relevant for assessing blockchain's suitability for enhancing algorithmic contact tracing. These aspects include data integration, transaction verification, and data reliability as discussed in this section.

The further processing of data gathered via algorithmic contact tracing is largely a problem of data integration (ie, one of combining tracing data with data from different sources, for example, diagnostic data from COVID-19 testing centers and

clinical data from EHRs). Here, blockchain can provide benefits by defining a standardized format for transaction data payloads and standard processing logic via smart contracts. Efforts to address data integration are underway, as exemplified by emerging standards at the intersection of blockchain and pandemic and epidemic surveillance [99]. There are, however, challenges concerning the integration with existing health record management systems, such as the cost of change incurred [100], ensuring regulatory compliance of an integrated information technology environment [101], dealing with privacy and confidentiality policies specific to health information (eg, implications of the Health Insurance Portability and Accountability Act in the United States [102] and the General Data Protection Regulation in the European Union [103]), or the immaturity of proposed standards that is detrimental to achieving interoperability [104].

Smart contracts [14,105] constitute agreements that are executed without the involvement of the concerned parties as part of a blockchain protocol. They are a key component of many distributed applications and can be implemented in various programming languages following different paradigms that come with various security features [106]. The common element is that they allow application developers to encode the logic that governs what constitutes a legitimate transaction on the blockchain. Such logic can validate endorsement policies and rules concerning data integrity, thereby ensuring the added content's correctness. Rules around data audit and system access that in centralized systems are commonly enforced by role-based access control mechanisms [107] could also be executed through smart contracts [108]. Conceivably, in the case of a contact tracing app, smart contracts could be developed by a trusted vendor and audited by a credible authority. Further confidence in its correct execution could be gained through formal verification [109]. Still, even in a flawless implementation, smart contracts can only be exploited partially here. While they provide value as a means of ensuring that confirmed case data originate from trusted sources and have not been tampered with, most contact tracing data are user generated and based on signals from outside of the system (eg, pseudonyms of devices in close proximity or geographic locations). For such data, a smart contract differentiating between a legitimate data set and an illegitimate one can, at best, be heuristic. This diminishes the usefulness of the transaction verification capabilities provided by blockchain technology.

Data reliability can be considered essential in contact tracing, where a loss of recent contact data could lead to participants at risk of infection going unnotified. Nodes on a public blockchain network can leave and join at will without risking data loss. Commonly, data are fully replicated between existing nodes and those who join the network. This technique allows for high degrees of redundancy, especially on public blockchains where the number of replicating nodes can be very large (eg, up to 23,000 in the case of Bitcoin [110]). Private blockchain deployments can run in arbitrary topologies, which makes the degree of redundancy they provide contingent on the configuration chosen by the designer of the system. Redundancy positively influences availability, as clients can select an alternative replica to interact with, in case of failure. This is, however, not a unique benefit of blockchain. High reliability can also be achieved via more traditional centralized data replication protocols used in the context of cloud computing, where data redundancy levels are often configurable [111].

Conclusions

Blockchain, although not in productive use in this context, has increasingly been discussed as a technology to support algorithmic contact tracing efforts targeting COVID-19. A question resulting from this trend is whether this technology can replace or enhance the centralized architectures that are operational today. To address this question, we examined blockchain-based contact tracing concepts discussed in the literature. Upon realizing similarities in their design, we derived an archetypal system architecture capturing their common characteristics. Subsequently, guided by an evaluation framework, we explored the potential benefits of this system architecture over conventional approaches to data storage. The results of this suitability evaluation indicate that blockchain-based protocols as currently presented do not provide benefits significant enough to warrant the prioritization of their implementation. This is primarily due to the incongruity between the centralization of organizational and administrative processes surrounding contact tracing and the decentralized nature of blockchain technology. Further technical arguments in support of this result are concerns about the impact of blockchain on the privacy of personal data, unclear benefits of blockchain's key features (ie, enhancing transparency, data provenance, and immutability), the challenges around integrating blockchain systems with existing sources of the health dataverse in legally compliant ways, and a lack of performance benefits over conventional information management systems. The result of the suitability analysis is reinforced by the fact that conventional, centralized, algorithmic contact tracing systems are already integral parts of the pandemic mitigation strategies of some of the countries that are most successful in controlling the spread of COVID-19. Instead of focusing on algorithmic contact tracing, future efforts to leverage blockchain technology in the fight against COVID-19 could turn to the assessment of other promising use cases for suitability. Health supply chain management, digital immunization passports, and the management of digital identity in the context of COVID-19 patient journeys are areas where blockchain might be more appropriate, not least because investments in technology infrastructure and stakeholder buy-in are more mature here.

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Authors' Contributions

MP wrote the initial draft of the manuscript. AH, TM, JRB, MTO, and HCR contributed additional content, edits, and references. SDO and ERM contributed edits and references. All authors approved the final draft.

Conflicts of Interest

TM is an employee of S-3 Research LLC, which is a start-up company funded and currently supported by the National Institutes of Health, National Institute on Drug Abuse, through a Small Business Innovation and Research contract for opioid-related social media research and technology commercialization. The author reports no other conflict of interest associated with this manuscript and has not been asked by any organization to be named on or to submit this manuscript. The other authors have no conflicts to declare.

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Abbreviations

ASCLEPIOS: Advanced Secure Cloud Encrypted Platform for Internationally Orchestrated Solutions in Healthcare
EHR: electronic health record

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Original Paper

Community and Campus COVID-19 Risk Uncertainty Under University Reopening Scenarios: Model-Based Analysis

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Abstract

Background: Significant uncertainty has existed about the safety of reopening college and university campuses before the COVID-19 pandemic is better controlled. Moreover, little is known about the effects that on-campus students may have on local higher-risk communities.

Objective: We aimed to estimate the range of potential community and campus COVID-19 exposures, infections, and mortality under various university reopening plans and uncertainties.

Methods: We developed campus-only, community-only, and campus × community epidemic differential equations and agent-based models, with inputs estimated via published and grey literature, expert opinion, and parameter search algorithms. Campus opening plans (spanning fully open, hybrid, and fully virtual approaches) were identified from websites and publications. Additional student and community exposures, infections, and mortality over 16-week semesters were estimated under each scenario, with 10% trimmed medians, standard deviations, and probability intervals computed to omit extreme outliers. Sensitivity analyses were conducted to inform potential effective interventions.

Results: Predicted 16-week campus and additional community exposures, infections, and mortality for the base case with no precautions (or negligible compliance) varied significantly from their medians (4- to 10-fold). Over 5% of on-campus students were infected after a mean of 76 (SD 17) days, with the greatest increase (first inflection point) occurring on average on day 84 (SD 10.2 days) of the semester and with total additional community exposures, infections, and mortality ranging from 1-187, 13-820, and 1-21 per 10,000 residents, respectively. Reopening precautions reduced infections by 24%-26% and mortality by 36%-50% in both populations. Beyond campus and community reproductive numbers, sensitivity analysis indicated no dominant factors that interventions could primarily target to reduce the magnitude and variability in outcomes, suggesting the importance of comprehensive public health measures and surveillance.

Conclusions: Community and campus COVID-19 exposures, infections, and mortality resulting from reopening campuses are highly unpredictable regardless of precautions. Public health implications include the need for effective surveillance and flexible campus operations.

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KEYWORDS

COVID-19; university reopening; community impact; epidemic model; model; community; university; safety; strategy; risk; infectious disease

Introduction

The COVID-19 pandemic has had devastating human, financial, and logistical impacts worldwide, including over 125 million infected and 2.75 million deaths as of March 2021 [1], radical changes to work and life routines, economic recession, and increased social inequities [2-5]. Among many other issues, significant uncertainties exist about the potential safety and consequences of reopening schools [6-9], heightened by

resurgences in infections and mortality and campus × community cross-exposure concerns [9,10]. Although much initial focus was on K-12 education [11-13], similar college and university reopening concerns exist [9,10,14].

As COVID-19 spread uncontrollably during the spring of 2020, nearly all K-12 and postsecondary schools suspended physical classes, with an estimated 50 million elementary students [13] and 19 million college students in the United States [15] shifting to online learning, homeschooling, and remote education, with experiences varied and often lacking [16-18]. Although a few universities decided early in summer 2020 to remain fully virtual for the following academic year, including the largest public university system in the United States [19,20], many schools decided to reopen under various structures. Since then, four events of import have occurred: several additional colleges and universities switched to full or partial online operations for the fall 2020 semester; COVID-19 has resurged in many regions; other schools have committed to opening as safely as possible; and debate has increased as to what best balances education, safety, and economic needs [21-26].

Examples of reopening approaches range from full on-campus operations with contact precautions; hybrid virtual/physical formats with some courses (or class meetings within given courses) taught virtually and others in-person; having only first- and/or second-year students on campus with all others virtual; student choice to take courses physically versus virtually; and (in the United States) accelerated semesters ending at the Thanksgiving holiday to reduce travel-based spread [27-29]. Efforts to limit on-campus exposures include reconfigured classrooms and dormitory spaces, precaution awareness campaigns, hotel room rentals to reduce living density, testing and tracing plans of varied rigor, isolation of returning students, dedicated living spaces for students with positive tests, and other strategies that attempt to reduce density and exposure rates [21,23,27,30-32].

Significant uncertainty, however, exists about the effectiveness of any of these plans [21,23,31,33]. The best current diagnostic tests have variable and poor clinical sensitivity [25,34] and turnaround delays, while incubation from the time of exposure to becoming symptomatic averages 3-5 days [35-37]. Furthermore, an estimated 30%-40% of positive individuals never exhibit symptoms [25,34,35], and on-campus compliance to distancing precautions generally is low [25,30,38,39]. Contact tracing, while helpful, may not work as well for COVID-19 given the above [9,33] and may be further limited in the campus context as students interact with many-fold more individuals (many unknowingly or unknown by name).

These uncertainties have prompted some to question university reopening safety [6,8,14,25,26,31,40], especially in urban university settings with significant geographically dispersed student populations [41]. Others have suggested COVID-19 might catalyze the reinvention of higher education [42-45], including criticisms of prioritizing economics, brand, and survival over safety [22,43,44,46]. The president of Paul Quinn College, by example, stated "Rushing to reopen our society and our schools is a mistake that will ultimately result in hundreds of thousands of citizens falling sick and worse. We should not let our own financial and reputational worries cloud our judgment about matters of life and death" [8]. In contrast, not reopening may have large economic and student development effects [47-49], although perhaps less of both effects compared to not reopening K-12 schools. Not reopening could also be untenable for colleges and universities that were already facing financial strains before COVID-19 emerged [48-50].

Although little empirical data exist on college reopening [40,51-56], experiences of preschool, summer camp, and K-12 programs have been varied [57,58], with some outbreaks traced back to only a few index cases [21]. Social gatherings of college-age students during summer 2020 also have resulted in outbreaks [38,58,59], including events and activities individuals were advised against but participated in nonetheless [30,38]. Despite early uncertainty, increasing evidence suggests student-aged individuals can carry and transmit the SARS-CoV-2 virus [35,58,60,61] and significant between-student spread occurs at college and high school levels [35,58,61] (in contrast to younger K-5 students [35,47,61,62]). The impact of campus opening on spread to the surrounding community, with higher percentages of at-risk individuals, has been less reported on.

Given these combined uncertainties, we developed single and multiple population COVID-19 spread models to investigate the predictability of potential community and campus impacts under various reopening scenarios. The intent is to provide model-based analysis to better inform decision-making at a critical time in the COVID-19 pandemic. Although similar model analyses have extensively studied other infectious disease policies [63-66], there has been little investigation of university reopening and the impact on surrounding communities.

Methods

Model Overview

We developed and validated single and multiple population ordinary differential equations (ODE) and agent-based models of COVID-19 spread within and between defined groups of individuals. The general model logic (Multimedia Appendix 1) was adapted from classic susceptible-exposed-infected-recovered (SEIR) frameworks [67,68] similar to those described elsewhere for many other infectious diseases [63-76]. The single population model describes spread dynamics within one defined population (eg, on-campus students or local community residents), whereas the multipopulation model additionally includes cross-exposure between two or more groups. Multiple change points were included for all parameters to allow for policy or behavior changes when fitting models to historical data.

State variables at time t include the numbers of individuals in population j that are free of and susceptible to COVID-19 ($S_j(t)$), exposed to COVID-19 but not yet infectious themselves ($E_j(t)$), COVID-19–positive and infectious to others ($I_j(t)$), recovered and not susceptible to reinfection ($R_j(t)$), and COVID-19–associated deceased ($D_j(t)$). Exposed individuals are assumed to have a small chance (p) of warding off an infection before becoming infectious. Recovered individuals

are assumed not able to be reinfected within at least a 16-week (one semester) time frame [37,77]. Each state variable is updated numerically at each time increment (set here to 0.01 days) based on its previous value, values of other state variables at the previous time step, and the equations governing their interdependent relationships, with this process continuing iteratively for 16 weeks.

For example, the number of individuals in the susceptible population ($S_j(t)$) is decremented by the number of newly exposed individuals ($S_j(t) \cdot expo_j$) and increased by the number who previously were exposed but did not develop infections, ($E_j(t) \cdot expr_j$), where the daily exposure rate $expo_j$, the average risk of transmission multiplied by the average number of contacts per day, is back-computed from the basic reproduction number R_0 (average number of new infections per infected individual) and recovery and mortality rates, and the recovery rate of noninfectious exposed individuals $expr_j$ is the inverse of the corresponding recovery time $t_{rec,\ nonj}$.

In turn, the number of exposed individuals is increased by $S_j(t) \cdot expo_j$ and decremented by the number who develop infections ($E_j(t) \cdot infe_j$), where the daily infection rate $infe_j$ is the ratio of the probability of becoming infected upon exposure $p_j$over the average incubation time t_{incj}. Infected individuals either recover or die at rates of $infr_j \cdot I_j(t)$ and $mort_j \cdot I_j(t)$, respectively, where the daily recovery and mortality rates are the inverse of the average recovery time $t_{rec,\ incj}$ and the ratio of the overall COVID-19 case fatality rate for that population (CFR_j) over the average time from infection until death t_{i2dj}, respectively.

The governing rate change dynamics for each state variable at each time step during numeric evaluation thus are the following:

$S_j(t)$ (susceptible; + not-infected/infectious (nor immune) after exposure – new exposures due to within-population and between-population contact with infectious individuals):

$E_j(t)$ (exposed; + new exposures – past exposures now infected/infectious – past exposures now not infected/infectious [now susceptible]):

$I_j(t)$ (infectious; + past exposures now infected/infectious – past exposures now not infected – deaths):

$R_j(t)$ (recovered; + infected individuals who recover [with immunity]):

$D_j(t)$ (deceased; + COVID-19–related deaths):

where

(rate at which people transition from susceptible to exposed)

(rate at which people transition from exposed to infected)

(rate at which people transition from infected to recovered)

(rate at which people transition from exposed to recovered)

(rate at which people transition from infected to deceased) and

(sum of all subpopulations in region i at time j)

where $\chi i,j$ = 1 if populations i and j interact and 0 otherwise and p_j = the proportion of exposed individuals that transition to infected (versus recovering to susceptible). The multipopulation models allow for separate parameter values for each population, such as based on their demographics, with a cross-exposure parameter (ri_j) defining the relative rate at which infectious individuals in one population expose susceptible individuals in the other (typically lower than within-population, assuming less interaction).

Parameter Estimation and Model Calibration

Model accuracy was validated using standard methods [65,78-82], cross-validation, and varied state and county empirical data (January to July 2020) exhibiting different epidemic patterns, magnitudes, and timings (Multimedia Appendix 2). Model results closely emulate historical data across multiple settings, with accuracy on par with or exceeding norms reported elsewhere [83-89] and with ≤1 change points generally providing good fits, suggesting good prospective short-term prediction capability.

Model inputs (Table 1) used in the community and campus models were estimated using a combination of published and grey literature, expert opinion, and search-based optimization. For campus inputs with uncertainty, we used Monte Carlo simulations to create 1000 synthetic results across plausible ranges, using the shown most likely, maximum, and minimum values to generate asymmetric triangular distribution random variates. Since little data exist about on-campus spread [21], for exposure rates we used the shown ranges for the average number of infected students divided by the exposed-to-infectious percentage.

For community populations, we further calibrated inputs via a particle swarm search algorithm to minimize root mean square error differences between historical and model-predicted

infections and mortality, running each parameter search 1000 times. For model fits with change points, separate values for all inputs were optimized for each time segment, with state variables at the start of each new time segment set to their values at the end of the prior segment.

Table 1. Model parameters in the COVID-19 campus × community epidemic models, estimated values, literature sources, and ranges used for parameter search and sensitivity analysis. "Rank order" indicates the relative significance of each parameter on campus (community; additional community) outcomes (16-week totals); only statistically significant factors are shown (α=.05).

Parameter	Definition	Lower bound	Most likely	Upper bound	Sources	Rank	
						Infection	Mortality
$R_{0,1}$	Average number of students who become infected by infectious students	0.66	1	3.4	[90]	2 (6; 3)	5 (—[a]; 3)
$R_{0,2}$	Average number of residents infected by infectious residents	0.66	—	3.4	[90], parameter search	5 (2; 2)	— (5; 4)
ri_j	Cross-exposure parameter (campus × community)	0.005	0.008	0.02	Estimated	6 (6; 5)	— (—; 8)
π_1	Proportion of student population initially infected at semester start	0.001	.01	.05	[91-93]	4 (—; 6)	6 (—; 9)
π_2	Proportion of community population initially infected at semester start	0.0016	.01	.016	[94]	— (4; 4)	— (7; 10)
p_j	Proportion of exposed people that become infected	0.5	0.9	1	Estimated	— (7; —)	3 (3; 5)
	Incubation duration (in days)	2	4.5	14	[95,96]	3 (3; 7)	7 (6; 7)
	Recovery duration (in days)	6	14	42	[97-99]	1 (1; 1)	2 (1; 1)
CFR_1	Fatality rate for college population	0.001	0.0092	0.016	[97,100]	— (—; —)	1 (—; —)
CFR_2	Fatality rate for community population	0.01	0.06	0.15	[101,102]	— (5; —)	— (2; 2)
	Number of days from infection until death	14	35	56	[99]	— (8; —)	4 (4; 6)

[a]Not available.

For initial disease prevalence in the local community and among arriving students, we also used expected values and probability intervals from a logistic growth curve fit to historical COVID-19 infection counts, estimating prevalence among arriving students at the start of the fall 2020 semester using a weighted average of prevalence predictions based on home locations. Resulting community and student prevalence ranges were validated against data reported in the media. Positive individuals at the start of the semester were assumed distributed between exposed but not yet infectious (24.3%) and infectious (75.7%) groups based on approximate relative durations that an average infected individual might spend in each state. All model inputs were based on published literature listed in Table 1 or aggregate state and county infection and mortality online data [103] and thus not subject to human subjects internal review board approval.

Reopening Scenario Analysis

Common university reopening scenarios were identified from literature and published surveys [7,19], generally belonging to one of several categories (see Table 2 for examples), which then were used to estimate plausible ranges for R_0 reductions. The most common approaches included primarily or fully in-person (35%), primarily or fully online (32%), and hybrid (19%) [7]. As examples, the University of Washington reopening plan [104] exemplifies a conservative approach, with more than 90% of courses taught online, courses relying on direct interactions (eg, medical and health sciences) taught in person with safety precautions, the majority of student services and advising taking place remotely, and any staff who can work remotely doing so. In contrast, Purdue University illustrates an opposite approach [105], with classes mainly taught on campus with contact precautions until the Thanksgiving break, relying on students to manage their personal safety.

Table 2. Representative examples of US university and college COVID-19 fall 2020 semester campus reopening plans.

Intervention description	Examples	Source	Estimated reduction in R_0 (%)
Remote coursework for classes over 50, testing, contact tracing, health surveillance in dorms	University of Washington	[104,106]	36
Remote option available, social distancing, shortened semester, flexible start dates for international students	Rice University	[107]	25
Face masks, social distancing, limited classes, some coursework online, fewer students living on campus, shorter semester	Stanford University	[108]	33
More online classes, masks, social distancing, testing, health surveillance, sanitizing and washing stations	Ohio State University	[109,110]	30
Some classes online, expanded housing, social distancing, face masks, staggered hours, increased cleaning, testing, tracing	Northeastern University	[32,111]	49
Most classes online except those for which in-person instruction is deemed necessary	California State University	[112,113]	12
Students back on campus for a shortened fall semester as long as they follow Connecticut reopening suggestions	Connecticut State institutions	[114,115]	46

As most reopening plans involve reducing either interpersonal contact or infection spread, we implemented these as multiplicative reductions in the reproduction number R_0, with effect sizes of individual actions estimated via literature estimates and expert opinion. Overall scenarios then were defined with estimated effects on R_0 spanning the base case of no change, small 25% cumulative reductions (eg, Rice University, Ohio State), moderate 50% reductions (eg, Northeastern University, Connecticut State), and 75% reductions as a best-case scenario for comparison, with each scenario coupled with initial student infection rates of 0.1%, 1%, 2%, and 5% based on university reporting.

For each scenario, 1000 model replications were run for campus alone, community alone, and campus × community combined to estimate additional cross-exposure impacts of each population on the other. For the campus × community cases, each of the 1000 community parameterizations were randomly coupled with the 1000 random sets of campus inputs, with the two populations interacting via 1000 random values of the cross-exposure parameter, *ri*, sampled from the range shown in Table 1.

Given that the ratio of campus-to-community population sizes may affect cross-infection results and prevention policies, we assumed three general settings: (1) an urban campus of 10,000 students with 100,000 residents living in the immediately surrounding residential areas or neighborhoods (in which off-campus students tend to reside); (2) a student body of the same size (10,000), but with fewer (40,000) residents living close to the campus; and (3) a smaller number of 2000 students with 40,000 residents living near campus. The first scenario might represent a large university in a major city, whereas the second might represent a large rural university, and the third a smaller undergraduate college in a nonurban setting, although these student-to-community populations (1:10, 1:4, and 1:20) can be extrapolated to other settings with similar ratios.

Monthly and total counts of COVID-19 exposures, infections, and deaths for each population were tabulated and plotted longitudinally. First inflection points (dates of steepest increases) for each outcome, scenario, and population were identified numerically, since in diffusion theory interventions after these points tend to be less effective. To estimate cross-exposure effects, pairwise differences were computed between each of the 1000 campus results and their campus × community counterparts, and similarly between each of the 1000 community results and their campus × community counterparts. For all model results, medians, standard deviations, and 95% probability intervals were computed, with 10% trimming to reduce any extreme outlier replicate effects.

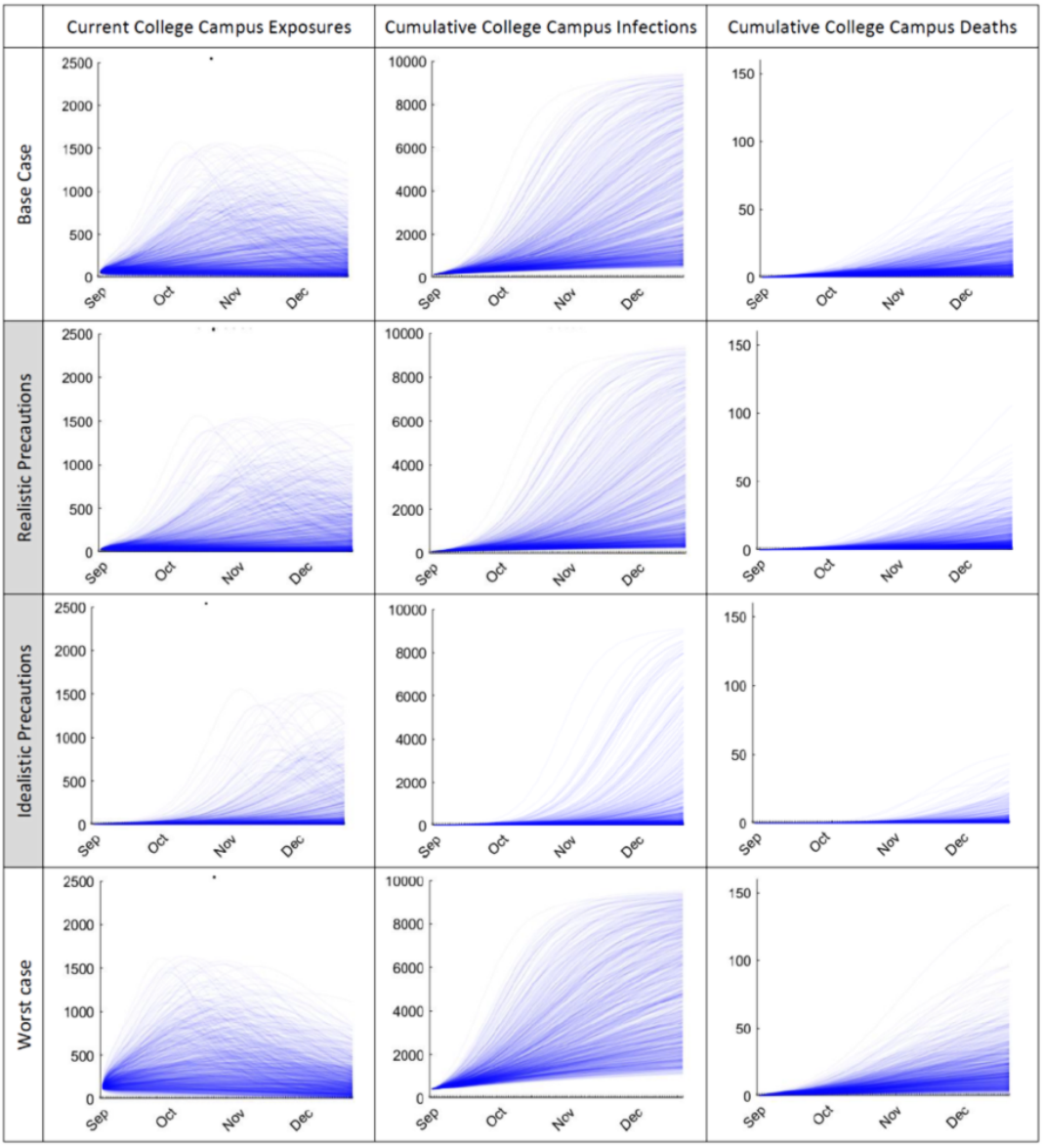
Sensitivity analyses were conducted to identify model inputs to which the mean and variance of results are most sensitive via central composite factorial experimental designs [116] as this could inform policy-making, interventions, and target setting. Results were analyzed using general linear models including linear and pairwise interaction terms for each outcome (replication means and variances of total and additional campus and community infections and deaths), with resulting effect coefficients normalized to their corresponding ranges and ranked according to statistical significance.

Results

On-Campus/Student Impact

Within any given assumptions for COVID-19 prevalence among arriving students and semester initialization precautions, the predicted number of students per 10,000 who might be exposed, be infectious, and die over a 16-week semester could vary by up to 10-fold (Figure 1). By semester end, under the base case (2% arrival prevalence, little returning precautions and/or effectiveness) predicted student outcomes range from 471-9458 infections (median 2286, SD 2627) and 0-123 deaths (median 9, SD 14).

Figure 1. Predicted number of college students per 10,000 who are currently exposed to COVID-19, have been infected to date, and have died to date over a 16-week fall 2020 semester (urban university example). Top row: base case scenario assuming no semester initiation precautions and disease prevalence of 2% among arriving students (equal to national and regional averages). Shaded middle rows (most likely cases): realistic (1%) and idealistic (0.1%) initial prevalence scenarios assuming good or great screening-on-arrival precautions, adherence, and effectiveness. Bottom row: worst case scenario (5% prevalence) assuming little-to-no arrival precautions, compliance, and effectiveness.



The more realistic case (1% arrival prevalence) reduces these consequences to a median of 1332 (SD 2552) infections and 5 (SD 12) deaths, with the steepest increases in exposures and infections typically occurring at midsemester onward (with important implications on geographic spread as students return to their home communities). Although less likely, idealistic (0.1%) and worst-case (5%) initial prevalence scenarios were also considered for comparison, given that epidemic prevalence might change in future semesters. The first would result in a median of 158 (SD 1760) infections and 1 death (SD 6 deaths) by semester end and the latter in 3996 (SD 2485) infections and 16 (SD 17) deaths.

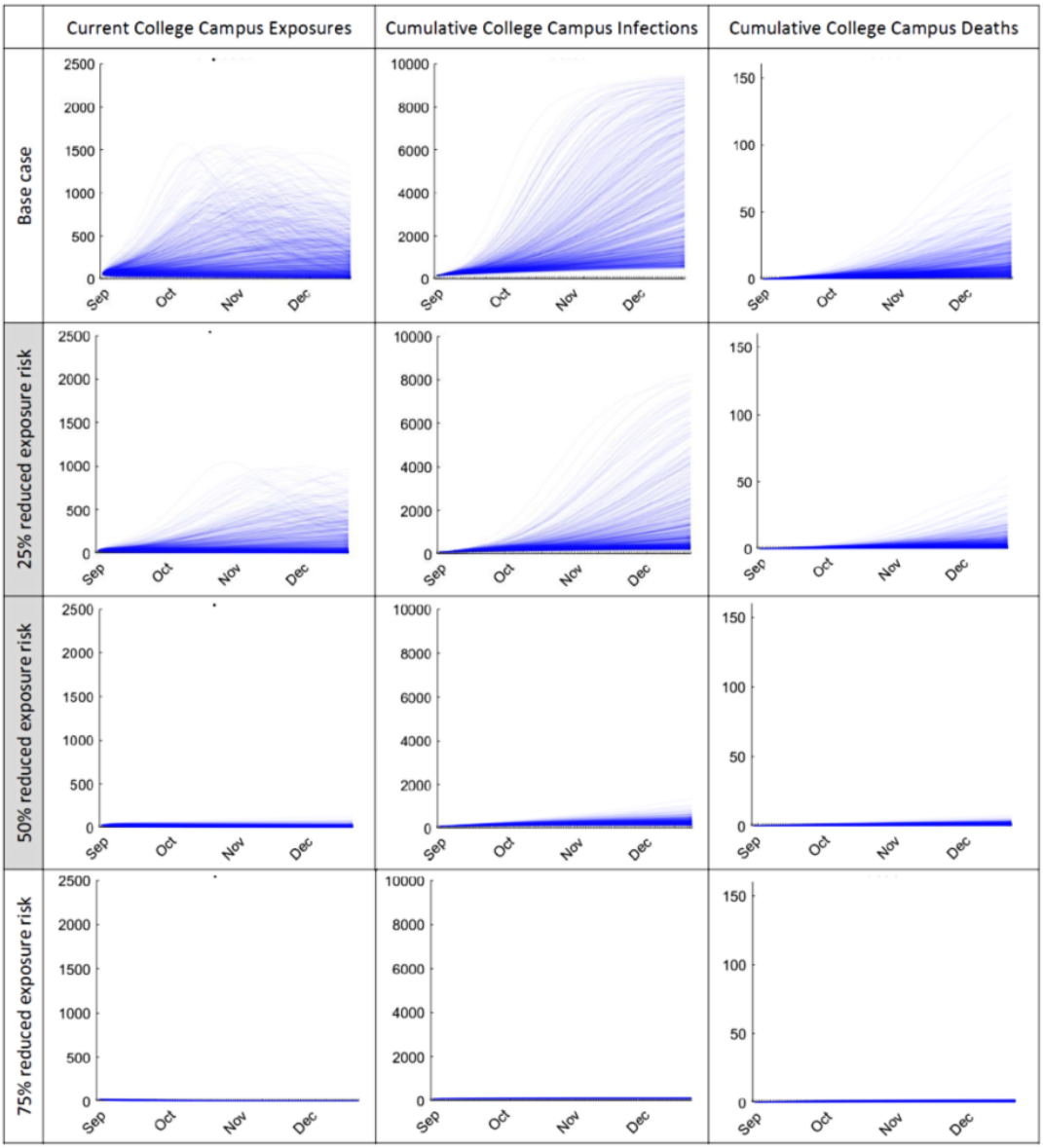
Note that the left-hand plots in Figure 1 depict the current number of exposed people on any given day (with each exposure spanning several days) in order to give an indication of the changing amount of contract tracing and isolation required, as well as the changing population risk, whereas the other plots depict the cumulative number of infections and deaths to date in order to summarize the total public health impact. Under the base case scenario, the number of active student exposures at any given time (eg, for contact tracing and isolation) ranged from 3-1576 per 10,000 individuals (eg, as high as 15% of a student population), with significant implications on resource planning and viability (Table 3). Under the two most likely scenarios, by midsemester the total number of infections might be as high (mean plus one standard deviation) as 810 per 10,000 students (with 4 deaths) or as low (mean minus one standard deviation) as 782 per 10,000 students (with 0 deaths).

Table 3. Predicted median number of monthly COVID-19 exposures, infections, and deaths per 10,000 students during fall 2020 (northeast US urban university example). Values in parentheses indicate 95% probability ranges.

Scenario	September			October			November			December		
	Exposure	Infection	Mortality	Exposure	Infection	Mortality	Exposure	Infection	Mortality	Exposure	Infection	Mortality
Base case	474 (175-1840)	318 (146-1181)	1 (0-3)	708 (160-4731)	510 (131-3561)	2 (1-11)	925 (124-3532)	685 (105-2946)	3 (0-16)	638 (74-1934)	522 (63-1576)	2 (0-12)
Realistic arrival precautions	245 (89-1011)	163 (74-639)	1 (0-2)	392 (84-3723)	278 (68-2777)	1 (0-8)	554 (67-4024)	411 (56-3304)	2 (0-14)	504 (41-2279)	389 (36-1874)	2 (0-12)
Idealistic arrival precautions	26 (9-113)	17 (7-69)	0 (0-0)	44 (9-769)	30 (7-476)	0 (0-1)	70 (7-3072)	49 (6-2133)	0 (0-5)	76 (5-2997)	56 (4-2366)	0 (0-8)
Worst case	1084 (415-3613)	744 (353-2398)	3 (1-8)	1377 (354-4623)	1026 (301-3895)	5 (1-17)	1225 (248-2840)	994 (221-2380)	5 (1-19)	624 (122-1406)	537 (114-1214)	3 (1-12)

Similar results occur assuming the various semester precautions summarized in Table 2, corresponding to plausible reductions in R_0 of 25%-50% (Figure 2). In general, current strategies to reduce exposure during a semester appear effective, although under most scenarios a concerning number of students still can become infected or die. Even in the very optimistic case of a 75% R_0 reduction, included for comparison as a hypothetical "best case" scenario, 95-132 infections (median 107) and 1 death per 10,000 students may occur by midsemester, increasing to 97-139 infections and 0-3 deaths by semester end.

Figure 2. Relative effectiveness of reopening and precaution strategies on reducing college campus student COVID-19 exposures at any given date, total infections to date, and total mortality to date per 10,000 students (fall 2020 semester, assuming 1% of students are infected or exposed at the start of the semester, urban university example). Top row: base case from Figure 1 for comparison; shaded middle rows (most likely cases): realistic precaution effectiveness and compliance cases; bottom row: idealistic precaution effectiveness and compliance. Reduced exposure risk refers to reducing R0.



Community Resident Impact

Figure 3 summarizes additional community (blue lines) and campus (red lines) impacts of reopening due to campus × community cross-exposure, assuming the same scenarios described above; for comparison, the top row shows the baseline number of community exposures, infections, and mortality without reopening. Local community impacts (Table 4) of opening with little-to-no semester operation precautions and/or adherence might range from 1-9768 additional community infections (median 158, SD 1131) and 0-491 additional community deaths (median 6, SD 53).

The two more realistic scenarios result in a total of (for 25% exposure reduction) 1-5577 additional community infections (median 56, SD 516) and 0-272 additional community deaths (median 3, SD 24), and (for 50% exposure reduction) 0-464 additional community infections (median 14, SD 45) and 0-23 additional community deaths (median 1, SD 2). For comparison, the hypothetical best-case scenario with 75% exposure reduction results in 0-33 additional community infections (median 2, SD 4) and 0-2 additional community deaths (median 0, SD 0.2).

Figure 3. Additional (red) community and (blue) college campus COVID-19 exposures, infections, and mortality due to community × campus cross-exposure (fall 2020 semester, prevalence among arriving students varied between 0.1%-2%, urban university example). No interaction: total outcomes assuming no interaction between school and community. Base case: additional outcomes due to campus reopening assuming little-to-no campus semester operation precautions, compliance, or effectiveness. Shaded rows (most likely cases): additional outcomes assuming likely and ideal cases for campus operation precautions, adherence, and effectiveness. Bottom row: additional outcomes under a best case scenario assuming very high campus semester operation precautions, compliance, and effectiveness.

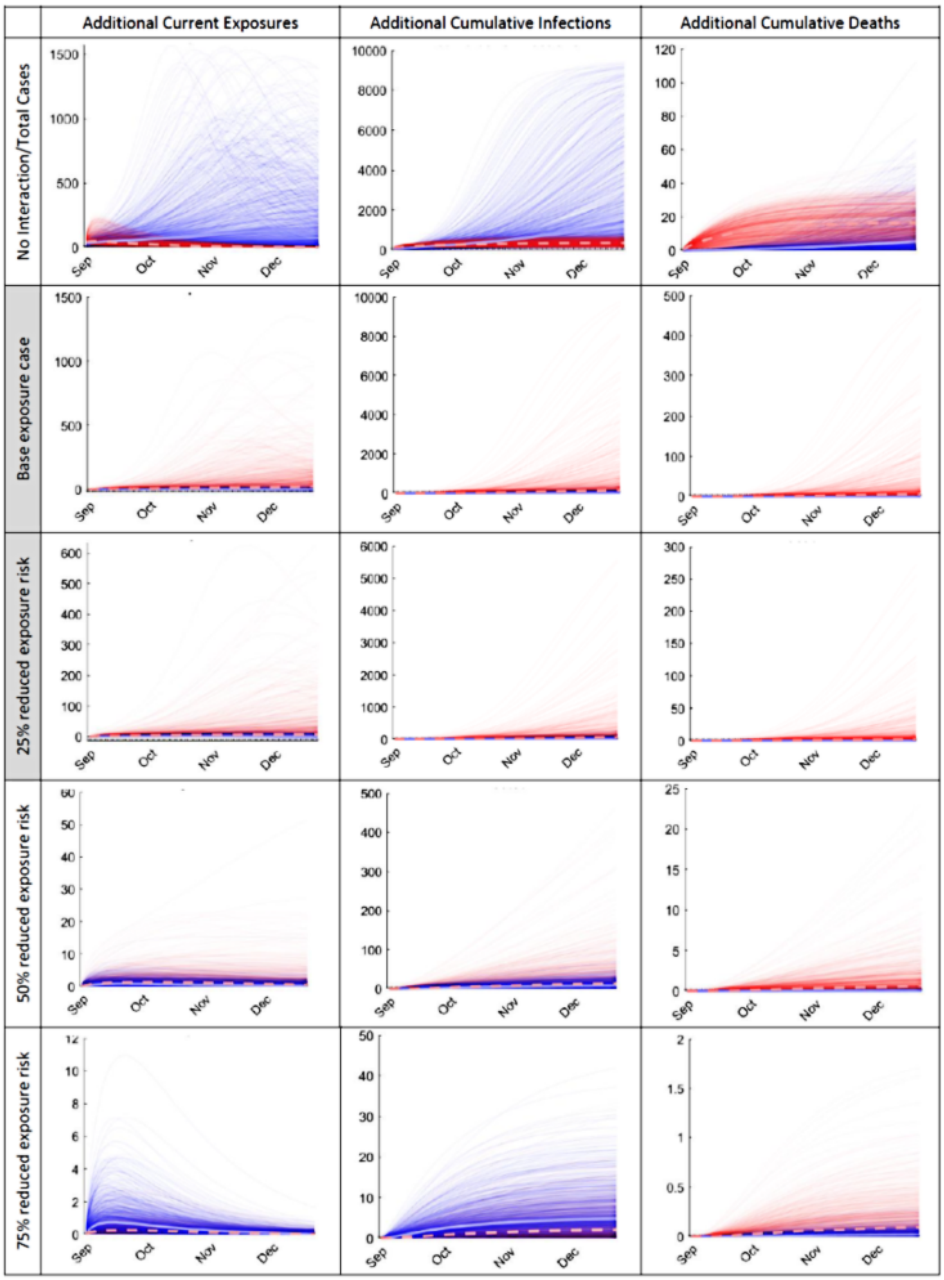


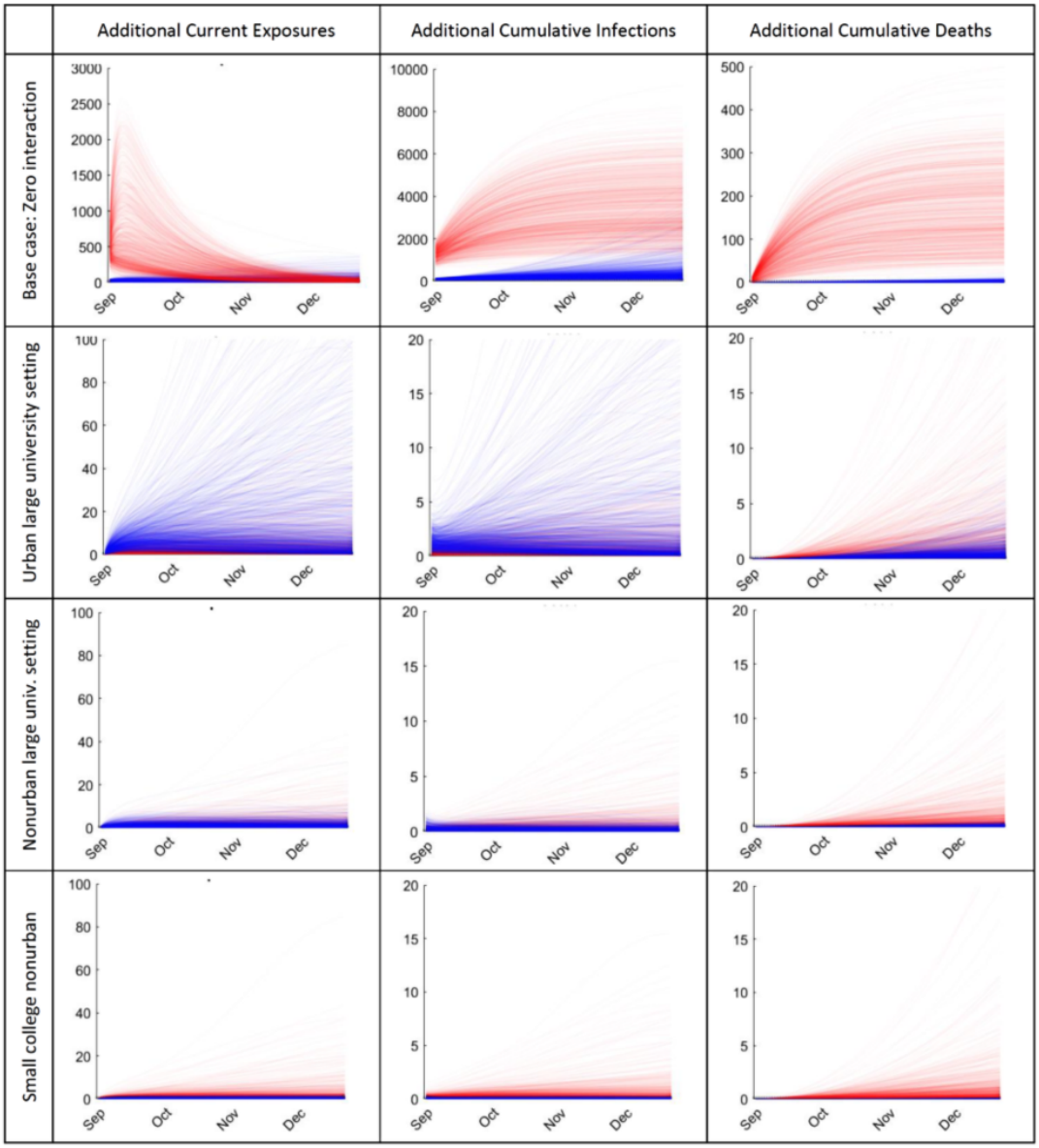
Table 4. Predicted monthly total campus and community COVID-19 outcomes (per 10,000) during the fall 2020 semester. (A) Total community resident outcomes assuming no university interaction, (B) additional community resident outcomes due to campus × community spread, and (C) additional university student outcomes (urban university example). Tabulated values are medians across 1000 replicates; values in parentheses indicate 95% probability ranges.

Scenario (exposure risk)	September			October			November			December		
	Exposure	Infection	Mortality	Exposure	Infection	Mortality	Exposure	Infection	Mortality	Exposure	Infection	Mortality
(A) Community outcomes assuming no university interaction (per 10,000)												
Monthly totals	11 (0-64)	158 (122-362)	6 (4-18)	4 (0-30)	175 (122-455)	7 (4-26)	1 (0-14)	181 (122-486)	7 (4-28)	1 (0-8)	182 (122-495)	7 (4-29)
(B) Additional community outcomes due to campus reopening (total)												
Base case	6 (1-24)	9 (2-26)	0 (0-1)	11 (1-69)	32 (6-126)	1 (0-4)	13 (1-148)	78 (10-415)	3 (0-10)	14 (1-180)	124 (14-755)	5 (1-19)
25% reduced exposure	3 (1-14)	6 (2-17)	0 (0-1)	4 (0-23)	17 (4-56)	1 (0-2)	6 (0-42)	32 (5-147)	1 (0-5)	6 (0-57)	48 (7-263)	2 (0-7)
50% reduced exposure	1 (0-4)	3 (1-7)	0 (0-0)	1 (0-3)	6 (1-16)	0 (0-1)	1 (0-3)	9 (2-23)	0 (0-1)	0 (0-2)	10 (2-29)	1 (0-1)
75% reduced exposure	0 (0-1)	1 (0-2)	0 (0-0)	0 (0-0)	1 (0-3)	0 (0-0)	0 (0-0)	1 (0-4)	0 (0-0)	0 (0-0)	1 (0-4)	0 (0-0)
(C) Additional university outcomes due to campus reopening (total)												
Base case	0 (0-5)	1 (0-10)	0 (0-0)	1 (0-8)	3 (0-30)	0 (0-0)	0 (0-10)	5 (0-56)	0 (0-0)	0 (0-8)	6 (0-76)	0 (0-0)
25% reduced exposure	0 (0-4)	1 (0-9)	0 (0-0)	0 (0-5)	2 (0-22)	0 (0-0)	1 (0-5)	3 (0-36)	0 (0-0)	0 (0-5)	4 (0-46)	0 (0-0)
50% reduced exposure	0 (0-3)	1 (0-7)	0 (0-0)	0 (0-2)	1 (0-14)	0 (0-0)	0 (0-1)	1 (0-19)	0 (0-0)	0 (0-1)	2 (0-21)	0 (0-0)
75% reduced exposure	0 (0-2)	1 (0-6)	0 (0-0)	0 (0-1)	1 (0-11)	0 (0-0)	0 (0-0)	1 (0-13)	0 (0-0)	0 (0-0)	1 (0-13)	0 (0-0)

The corresponding impact of the community on student outcomes is smaller, ranging from 0-390 additional student infections (median 21, SD 38) and 0-2 additional student deaths (median 0, SD 0.2) for the base case to 0-42 additional student infections (median 5, SD 6) and 0 additional student deaths (median 0, SD 0.04) for the idealistic case (75% exposure reduction). The two more likely cases result in (for 25% exposure reduction) 0-279 additional student infections (median 17, SD 30) and 0-1 additional student deaths (median 0, SD 0.1), and (for 50% exposure reduction) 0-115 additional student infections (median 8, SD 12) and 0-1 additional student deaths (median 0, SD 0.06).

To estimate the impact of school size and location, Figure 4 compares results under other student-to-community population sizes, assuming the same arrival prevalence and campus operation precautions, compliance, and effectiveness scenarios. While intuitive differences exist in raw totals, results are similar and scale-invariant after adjusting for population size. For example, multiplying results for the second case of 40,000 residents by 2.5 yields similar curves to those for the first case of 100,000 residents. This suggests that the above results may generalize to other settings and that between-location differences in epidemic patterns (and therefore in public policies to limit spread) likely arise from variations in campus × community interaction, rather than in population ratios.

Figure 4. Impact of school-to-community population sizes on predicted additional community resident (red) and student (blue) COVID-19 current exposures, total infections, and total deaths per 10,000 individuals during the fall 2020 semester, assuming 1% prevalence among returning students and effective campus operations precautions (50% R0 reduction). Urban large university: 10,000 students, 100,000 community residents; nonurban large university: 10,000 students, 40,000 community residents; small college nonurban: 2000 students, 40,000 community residents.



Finally, factorial sensitivity analysis produced the relative parameter rankings shown in the two rightmost columns of Table 2, which follow intuition and serve as further model validation. The most statistically significant factors (main effects) affecting the expected (Multimedia Appendix 3) and variation (Multimedia Appendix 4) in total campus infections were recovery time, $R_{0,campus}$, incubation time, initial prevalence among arriving students, and $R_{0,community}$. Similarly, for total community infections, the most important factors were recovery time, $R_{0,community}$, incubation time, initial prevalence among community residents, and community case fatality rate. Numerous interaction terms were also significant in both cases, as would be expected in such a model.

For additional community infections, no dominant factors that affect either magnitude or variability of outcomes were evident beyond the basic reproduction numbers of each population ($R_{0,campus}$, $R_{0,community}$) and the campus × community cross-exposure rate *ri*. The large number of other statistically significant main effects and interaction terms also underscore the multidimensional challenge of predictably limiting community impact and by extension the importance of effective surveillance and mitigation.

Discussion

Principal Findings

The COVID-19 pandemic continues to be a significant public health crisis, with infections and mortality in many regions meeting or exceeding those in early 2020 before physical distancing and closures were implemented. With many colleges and universities reopening, model-based analyses can help inform these important decisions as well as the degree of uncertainty in the resulting outcomes. Three important results of the present analysis are the following: (1) infections and mortality from campus reopening are highly variable and nearly

impossible to predict with any certainty, (2) reopening campuses can significantly impact local communities even under best-case scenarios, and (3), while few exist, prevention and public health measures that target campus × community exposure could be effective.

While conditions may exist under which reopening is relatively safe to the local community, at present these appear in the significant minority. Our results also agree in general with emerging empirical data from the fall 2020 semester, including reports that COVID-19 deaths in US communities with open colleges roughly doubled from August to December 2020, compared with a smaller 58% average increase in communities without colleges. Genetic sequencing results further suggest that many deaths in college towns were of older people who had contact with infected students [117].

Several important public health implications of our results exist. First, decisions about whether to open in future academic terms or epidemics should be informed by updated model inputs, projections of local conditions, and campus × community public health measures. Second, since any trajectory within the produced intervals could occur, reopening decisions should consider these ranges rather than averages alone. Third, given the wide uncertainties in results from reopening, criteria should be established for rapidly detecting when to tighten precautions. Fourth, contact tracing and isolation capabilities should be ensured to be sufficient to respond to the range of model results.

Like any model-based analysis, results herein have some limitations and simplifications. A common barrier in such models is data availability for input estimation and results validation (hence our search-based approach). The deterministic ODE modeling framework ignores inherent variability and population heterogeneity [118], motivating our use of Monte Carlo analysis, parameter search replicates, and randomly sampled scenarios. Standard model simplifications include limiting the number of populations (eg, one overall homogenous community population), limiting spread to just SARS-CoV-2 (eg, ignoring seasonal influenza, substance abuse [75,76], and co-epidemic impacts), and not time-varying precaution compliance as concerns and vigilance relax or heighten over time. Some scenarios were also included for potential insights rather than being feasible in practice (eg, 75% reduction in R_0, near 100% precaution compliance).

Further work could expand on these results, including addressing some of the above simplifications, rerunning analyses for future semesters using more recent data for model calibration, and considering more heterogeneity in community and student populations. Future work could also seek to determine combined conditions (reduced prevalence, vaccine effectiveness, improved precaution methods, etc) under which outcomes are both safer and more certain. Public health reopening and precaution decisions at citywide or statewide levels also might be examined, such as alternating on-campus semesters or limiting combined student densities, to manage net community risks.

Conclusion

Controlling the COVID-19 pandemic is extremely critical. Mathematical models can offer valuable insights to inform important public health and policy decisions, including potential community and campus impacts from university reopening. The analysis summarized herein suggests that outcomes over a 16-week semester can be highly unpredictable under any set of assumptions or precautions, with three important implications: (1) community impacts from campus reopening are highly difficult to predict in advance, (2) on- and off-campus surveillance and response methods therefore are critical, and (3) additional precautions to reduce impacts of open campuses on local communities appear warranted.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

General logic of campus × community two-population COVID-19 disease spread model. Susceptible: individuals not currently infected but who can become infected; exposed: individuals who are exposed and potentially infected but not yet infectious to others; infected: individuals who are infected and can infect others; recovered: individuals who were infected, survived, and cannot become reinfected nor infect others within the study time frame; dead: individuals who were infected and died from COVID-19 or complications.

[PNG File , 92 KB - publichealth_v7i4e24292_app1.png]

Multimedia Appendix 2

Examples of COVID-19 model accuracy (2020): (A) US state (shown: Massachusetts, California, and Florida) and (B) US county (shown: Dougherty County, GA; Eagle County, CO; and Suffolk County, MA). Normalized root mean square errors, summarized in figure legends, show decent model accuracy results across multiple settings.

[PNG File , 212 KB - publichealth_v7i4e24292_app2.png]

Multimedia Appendix 3
Impact expectation.
[DOCX File , 35 KB - publichealth_v7i4e24292_app3.docx]

Multimedia Appendix 4
Impact predictability.
[DOCX File , 35 KB - publichealth_v7i4e24292_app4.docx]

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Abbreviations

ODE: ordinary differential equation

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Review

Convalescent Plasma for the Prevention and Treatment of COVID-19: A Systematic Review and Quantitative Analysis

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Abstract

Background: The COVID-19 pandemic, caused by a novel coronavirus termed SARS-CoV-2, has spread quickly worldwide. Convalescent plasma (CP) obtained from patients following recovery from COVID-19 infection and development of antibodies against the virus is an attractive option for either prophylactic or therapeutic treatment, since antibodies may have direct or indirect antiviral activities and immunotherapy has proven effective in principle and in many clinical reports.

Objective: We seek to characterize the latest advances and evidence in the use of CP for COVID-19 through a systematic review and quantitative analysis, identify knowledge gaps in this setting, and offer recommendations and directives for future research.

Methods: PubMed, Web of Science, and Embase were continuously searched for studies assessing the use of CP for COVID-19, including clinical studies, commentaries, reviews, guidelines or protocols, and in vitro testing of CP antibodies. The screening process and data extraction were performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Quality appraisal of all clinical studies was conducted using a universal tool independent of study designs. A meta-analysis of case-control and randomized controlled trials (RCTs) was conducted using a random-effects model.

Results: Substantial literature has been published covering various aspects of CP therapy for COVID-19. Of the references included in this review, a total of 243 eligible studies including 64 clinical studies, 79 commentary articles, 46 reviews, 19 guidance and protocols, and 35 in vitro testing of CP antibodies matched the criteria. Positive results have been mostly observed so far when using CP for the treatment of COVID-19. There were remarkable heterogeneities in the CP therapy with respect to patient demographics, donor antibody titers, and time and dose of CP administration. The studies assessing the safety of CP treatment reported low incidence of adverse events. Most clinical studies, in particular case reports and case series, had poor quality. Only 1 RCT was of high quality. Randomized and nonrandomized data were found in 2 and 11 studies, respectively, and were included for meta-analysis, suggesting that CP could reduce mortality and increase viral clearance. Despite promising pilot studies, the benefits of CP treatment can only be clearly established through carefully designed RCTs.

Conclusions: There is developing support for CP therapy, particularly for patients who are critically ill or mechanically ventilated and resistant to antivirals and supportive care. These studies provide important lessons that should inform the planning of well-designed RCTs to generate more robust knowledge for the efficacy of CP in patients with COVID-19. Future research is necessary to fill the knowledge gap regarding prevention and treatment for patients with COVID-19 with CP while other therapeutics are being developed.

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KEYWORDS

COVID-19; SARS-CoV-2; antibodies; convalescent plasma; immunotherapy; prevention; treatment; review; quantitative; therapeutic; immunology; research; literature; knowledge; recommendation

Introduction

SARS-CoV-2, the cause of COVID-19, was declared a pandemic in early 2020 by the World Health Organization [1,2]. This is the third coronavirus to emerge in the past two decades, causing multinational outbreaks and carrying substantial morbidity and mortality [3]. COVID-19 is characterized by a spectrum of symptoms, ranging from mild subclinical infection with self-limiting respiratory tract illness (dry cough, fever, fatigue, difficulty breathing) to severe progressive manifestations (acute respiratory distress, hypercoagulation, hyperinflammation, multi-organ dysfunction, death) in high-risk patients with known comorbidities (advanced age, diabetes, obesity, cardiopulmonary disease) [4,5]. Case-fatality rates range from 4% to 50%, with higher mortality observed in the most critically ill [6]. Growing evidence also suggests that some patients with COVID-19, including those with milder symptoms, will have a prolonged course of recovery including fatigue, cognitive impairment, and cardiopulmonary dysfunction [7]. As such, COVID-19 represents an overwhelming universal health crisis [8], and the burden of this disease continues to threaten lives and livelihoods worldwide [9]. As SARS-CoV-2 and its emerging new mutant strains (which may be associated with an increased efficiency of viral replication, transmission, and virulence in humans) continue to spread globally, international research efforts are being accelerated to identify effective preventive and therapeutic approaches to mitigate its impact [10-12].

The magnitude and urgency of this public health emergency has prompted global scientific collaborations to seek rapid solutions via repurposing of previously approved broad-spectrum antivirals (remdesivir, ritonavir, hydroxychloroquine, interferon) [13,14] and therapeutic doses of corticosteroids (dexamethasone, hydrocortisone, methylprednisolone) [15,16] for high-risk patients while fast-tracking development of vaccines and other novel therapeutics [17]. To that end, great advances in understanding the biology of this new coronavirus and the natural history of the disease have been achieved [18,19]. Moreover, the unprecedented development of multiple COVID-19 vaccines capable of eliciting immunological protection, in less than a year from identification of the causative agent, has been a remarkable success and remains the best hope for ending this pandemic [20].

Despite this incredible progress on COVID-19, many challenges remain post vaccine development including ongoing vaccine deployment, large-scale production and distribution of billions of vaccine doses [21], and uncertainty over the effectiveness of current vaccines against more transmissible new variants [22]. These factors, combined with public hesitation around vaccination, have casted doubt on the likelihood of achieving worldwide herd immunity in the near future [23]. Consequently, other therapeutic strategies to impair virus infection or to counteract further disease spread are still needed, at least until more effective drugs are available or vaccines are distributed and administered to everyone [24].

In the absence of definitive treatment against this new human pathogen, clinical management of hospitalized, severely ill patients remains mainly supportive care, including oxygen and mechanical ventilation, and is based largely on preclinical studies or previous experience with severe acute respiratory syndrome–related coronavirus (SARS-CoV) [25]. Thus, an effective evidence-based therapeutic intervention is urgently needed to reduce the morbidity, mortality, and length of in-hospital stay for patients with COVID-19.

Passive immunotherapy with convalescent plasma (CP), hyperimmune γ-globulin, or artificially produced monoclonal antibodies are beneficial for treatment or prophylaxis of several infections, and these approaches are under investigation as potential therapeutic modalities for the management and prevention of COVID-19 [26]. Passive immunotherapy with human convalescent blood products, in particular CP, is a promising strategy for the prevention and treatment of COVID-19 [27-29]. Although further research is needed to determine the utility of immunotherapy with CP or monoclonal antibodies for the treatment of patients who are symptomatic and potentially for use as postexposure prophylaxis, initial findings in limited clinical trials suggest these interventions are safe and can be effective, particularly when administered early in the course of treatment [29]. Experience suggests that CP therapy could be used as an empirical treatment modality to prevent further progression or promote early recovery in patients who are critically ill with COVID-19 [30,31]. CP has been used safely for decades to treat infectious diseases where no specific treatment is available [32,33]. In the late 19th and early 20th century, CP was given to treat a wide range of viral infections, including diphtheria, polio, measles, mumps, and Spanish influenza A (H1N1) [34-36]. Although no randomized trials were conducted, a retrospective meta-analysis of studies on the use of CP during the Spanish influenza flu pandemic showed a significant decrease in mortality in patients who received CP versus those given plasma from unexposed donors [37]. After World War II, plasma became a valuable pharmaceutical component, which used it for diverse products to successfully treat everything from bleeding disorders to immune deficiencies to hypovolemic shock [38]. Since then, CP has been used in outbreaks of Ebola and other coronavirus diseases including SARS-CoV and Middle East respiratory syndrome–related coronavirus (MERS-CoV) infection with varying efficacy [33]. CP was proven to be efficacious in patients with severe 2009 pandemic H1N1 flu, reducing respiratory tract viral load, serum cytokine responses, length of hospital stay, and patient mortality [39]. CP therapy involves transfusing whole or fractionated plasma, collected from patients that have recently recovered from SARS-CoV-2 infection, to confer passive humoral

immunity in people who are infected or at risk of infection [29,40]. Furthermore, CP therapy has advantages over other proposed treatment: it requires low technology (and therefore it can be produced where required independent of pharmaceutical companies), it is low cost and has strong biological plausibility, and it has potential for rapid development and deployment (production is easily scalable as long as there are sufficient donors) [41-43]. Accordingly, on March 24, 2020, the Food and Drug Administration (FDA) approved the use of CP therapy as an emergency investigational new drug to treat patients with serious or immediately life-threatening COVID-19 infections [44]. Subsequently, on August 23, 2020, the FDA issued an Emergency Use Authorization (EUA) for CP for treating COVID-19 [45]. According to the FDA regulation, the plasma must be collected from recovered patients who can donate blood, have had no symptoms for 14 days, and have had negative results on COVID-19 tests. Both single-donor and pooled immuno-globulin products currently prioritize collection of convalescent donor plasma with high levels of neutralizing antibodies. Based on the preliminary data from clinical trials and considering the United States National Institute of Health and FDA recommendation, remdesivir and CP are the most promising potential for COVID-19 treatment [46]. CP for treating COVID-19 is accessible via the regulatory pathways (investigational new drug regulatory pathway). Another is expanded access, also called “compassionate use” emergency Investigational New Drug Application (an investigational medical product), to treat patients [47]. It should be noted that, currently, Regeneron’s REGN-COV2 and Lilly’s LY- CoV555, both of which are cocktail therapies comprising receptor binding domain (RBD)–reactive antibodies, have also been granted EUA for COVID-19 by the FDA [48,49].

On the other hand, systematic reviews have been conducted for current medications that have been used for the treatment of COVID-19. A comparative analysis of three treatment modalities for COVID-19, chloroquine and hydroxychloroquine, CP, and remdesivir, found that each modality had both favorable and unfavorable characteristics, but none showed clear evidence of benefit for early outpatient disease or prophylaxis; in particular, chloroquine or hydroxychloroquine is no longer a viable option [50], while CP therapy appeared to show clinical advantages for inpatient use [14]. Moreover, meta-analysis of the safety and efficacy of various interventions including the three treatments and dexamethasone or lopinavir-ritonavir showed that dexamethasone and remdesivir might be beneficial for patients with COVID-19, but the certainty of the evidence was low to very low, so more trials are needed [51].

Studies are currently underway to evaluate use of CP as treatment for patients with severe COVID-19 and to prevent infection (prophylaxis) in certain high-risk patients exposed to COVID-19. Currently, CP is being given to small numbers of hospitalized patients with severe or life-threatening COVID-19 illness [52]. Several case reports suggest treatment is helpful, but larger studies are still needed. Although there is a lot that is unknown, CP may work best for patients earlier in the disease course [53,54]. Therapy using CP may also be beneficial for prophylaxis against SARS-CoV-2 in individuals who are at high risk; there is considerable interest to leverage CP for frontline health care workers, first responders, other caregivers, and vulnerable individuals with underlying medical conditions [55,56]. This strategy has been previously used in SARS-CoV and MERS-CoV outbreaks [57]. Although the evidence for CP therapy remains inconclusive, preliminary trials for CP suggest that there may be some benefits, and there is growing consensus that CP is an important first-line immunotherapy for emerging viral infections when other specific treatments are not available [58]. Currently, several countries and health institutions are collecting CP for either empirical treatment or clinical trials [55,59]. However, research to date is at a high risk of bias, and randomized control trials are desperately needed to determine the efficacy and safety of this therapeutic option.

There are many ongoing trials and reviews, perspectives, commentaries, and guidelines published every day related to all aspects of COVID-19 CP, ranging from donor selection, plasma collection, testing, and storage to clinical use. In this paper, we sought to review all aspects of CP use for COVID-19, from detection of the level and activity of CP antibodies to appraisal of the quality and meta-analysis of original clinical studies of CP therapy, to characterize the knowledge gap and provide recommendations for future directions.

Methods

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [60].

Search Strategy

We searched relevant databases including PubMed, Web of Science, and Embase from June 19, 2020, for published and unpublished trials with no limitations on starting date, with the terms COVID-19 OR SARS-CoV-2 OR “coronavirus* 2019” AND convalescent plasma/ser*; we continued the search and updated the review during the manuscript preparation until October 22, 2020. Both plasma and serum or sera have been used in the literature. In this review, plasma is representative for both terms.

Data Abstraction

Titles and abstracts were screened to determine relevance and, if deemed appropriate, the full article was reviewed. Additional publications were selected from the cross-references listed in the original papers and from the cited articles. Disagreements were resolved by consensus or with another review author. The same strategy was used for data extraction and study appraisal as described later.

Study Eligibility Criteria

Experimental (randomized controlled trials [RCTs], quasi-RCTs, non-RCTs), quasi-experimental (controlled before-after studies, interrupted time series), and observational (cohort, case-control) studies are eligible if they examined CP or serum for prevention, diagnosis, or treatment of COVID-19.

Review articles were excluded unless they were focused on or directly related to CP (eg, passive immunotherapy) for COVID-19. Papers on antibody detection and immunity were also excluded unless specifically related to CP.

Data Extraction and Study Appraisal

All literature search results were screened independently by two reviewers. The commentaries in support of the use of CP for COVID-19 were considered positive, those suggesting improvements in CP treatment were categorized as neutral, and precautions against CP were determined to be negative. The review type was determined according to a typology of reviews by Grant and Booth [61]. The quality appraisal of included clinical studies was conducted using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool [62]. Specifically, each clinical study was evaluated for the following components: sample selection, study design, identification and treatment of confounders, blinding of outcome assessors and participants, reliability and validity of data collection methods, and withdrawals and dropouts. The overall rate of each study was determined by assessing the six component ratings. Those with no weak ratings and at least 4 strong ratings were rated strong. Those with less than 4 strong ratings and 1 weak rating were considered moderate. Those with 2 or more weak ratings were rated weak.

Analyses

Studies were analyzed separately according to their design (case report, case series, observational, or randomized trials). Clinical and methodological heterogeneities across the studies were assessed by examining the details of the patients, the baseline data, the interventions, and the outcomes to determine whether the studies were sufficiently similar.

For disease severity, severe COVID-19 is a clinical situation in which the patient has dyspnea, tachypnea (respiratory rate≥30 breaths/minute), blood oxygen saturation≤93% on room air, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 PaO_2/FiO_2<300, or lung infiltrates >50% within 24-48 hours on chest x-ray [63]. Life-threatening disease is defined as respiratory failure, septic shock, or multiple organ dysfunction or failure [63].

Case and randomized controlled studies were combined in meta-analyses using Review Manager (Version 5.4, The Cochrane Collaboration). Data were pooled using an inverse variance method and analyzed using a random-effects model, as this approach accommodates clinical and statistical variations. Odds ratios (ORs) and 95% CIs were used as statistical measures for mortality, clinical improvement, and viral clearance as a dichotomous outcome. Mean and SD were the statistical measure used to describe length of hospital stay. In studies that reported data in medians and IQRs, mean and SD were estimated using the sample size in each study arm, the medians, and the first and third IQRs as demonstrated in the method published by Wan et al [64]. Heterogeneity was determined using the I^2 statistic and the chi-square test. High values of both tests (I^2>40%, a significant chi-square value with P<.05) demonstrate high levels of inconsistency and heterogeneity.

Results

Overall Findings

As illustrated in Figure 1, we reviewed 438 titles and abstracts and identified 243 manuscripts relevant to five areas of focus or types: (1) original clinical studies; (2) commentary in the form of letter to the editor, correspondence or editorial, brief communication, opinions, perspectives, and viewpoints; (3) review of the use of CP; (4) protocol or guidance for clinical trials or production of CP; and (5) in vitro testing of CP.

A total of 243 articles were included in this review. As summarized in Table 1, they can be stratified as follows: 64 clinical studies (20 case reports, 31 case series, 11 case-control studies, and 2 RCTs), 79 commentary articles, 46 reviews, 19 guidance and protocols, and 35 in vitro testing of CP antibodies.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. The literature search was conducted on June 19 and updated on October 22, 2020. The screening, full-text review, and extraction were managed online using Covidence. CP: convalscent plasma.

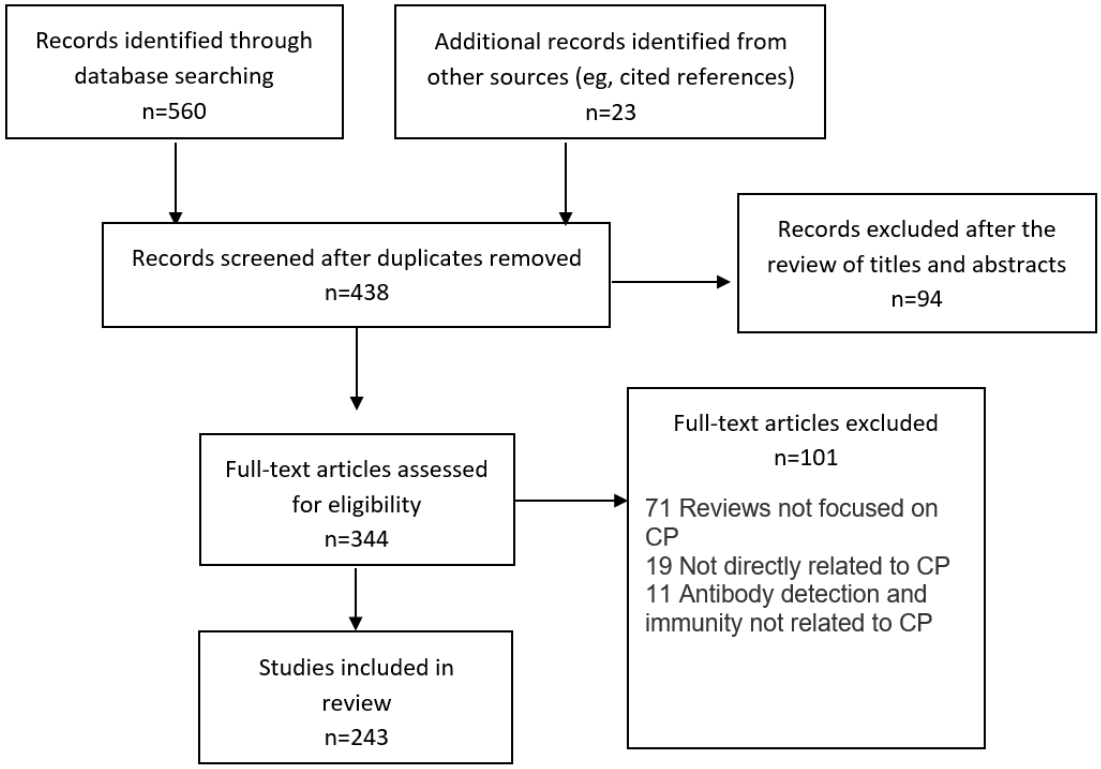


Table 1. Summary of literature.

Article type[a] and group	Articles, n	Summary	References
Clinical studies	64		
Case reports		A single severe or critically ill COVID-19 patient of different ages (6-100 years), either previously healthy or with comorbidities (cancers, organ transplantation, immunodeficiency, hypertension, diabetes, cerebral hemorrhage, cardiopulmary disease, or pregnancy), was successfully treated with one or two doses of CP[b] (150-250 mL per dose; anti–SARS-CoV-2 IgG titer 1:13.3-1:700) in combination with antiviral or anti-inflammatory drugs (favipiravir and hydroxychloroquine, enoxaparin, methylprednisolone, remdesivir, lopinavir or ritonavir, prednisone), antibiotic therapy (azithromycin, ceftriaxone moxifloxacin, piperacillin, tienam), antifungal medication (fluconazole), or prophylactic low-molecular-weight heparin	• Al Helali et al 2020 [65] • Anderson et al 2020 [66] • Bao et al 2020 [67] • Cinar et al 2020 [68] • Clark et al 2020 [69] • Figlerowicz et al 2020 [70] • Grisolia et al 2020 [71] • Hahn et al 2020 [72] • Hartman 2020 [73] • Im et al 2020 [74] • Jafari et al 2020 [75] • Jiang et al 2020 [76] • Karataş et al 2020 [77] • Khan et al 2020 [78] • Kong et al 2020 [79] • Mira et al 2020 [80] • Rodriguez et al 2020 [81] • Soleimani and Soleimani 2020 [82] • Xu et al 2020 [83] • Zhang et al 2020 [84]
Case series		31 clinical studies involving two or more COVID-19 patients of different ages (14-91 years) and disease severity (eg, hospitalized, moderate, severe, or life-threatening), either previously healthy or with comorbidities (cancer, hypertension, immunosuppression, organ transplantation) that were treated with various doses of CP (200 mL to 3 × 200 mL) in addition to supportive care, antiviral therapy, antibiotics, steroids, or anticoagulation treatment.	• Ahn et al 2020 [85] • Abdullah et al 2020 [86] • Bradfute et al 2020 [87] • Diorio et al 2020 [88] • Enzmann et al 2020 [89] • Erkurt et al 2020 [90] • Fung et al 2020 [56] • Gemici et al 2020 [91] • Hartman et al 2020 [63] • Ibrahim et al 2020 [92] • Bobek et al 2020 [93] • Jin et al 2020 [94] • Joyner et al 2020 [95-97] • Liu et al 2020 [98] • Maor et al 2020 [99] • Naeem et al 2020 [100] • Olivares-Gazca et al 2020 [101] • Pal et al 2020 [102] • Rahman et al 2020 [103] • Salazar et al 2020 [104] • Shen et al 2020 [105] • Tremblay et al 2020 [106] • Wei et al 2020 [107] • Wang et al 2020 [108] • Wu et al 2020 [109] • Xi et al 2020 [110] • Ye et al 2020 [111] • Zhang et al 2020 [112] • Zeng et al 2020 [113]
Observational (cohort, case-control studies)		11 cohort, case-control studies of a CP treatment group (6-316 patients) and a matched control (12-1430 patients) of severe or life-threatening COVID-19 patients to compare clinical and laboratory outcomes including all-cause mortality, total hospitalization days, and patients' need for intubation between the two groups.	• Abolghasemi et al 2020 [114] • Duan et al 2020 [115] • Hegerova et al 2020 [116] • Liu et al 2020 [117] • Perotti et al 2020 [118] • Rasheed et al 2020 [119] • Roger et al 2020 [120] • Salazar et al 2020 [121] • Xia et al 2020 [122] • Xiao et al 2020 [123] • Zeng et al 2020 [124]

Article type[a] and group	Articles, n	Summary	References
RCT[c]		Two RCTs of 86 hospitalized and 103 severe or life-threatening COVID-19 patients randomized at 1:1 ratio for standard of care therapy with and without CP. The primary outcome was mortality and time to clinical improvement.	• Gharbharan et al 2020 [125] • Li et al 2020 [126]
Commentary (correspondence, editorial, letter to the editor, opinions, perspectives, viewpoints)	79		

Article type[a] and group	Articles, n	Summary	References
Positive		These are commentaries that supported clinical use and evaluation of CP for COVID-19 treatment based on the unique immunomodulatory properties of CP and historical and current data for its safety and efficacy against coronaviruses including SARS-CoV-2 but suggested limitations, future clinical investigations, and a variety of aspects to be considered for the optimal use of CP for COVID-19 including CP donor selection, CP collection and testing, manufacturing turnaround time, cost and the logistics of storage, distribution, treatment population, and administration timing and dosing.	• Alghamdi and Abdel-Moneim 2020 [127] • Alzoughool and Alanagreh 2020 [128] • Borlongan and Sanberg 2020 [129] • Cantore and Valente 2020 [130] • Casadevall and Pirofski 2020 [34] • Casadevall et al 2020 [131] • Chen et al 2020 [28] • Cheraghali et al 2020 [132] • Gazzaruso et al 2020 [133] • Farhat et al 2020 [134] • Focosi et al 2020 [135] • Franchini 2020 [136] • Franchini et al 2020 [137-139] • Islam et al 2020 [140] • Kesici et al 2020 [141] • Knudson and Jackson 2020 [142] • Kumar et al 2020 [143] • McAllister et al 2020 [144] • Montelongo-Jauregui et al 2020 [36] • Morabito and Gangadharan 2020 [29] • Nnaji et al 2020 [145] • Pau et al 2020 [146] • Perez-Cameo and Marin-Lahoz 2020 [41] • Rabelo-da-Ponte et al 2020 [147] • Roback and Guarner 2020 [148] • Roberts et al 2020 [149] • Rubin 2020 [47] • Sabando Velez et al 2020 [150] • Sahu et al 2020 [151] • Sheikh and Baig 2020 [152] • Sheridan 2020 [43] • Syal 2020 [153] • Teixeira da Silva 2020 [154] • The Lancet Haematology 2020 [155] • Tonn et al 2020 [156] • Wong and Lee 2020 [157] • Yoo 2020 [158] • Zhao and He 2020 [159] • Zhu et al 2020 [160]
Neutral		This group of articles highlighted both pros and cons of CP therapy and alternative therapeutic options (eg, equine polyclonal antibodies) for COVID-19, and raised questions regarding neutralizing antibodies, donor selection, collection, testing and qualification of CP, time frame for transfusing CP to recipients, transfusion volume, quality of evidence for the safety, efficacy, and ethics of clinical trials of CP therapy.	

Article type[a] and group	Articles, n	Summary	References
			• Tamburello and Marando 2020 [161] • Begum and Ray 2020 [162] • Bloch 2020 [163] • Brown 2020 [164] • Casadevall et al 2020 [165,166] • Cunningham et al 2020 [167] • Dhanasekaran et al 2020 [168] • Dzik 2020 [169] • Estcourt and Roberts 2020 [170] • Farrugia 2020 [171] • Fleming and Raabe 2020 [172] • Focosi 2020 [173] • Garraud 2020 [174] • Gniadek and Donnersberger 2020 [175] • Han and Zhou 2020 [176] • Langhi et al 2020 [177] • Lanza and Seghatchian 2020 [178] • Mahase 2020 [179] • Mahase 2020 [180] • Malani et al 2020 [58] • Adiwinata Pawitan 2020 [181] • Prajapati 2020 [182] • Saverino 2020 [183] • Stevens et al 2020 [184] • Tedder and Semple 2020 [185] • Van den Berg et al 2020 [186] • Verkerke and Maier 2020 [187] • Xi 2020 [188] • Zeng et al 2020 [189] • Zylberman et al 2020 [190]
Negative		This group of commentaries suggested that the risks associated with CP use (eg, adverse effects and blood-borne pathogen transmission) outweighed its benefits or other therapeutics for COVID-19.	• Caccamo et al 2020 [191] • Ferreira and Mostajo-Radji 2020 [192] • Joob and Wiwanitkit 2020 [193] • Sanfilippo et al 2020 [194,195] • Wiwanitkit 2020 [196]
Review	46	46 different types of reviews (a total of 10 review types with unique features in terms of prescribed and explicit methodologies) on CP for treatment of virus infectious diseases (eg, SARS[d], MERS[e], EBOV[f], and H1N1) and COVID-19 with safety and efficacy as main outcomes and recommendations. Some reviews also covered other aspects related to CP use, such as SARS-CoV-2 immunology, mechanism of action, CP donor selection, CP collection, pooling technologies, pathogen inactivation systems, banking of CP, timing and dose of CP treatment, patient selection, risk-benefit analysis, and list of ongoing registered clinical trials.	

Article type[a] and group	Articles, n	Summary	References
Rapid review			• Barone and DeSimone 2020 [197] • Majbour and El-Agnaf 2020 [198]
State-of-the-art review			• Brown and McCullough 2020 [199] • Focosi et al 2020 [27]
Scoping review			• Cao and Shi 2020 [200] • Zheng et al 2020 [201]
Review of the evidence			• de Alwis et al 2020 [202] • Fischer et al 2020 [203] • Mucha and Quraishy 2020 [204]
Systematic review and meta-analysis			• Chai et al 2020 [205] • Devasenapathy et al 2020 [206] • Piechotta et al 2020 [207] • Sarkar et al 2020 [208] • Sun et al 2020 [209]
Overview			• Abdollahi et al 2020 [210] • Annamaria et al 2020 [211] • Anudeep et al 2020 [212] • Bloch et al 2020 [55] • Venkat Kumar et al 2020 [213] • Gasparyan et al 2020 [214] • Iftikhar et al 2020 [215] • Li et al 2020 [216] • Lindholm et al 2020 [217] • Murphy et al 2020 [218] • Sayinalp et al 2020 [219] • Subbarao et al 2020 [220]
Mixed studies review			• Pawar et al 2020 [221]
Systematic review			• Bakhtawar et al 2020 [222] • Chen and Xia 2020 [223] • Rajendran et al 2020 [224] • Valk et al 2020 [225] • Wooding and Bach 2020 [57]
Critical review			• Focosi and Farrugia 2020 [226] • Nagoba et al 2020 [227] • Psaltopoulou et al 2020 [228] • Tiberghien et al 2020 [59]
Literature review			• Choi 2020 [52] • Khulood et al 2020 [229] • Chua Vi Long et al 2020 [230] • Ouyang et al 2020 [231] • Piyush et al 2020 [232] • Rojas et al 2020 [233] • Selvi 2020 [234] • Sharun et al 2020 [235] • Sullivan and Roback 2020 [236] • Yigenoglu et al 2020 [237]
Protocol/guidance	19	These are protocols for clinical trials to evaluate the safety and efficacy of CP in treating COVID-19 patients, guidelines or programs for CP donor selection, CP preparation, laboratory examination, storage, distribution, dose, frequency and timing of CP administration, targeted patients, parameters to assess response to the treatment and long - term outcome, adverse events, and CP application in resource-limited countries and in pediatrics and neonates.	

Article type[a] and group	Articles, n	Summary	References
Preparation/production of CP			• Accorsi et al 2020 [238]
Protocol for a nonrandomized trial			• Albalawi et al 2020 [239]
Clinical study and application of CP			• Al-Riyami et al 2020 [240]
Conceptual framework			• Albahri et al 2020 [241]
Expert opinion, survey of group members, and review of available evidence			• Bloch et al 2020 [242]
COVID-19 CP program			• Blackall et al 2020 [243] • Budhai et al 2020 [244]
Study protocol for RCTs			• Chowdhury et al 2020 [245] • Eckhardt et al 2020 [246] • Janssen et al 2020 [247]
Perspective document of the Working Party on Global Blood Safety of the International Society of Blood Transfusion			• Epstein and Burnouf 2020 [248]
Commentary			• Epstein et al 2020 [249]
Guidance for treating early to moderate COVID-19 patients with CP			• Hassan et al 2020 [250]
Initiative for provision of CP			• Ipe et al 2020 [251]
A pilot program of CP collection			• Li et al 2020 [252]
Strategy and experience			• Pei et al 2020 [253]
One arm proof-of-concept clinical trial protocol			• Perotti et al 2020 [254]
An apheresis research project proposal			• Seghatchian and Lanza 2020 [255]
Authority guide by Turkish Ministry of Health			• Yilmaz et al 2020 [256]
In vitro testing of convalescent plasma	35		

Article type[a] and group	Articles, n	Summary	References
ELISA[g] with virus antigens (eg, spike and NP[h] protein sequences) or recombinant ACE-2[i] as substrates		An ELISA could be a high-throughput competitive assay to detect different antibody types against SARS-CoV-2 in serum and plasma from convalescent patients; to estimate the neutralizing capacity of antispike protein antibodies to block interaction with the human ACE-2 required for viral entry; and to identify candidate sera for therapeutic use. A combination of antigenic targets (NP, spike protein, S-RBD[j]) may improve the accuracy of IgG detection in CP donors.	• Amanat et al 2020 [257] • Byrnes et al 2020 [258] • Gattinger et al 2020 [259] • Zhang et al 2020 [84] • DomBourian et al 2020 [260]
Pseudovirus capture assay, VN[k] assay using SARS-CoV-2 strains and Vero-E6 cells		In vitro evaluation of CP potency for COVID-19 treatment could be measured by its binding capacity to the SARS-CoV-2 spike protein and neutralizing activity against pseudotyped and chimeric viruses and authentic SARS-CoV-2, which is useful to identify donors with high titers for CP for COVID-19 therapy. There were individual differences in the antibody level (neutralizing antibody titers <1:16 to >1:1024) and its changes over 12-60 days since onset of symptoms among representative convalescent patients.	• Ding et al 2020 [261] • Ianevski et al 2020 [262] • Schmidt et al 2020 [263] • Wang et al 2020 [264] • Muruato et al 2020 [265]
Immunoassays for anti–SARS-CoV-2 IgM, IgG, and IgA based on SARS-CoV-2 SP		CP collected from adults who met all criteria for donating blood had confirmed COVID-19 by positive SARS-CoV-2 PCR[m] test and completed resolution of symptoms at least 14 days prior to donation showed a wide range of antibody levels. Total anti–SARS-CoV-2 NP antibody strength correlated with time from symptom resolution to sample collection and symptom duration. There was a decline in the IgG level over a short duration of 10 days. RBD[n]-specific serum IgG, IgM, and IgA COVID-19 convalescent patients continued to decline from 28 to 99 days after hospital discharge. Anti–SARS-CoV-2 spike protein IgG antibody strength correlated with age and hospitalization for COVID-19.	• Ragnesola et al 2020 [266] • Yang et al 2020 [267] • de Assis et al 2020 [268] • Dulipsingh et al 2020 [269] • Ikegami et al 2020 [270] • Ma et al 2020 [271]
PCR-based tests		SARS-CoV-2 neutralizing antibodies were detectable as early as 10 days after onset of symptoms and continue to rise, plateauing after 18 days and were not altered by amotosalen and UV-A radiation to inactivate potentially contaminating infectious pathogens in CP. Detectable viral RNA in older COVID-19 patients screened for CP donation even 12-24 days after symptom resolution.	• Danh et al 2020 [272] • Hartman et al 2020 [273]
VN assays based on pseudotyped and live SARS-CoV-2 virus, and anti–SARS-CoV-2 IgM, IgG, and IgA ELISA based on virus antigens and ACE-2		The levels of anti–SARS-CoV-2 IgM, IgG, and IgA and the neutralization capacity of CP showed a wide range and changed over time after the onset of COVID-19 symptoms and declined within the first 3 months following diagnosis, suggesting an optimal time period for CP collection. Both could be associated with donor's age, sex, weight, COVID-19 severity, days between disease onset and plasma collection. There were various degrees of positive correlations (coefficients 0.21-0.87) between the VN and ELISA results. Some commercial ELISA can perform effectively as surrogate assays for predicting neutralizing antibody titres.	• Abe et al 2020 [274] • Beaudoin-Bussières et al 2020 [275] • Benner et al 2020 [276] • Boonyaratanakornkit et al 2020 [277] • Gniadek et al 2020 [278] • Patel et al 2020 [279] • Harvala et al 2020 [280] • Wendel et al 2020 [281] • Zeng et al 2020 [282] • Dogan et al 2020 [283] • Jungbauer et al 2020 [284] • Li et al 2020 [285] • Ni et al 2020 [286] • Robbiani et al 2020 [287] • Salazar et al 2020 [288] • Weidner et al 2020 [289]
Biophysical antibody profiling		CP antibodies can elicit Fc-dependent functions beyond viral neutralization such as complement activation, phagocytosis, and antibody-dependent cellular cytotoxicity against SARS-CoV-2.	• Natarajan et al 2020 [290]

[a]The articles were classified into five types: 64 clinical studies (20 case reports, 31 case series, 11 case-controlled and two RCTs), 79 commentary articles, 46 reviews, 19 guidance and protocols, and 35 in vitro testing of CP antibodies. The details are shown in Table S1 in Multimedia Appendix 1.

[b]CP: convalescent plasma.

[c]RCT: randomized controlled trial.

[d]SARS: severe acute respiratory syndrome.

[e]MERS: Middle East respiratory syndrome.

[f]EBOV: Ebola virus.

[g]ELISA: enzyme-linked immunosorbent assay.

[h]NP: nucleocapsid protein.

[i]ACE2: angiotensin converting enzyme 2.

[j]S-RBD: spike protein receptor-binding domain.

[k]VN: virus neutralization.

[l]SP: spike protein.

[m]PCR: polymerase chain reaction.

[n]RBD: receptor-binding domain.

All clinical studies are therapeutic use of CP focusing on safety and efficacy, and they are further reviewed in the following section. The commentaries cover various aspects of CP, ranging from critiques of clinical studies [131,137,148,163,176,189] and literature review [145,221] to the stability of antibodies in CP [156,291], relevant news [180], and a response letter [164], while a majority focused on the safety and efficacy of CP. Most commentaries were in favor of CP therapy for COVID-19, recognizing the need for more high-quality evidence from large and well-designed clinical trials to show its efficacy, and other issues (eg, CP collection) still need to be addressed. Some commentaries proposed alternative or complementary CP-based approaches to COVID-19 that possess fewer risks [178,182] but may not be immediately available for clinical use. Only a few commentaries put more emphases on the potential risks over benefits of CP therapy [191-194,196].

In a particular correspondence, a metadata analysis of the efficacy of CP treatment based on 9 clinical studies (mostly case series) suggested that CP reduced viral loads (risk ratio 0.13, 95% CI 0.09-0.18; *P*<.001; n=75) and C-reactive protein levels (ratio of mean [ROM] 0.11, 95% CI 0.01-0.86; *P*<.05; n=42), and improved the clinical status of patients with COVID-19 (ROM 0.53, 95% CI 0.36-0.79; *P*<.01; n=149) when compared to baseline (date of CP transfusion) [147]. In addition, the effects of CP on C-reactive protein levels and clinical improvement were not associated with the patient's age and the use of antivirals, antibiotics, and hydroxychloroquine. Several commentary papers and reviews advocated for the rationale of developing fast access to CP collection and treatment of patients with COVID-19 [34,47,59,148,199,229]. Among the reviews, most were descriptive overviews of existing literature and recommendations for clinical use and trial without any search strategies. Few were conducted following the PRISMA guidelines [222,224,225]. It is noteworthy that 1 systematic review and meta-analysis was on the safety and efficacy of CP therapy for other severe respiratory viral infections to provide indirect evidence for CP therapy for COVID-19 [206], and another 2 systematic reviews and meta-analyses were on completed and ongoing clinical studies on the safety and efficacy of CP or hyperimmune immunoglobulin transfusion in the treatment of COVID-19 [207,208]. One review and meta-analysis included 20 studies (1 RCT, 3 controlled nonrandomized studies of interventions, 16 noncontrolled nonrandomized studies of interventions) with 5443 participants [207]. The meta-analysis of 4 controlled studies (1 RCT and 3 controlled nonrandomized studies of interventions) with 339 patients could not support any effects of CP treatment on all-cause mortality at hospital discharge, time to death, or improvement of clinical symptoms at 7 days. The review also investigated the safety of CP based on 14 studies (5201 participants, with 5000 participants from 1 noncontrolled nonrandomized studies of intervention) and found very low-certainty evidence for safety. The review was recently updated, which included 19 studies with 36,081 patients treated by CP, and made the same conclusion [205]. The other review included 7 studies, including 2 RCTs and 5 cohort studies, with a total of 5444 patients [208]. The meta-analysis indicated that CP therapy reduced mortality and increased viral clearance and clinical improvement. It confirmed the safety of CP transfusion with very low incidence of serious adverse events. However, the risk of bias and quality assessment in both reviews indicated that the evidence for the efficacy and safety of CP therapy was of low quality, suggesting the need for a large well-designed RCT. In addition, a survey has been conducted for current registered clinical trials of CP therapy for COVID-19, including a description of their characteristics such as study design, patient populations, outcomes, eligibility criteria for CP donors, CP collection, antibody titer, and CP dose [218].

Protocols, programs, and standards have been developed to select donors and collect, process, characterize, store, distribute, and apply CP to patients in need [238,240,242,250], and to conduct clinical trials [239,246,247,254]. Regional and national programs for COVID-19 CP have been established [243,244] as well as a multi-criteria decision-making frame for both CP donor and receipt selection [241].

Some key findings and implications from the in vitro testing studies of CP antibodies should be considered: a variety of methods have been developed to measure CP antibody titers including gold standard neutralization assay using living SARS-Cov-2 [261,262]; enzyme-linked immunosorbent assay (ELISA) using the antigens derived from the virus, mostly in a microplate platform [257,258] and a few in lateral flow [266], microsphere [267], and microarray platforms [268]; and other methods (eg, polymerase chain reaction [PCR] tests) [272,273]. A number of studies showed a wide range of levels and neutralizing activities of anti–SARS-CoV-2 [264,267,289]. The neutralizing antibody levels declined within the first 3 months following diagnosis, suggesting a short optimum time window for the collection of CP with high neutralizing antibody titers [280]. A significant decrease was also observed in the antibody binding to the spike protein of SARS-CoV-2 and neutralizing capacity of plasma from convalescent donors at 6 and 10 weeks after symptoms onset [261]. The short duration of neutralizing antibody titers within months may have important implications

for immunity and ongoing efforts to deploy CP for prevention and therapy of COVID-19 [165]. There is a significant correlation to various extents between ELISA-measured immunoglobulin (IgG) titer and neutralizing antibody titer [87,257,274,276,278-280,283-285,288,289]. However, the ELISA-determined anti–SARS-CoV-2 IgG did not always inhibit the virus receptor binding [259]. Antibody binding to SARS-CoV-2 spike glycoprotein as measured by pseudovirus capture assay did not always translate into neutralization [261].

Highly sensitive and specific platforms for the detection of anti–SARS-CoV-2 antibodies are becoming increasingly important for evaluating potential CP donors and identifying individuals with seroconversion [292]. Various platforms demonstrate significant correlations with a SARS-CoV-2 plaque reduction neutralization assay, suggesting their use for screening of individuals who have recovered from SARS-CoV-2 infections. Notably, a novel multiplexed solid-phase chemiluminescence immunoassay has been developed and commercially available from Meso Scale Discovery for simultaneous detection of IgG binding to four SARS-CoV-2 antigens (trimeric spike, spike RBD, spike N terminal domain, and nucleocapsid antigen) and the quantification of antibody-induced angiotensin-converting enzyme 2 (ACE-2) and ACE-2–binding inhibition (pseudo-neutralization assay) [293].

In addition to neutralization and immune assays, biophysical and functional evaluation of CP showed that it may have diverse antiviral effects against SARS-CoV-2 beyond neutralization, namely, antibody-dependent cellular cytotoxicity, phagocytosis, and complement activation [290]. Moreover, CP could act not only on the viral infection but also on the antithrombin deficiency to reduce thromboembolic events [133].

Findings of Clinical Studies

As summarized in Table 2, there are considerable heterogeneities among the clinical studies in terms of the populations, the amount of CP received, and a variety of comparators. The CP therapy studies differed in the following aspects: patient demographics (eg, age, gender, and comorbidities), donors' selection (ie, age, gender, diagnosis of SARS-CoV-2 infection and of recovery, and anti–SARS-CoV-2 antibody titer required for plasma donation), plasma collection and biologic qualification (number, volume and frequency of donations, infectious disease markers, and pathogen inactivation), and treatment and disease characteristics (dose and timing of administration, stage of the disease at which to start CP treatment).

Table 2. Summary of original clinical studies of CP therapy for COVID-19. The studies were stratified according to the study design.

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Case report					
Al Helali et al 2020 [65]	A previously healthy male 55 years of age with severe COVID-19	Not reported	About 300 mL CP was transfused over 1 h in addition to other therapeutics: favipiravir, hydroxychloroquine, enoxaparin, paracetamol, diphenhydramine	A significant radiological and clinical improvement in a few days after CP transfusion and negative PCR[b] test for COVID-19 in <48 h and discharged 12 days post transfusion	No significant adverse effects
Anderson et al 2020 [66]	A pregnant critically ill female 35 years of age with COVID-19 and past medical history for type 2 diabetes mellitus, asthma, and class III obesity	Not reported	One unit of CP on the day of admission at ICU[c] and supportive care and therapeutic agents	Discharged on day 14 with no further issues afterward and continuing antenatal care with both primary obstetric office and maternal fetal medicine specialists	Not reported
Bao et al 2020 [67]	A critically ill man 38 years of age infected by SARS-CoV-2 and had cerebral hemorrhage	Not reported	150-200 ml CP of type A Rh positive was given twice 9 days after hospital admission in addition to antiviral and antibacterial treatment	Both SARS-CoV-2 nucleic acid tests were negative (24 h interval) 2 days after the transfusion, and the patient's symptoms gradually stabilized	Not reported
Cinar et al 2020 [68]	A male patient 55 years of age with severe COVID-19 and active myeloid malignancy, disseminated tuberculosis, and kidney failure	Collected using Trima Accel Automated Blood Collection System from a donor who had previously recovered from COVID-19 and met universal donation criteria, anti–SARS-CoV-2 IgG titer 6.6	200 mL of CP on fifth day of symptom onset and another 200 mL of CP at ICU, in combination with antiviral and anticytokine drugs	SARS-CoV-2 was negative, discharged from the hospital with full recovery	No adverse reaction or complication
Clark et al 2020 [69]	Immunocompromised woman 76 years of age with persisting COVID - 19 following therapeutic lymphocyte depletion	Not reported	CP transfused at day 50 after symptom onset over 2 days (200 mL/day) in addition to treatment with lopinavir/ritonavir and prednisone	Rapid improvement in health condition, allowing definitively withdrawing oxygen, apyrexia ensued, and negative SARS-CoV-2 test; discharged on day 69	No adverse events
Figlerowicz et al 2020 [70]	A girl 6 years of age with severe COVID-19	CP inactivated using methylene blue with anti–SARS-CoV-2 IgG at a titer of 1:700	CP transfused once in a 200-mL dose at 5 weeks from the beginning of the disease and treatment with antiviral drugs and immune modulators, antibiotics, and antifungal drugs	SARS-CoV-2 was negative for the next 3 weeks after CP therapy. The hematologic parameters did not improve after SARS-CoV-2 elimination.	No adverse events

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Grisolia et al 2020 [71]	A woman 29 years of age at 24 2/7 weeks of gestation	Not reported	The patient was transfused with 300 mL of CP on day 7 from onset of symptoms and another 300 mL of CP on day 12, and treated with antibiotics, low-molecular-weight heparin, hydroxychloroquine, and methylprednisolone	The patient's clinical condition rapidly improved as shown by normalization of laboratory tests, body temperature, O_2 saturation, and vital signs within 3 days of the second CP transfusion, discharged 13 days after admission	No adverse effects
Hahn et al 2020 [72]	A previously healthy man in his 70s with severe COVID-19 admitted to ICU	Obtained from two blood donors with one being diagnosed with high-level anti–SARS-CoV-2 IgG antibody	A total of 900 ml of CP was transfused at a slow infusion rate on day 31 after admission and treatment with a respirator, muscle relaxants, and antibiotics	The patient became afebrile and was tested negative for SARS-CoV-2 the following day after CP therapy, gradually improved and was weaned from the ventilator and discharged alive from the ICU on day 63	Not reported
Hartman et al 2020 [73]	A man 62 years of age with a history of moderate persistent asthma, sinus bradycardia, chronic obstructive pulmonary disease, and newly diagnosed COVID-19	Not reported	The patient received 217 mL of CP with no other interventions at the time estimated 7 days after onset of symptoms (cough and shortness of breath)	The patient showed rapid improvement in symptoms and electrocardiogram findings, and was discharged 36 hours after the transfusion	Not reported
Im et al 2020 [74]	A man 68 years of age with severe COVID-19	A donor with ABO blood group A (Rh-positive) incompatible with the patient ABO blood group B (Rh-positive)	250 mL of CP at 16 days after symptom onset for 2 consecutive days with mechanical ventilation and ECMO[d], steroid, heparinization, and antibiotic treatment	The patient showed clear improvement in respiratory distress and fever symptoms for 3 days after the CP transfusion; discharged without any detectable virus or other complications	No evident acute adverse effect
Jafari et al 2020 [75]	A woman 26 years of age with a twin pregnancy at 36 weeks and 1 day gestation with confirmed COVID-19	Not reported	One unit of CP was transfused on the sixth day after hospital admission in addition to favipiravir and oxytocine	The patient showed dramatic clinical and radiologic improvements and was discharged 2 weeks after admission with no infection of the newborns	Not reported
Jiang et al 2020 [76]	A kidney transplant female recipient 70 years of age with immunosuppression; severe COVID-19; and a history of chronic bronchitis, hypertension, and hyperlipidemia	Collected by apheresis from a donor who had recovered from SARS-CoV-2 infection for >14 days, with an ELISA[e] antibody titer >1:1000	200 mL CP was administered at day 4 and 11 after admission in addition to treatment with moxifloxacin, piperacillin, methylprednisolone, tienam, and fluconazole	The patient's body temperature became normal and chest CT[f] was significantly better than at admission, and the patient was discharged on day 30	Not reported

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Karataş et al 2020 [77]	A man 61 years of age with a history of ASCT[g] for lymphoma with persistent positive tests for SARS-CoV-2 RT-PCR[h] and fever	Obtained using Trima Accel Automated Blood Collection System from a donor satisfying universal donation criteria and recovered from COVID-19 disease; ELISA IgG titer 13.3	CP transfusion on the 40th day of the infection (dose not specified)	After the CP transfusion, his fever resolved after 3 days. He was discharged from the hospital on the 78th day of hospitalization; viral shedding remained positive as demonstrated by RT-PCR	Not reported
Kong et al 2020 [79]	A mild COVID-19 male 100 years of age with a 30-year record of hypertension, abdominal aortic aneurysm, cerebral infarction, prostate hyperplasia, and complete loss of cognitive function for the preceding 3 years	Collected via plasmapheresis from a donor who had recovered from COVID-19 for more than 2 weeks and had a SARS-CoV-2 S-RBD[i]–specific IgG titer >1:640	The patient received CP twice: 200 ml on the seventh day of hospitalization and 100 ml on the 11th day of hospitalization	Patient's viral load decreased significantly, by a factor of ~18, 24 h after the first transfusion of convalescent plasma and then became undetectable after the second, discharged on day 13 of hospitalization	Not reported
Mira et al 2020 [80]	A male patient 39 years of age with severe COVID-19 and XLA[j], receiving monthly immunoglobulin replacement therapy	IgG antibodies against either the spike or nucleocapside viral proteins with a titer ≥1:320	200 mL, single dose, on day 23 after admission	After 24 h of infusion, fever ceased without subsequent reappearance and with progressive improvement of asthenia. After 48 h of infusion, no detectable virus in qPCR[k] from nasopharyngeal exudate	Not reported
Soleimani and Soleimani 2020 [82]	A woman 30 years of age (gravid 3, parity 2) at her 21 and 2/7 weeks gestation with ARDS[l] caused by SARS-CoV-2 infection	Not reported	CP was administered in addition to lopinavir/ritonavir and azithromycin and early methyl prednisolone therapy	A mild clinical improvement and decrease in inflammatory markers; normal growth of the fetus	Not reported
Xu et al 2020 [83]	A man 65 years of age with severe COVID-19	Collected from two convalescent patients; no details provided	CP was given at a 400-mL dose on day 1 and 2 after admission, and hydroxychloroquine was orally administrated for a week	On day 11 after CP transfusion, temperature returned to normal and mechanical ventilation was withdrawn, the RNA test remained positive in throat swab, and CT revealed severe pulmonary lesions	No apparent side effects
Zhang et al 2020 [84]	A critically ill female 64 years of age with hypertension and diabetes	Collected by apheresis from a male 37 years of age with blood type O at 36 days after symptom onset and 17 days after discharge; CP IgG titer >1:320 by ELISA	200 mL CP on day 17 of hospitalization while receiving invasive mechanical ventilation	The patient did not require mechanical ventilation 11 days after plasma transfusion and was transferred from ICU to a general ward	No adverse event
Case series					

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Ahn et al 2020 [85]	A previously healthy man 71 years of age and a woman 67 years of age with a medical history of hypertension, both diagnosed with severe COVID-19	Obtained with Spectra Optia apheresis system from a male donor in his 20s who had recovered from COVID-19 for 21 and 18 days, respectively, and met the blood donor eligibility criteria for plasma donation. ELISA optical density ratio for anti–SARS-CoV-2 IgG was 0.586 and 0.532 (cutoff value 0.22)	A total 500 mL of CP was divided into two doses and given over 1 hour for each dose at 12-hour intervals after 22 days from the onset of symptoms in case 1 and 7 days in case 2	SARS-CoV-2 became negative in both cases: case 1 underwent a tracheostomy and currently was successfully weaned from the mechanical ventilator; case 2 was successfully extubated and discharged from the hospital on day 24	No adverse reaction occurred after the administration of CP
Abdullah et al 2020 [86]	A male 46 years of age and a male 56 years of age, both with hypertension and severe COVID-19	Collected from a recovered moderate COVID-19 patient after performing necessary investigations for donor plasma (hemoglobin level and viral screen) but not antibody tests	Deteriorated despite supportive care and antiviral therapy: 200 mL of CP at day 3 of hospitalization (day 7 after symptom onset) in case 1; day 10 of hospitalization (day 13 after symptom onset) in case 2	Improve clinically 4 days and 70 h after CP, discharged from the hospital 16 and 21 days after admission with three consecutive negative RT-PCR tests each with at least 24 h apart	Not reported
Bradfute et al 2020 [87]	12 hospitalized COVID-19 patients (8 males and 4 females) with a median age of 52 (range 39-91) years, 9 obese patients, 10 patients in the ICU, and 2 on the general ward	Collected by apheresis from donors ≥28 days after positive PCR test, with complete recovery from COVID-19 and a median of neutralizing antibody titer of 1:40 (range, undetectable to 1:160)	Patients received one unit (200 mL) CP at a median of 8.5 (range 6-16) days after the onset of symptoms and a median 3.5 (range 1-10) days after hospitalization	Temporal increases in neutralizing antibody titers and IgG/IgM levels, gradual decreases in viral loads, with two deaths within 14 days after CP transfusion	No serious adverse events
Diorio et al 2020 [88]	Four critically ill children with COVID-19; 14-18 years; female; varied antibody titer levels pretransfusion	Collected from donors proven positive for SARS‐CoV‐2 by a laboratory test; and either ≥14 days from symptom resolution with a repeat negative test for SARS‐CoV‐2 or ≥28 days from symptom resolution without the repeat test. RBD-specific IgG titer <1:160 to >1:6000	200-220 mL of CP at 7-14 days after symptom onset	1 died; 2 showed no clinical improvement; 1 recovered	No emergent adverse events related to CP infusion
Enzmann et al 2020 [89]	16 critically ill COVID-19 patients with most (12 patients) underlying cardiovascular disease	Not reported	Not reported	In-hospital mortality rate was 31% and median length of hospital stay was 19 (8-36) days	No apparent adverse effects

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Erkurt et al 2020 [90]	26 (8 females and 18 males) severe COVID-19 patients (mean age 67.4, SD 15.5 years)	Collected via apheresis ≥14 days after complete recovery from the eligible blood donors who had mild or moderate COVID-19 with positive antibodies	200 mL of CP was administered at a mean 13.87 (SD 6.5) days after admission in addition to supportive treatment, hydroxychloroquine, azithromycin, and favipiravir	The patients who did not need mechanical ventilation improved with CP treatment, while 6 of 17 patients on mechanical ventilation were dead	No severe adverse reactions
Fung et al 2020 [56]	4 immune-suppressed patients (males: two were aged 42 years and one was aged 62 years; female: one aged 65 years) with or at risk of progression to severe or life-threatening COVID-19	Collected per FDA[m] guidance from donors with confirmed COVID-19 and resolution of symptoms within 14-28 days and a negative PCR test or >28 days without a PCR test; ELISA anti–SARS-CoV-2 spike protein IgG titer >1:400	Approximately 200 mL of CP was transfused at 4-27 days following symptom onset	All patients were clinically improved, with 2 discharged home and fully recovered, and 2 discharged to skilled nursing facilities	No adverse reactions
Gemici et al 2020 [91]	40 consecutive patients (median age 57.5 years and 72.5% male) with severe COVID-19	Collected from eligible blood donors recovered from COVID-19 with negative laboratory results and symptom free for ≥14 days	Patients received a median of 2 (range 1-3) units of CP at median time of 5 days from the diagnosis in addition to antiviral therapy	90% of patients who received CP outside ICU totally recovered at a median of 9 days after the transfusion, and half of the patients treated in ICU were free of mechanical ventilation	No TRALI[n] or severe allergic reactions
Hartman et al 2020 [63]	16 (7 female) severe and 15 (3 female) life-threatened patients	Collected from a local donor recruitment and referral program	Dose and timing not reported	Respiratory support requirements began on or about day 7 following CP transfusion, especially in the severe patients	Not reported
Ibrahim et al 2020 [92]	38 hospitalized, severely (n=16) or critically ill patients (n=22) with confirmed COVID-19 (mean age 63, SD 12 years; 18 female); 31.5% had three or more comorbidities, with 68% having hypertension and 47% having diabetes	Collected by apheresis from adults who were confirmed positive and had recovered from SARS-CoV-2 with negative PCT test for the virus and had total anti–SARS-CoV-2 titer >1:320	ABO-compatible CP was given in two consecutive 200-mL infusions (mean 18.7, SD 9.0) days following symptom onset. Another unit of CP was given to those with undetectable anti–SARS-CoV-2 antibodies.	24 (63%) recovered and were discharged from the hospital, and 14 (37%) died. The survival patients received CP earlier in their course of disease (mean 15.3, SD 6.9 days) and hospital stay (mean 8.4, SD 6.8 days) compared to those who died with mean durations of 24.5 (SD 9.6) days and 16.6 (SD 9.5) days, respectively.	No adverse effects except for a transient transfusion reaction (fever and hematuria) within 2 h of CP infusion in 1 patient

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Bobek et al 2020 [93]	2 critically ill Hungarian patients (males 59 and 72 years of age) with COVID-19, hypertension, and cardiovascular disease	Collected by plasmapheresis from recovered COVID-19 patients who had been asymptomatic for at least 2 weeks, negative PCR tests, and IgG-type antibody detectable by ELISA	3 × 200 mL of CP with the first dose administered on the fourth day of the patient's ICU mechanical ventilation	Both showed improved oxygenation and inflammatory decreased markers, and were weaned from mechanical ventilation within 2 weeks	No severe adverse effects
Jin et al 2020 [94]	3 patients (males 10, 24, and 40 years of age) with XLA, hospitalized for COVID-19	CP containing anti-spike protein titer 1≥:320	Two units of 200 mL ABO-compatible CP were given on days 16, 22, or 44 of illness when there was minimal improvement on other therapies	Various clinical and laboratory improvements including increases in antibody titers; discharged within days after CP transfusion	Not reported
Joyner et al 2020 [95]	5000 hospitalized adults (median age of 62) with 81% having severe or life-threatening COVID-19 and 66% admitted to ICU	ABO-compatible CP	CP dose of 200-500 mL	The incidence of SAEs[o] was less than 1%, and the mortality rate at the seventh day after CP transfusion was 14.9%	Of 36 SAEs, 7 and 11 incidents of TACO[p] and TRALI, respectively, were judged as related to CP transfusion
Joyner et al 2020 [96]	20,000 hospitalized adults (aged 20-80 years) with severe or life-threatening COVID-19	ABO-compatible CP with no minimum neutralizing antibody titer level donated by recently recovered COVID-19 survivors	CP dose of 200-500 mL	141 SAEs classified as transfusion reactions were reported (<1% of all transfusions); 38 thromboembolic or thrombotic events and cardiac events were related to the transfusion. The mortality rate at the seventh day after transfusion was 13.0%.	Of 141 SAEs, there were 36 reports of TACO, 21 reports of TRALI, and 21 reports of severe allergic transfusion reaction
Joyner et al 2020 [97]	35,322 hospitalized patients with (or at risk of) severe or life-threatening acute COVID-19 and a diverse representation of gender, age, weight status, race, and ethnicity	Collected from recently recovered COVID-19 survivors without symptoms for ≥14 days, and the antibody levels in the units collected were unknown at the time.	All patients were treated with at least one unit (~200 mL) of CP with the option to administer additional doses if clinically justified in addition to adjunctive COVID-19 medications	A gradient of 7- and 30–day mortality associated with higher IgG levels in CP and early CP transfusion within 3 days of COVID-19 diagnosis	Reported in Joyner et al 2020 [96]
Liu et al 2020 [117]	3 critically ill male patients with COVID‐19 (42, 56, and 58 years of age; two healthy; one with hypertension)	Collected from COVID-19 survivors who had fully recovered and tested negative for the virus and a total anti–SARS-CoV‐2 IgG titer of 160	Patients were transfused with 200-225 mL CP between 20 and 30 days after disease onset at the critical illness stage in addition to standard care	No therapeutic effect of CP was observed in any of the patients	Not reported

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Maor et al 2020 [99]	49 patients (median age 64.0, IQR 50.5-76.0 years; 35 males) with moderate and severe COVID-19 and comorbidities (diabetes and hypertension) in one-third of the patients	Collected by apheresis procedure from recovered COVID-19 patients eligible for plasma donation and >14 days since the last negative PCR test; neutralizing antibody titer 1:20-1:2560	The first dose of 200 mL CP was transfused at a median of 10.0 (IQR 4.0-14.0) days after PCR diagnosis, followed by a second unit of 200 mL 24 h later, in addition to various standard of care	At day 14 after the first CP dose, 24 patients improved, 9 died, and 13 were ventilated. More patients improved when treated with CP containing higher antibody levels or earlier.	No serious adverse events except that one developed a rash that responded to antihistamine therapy
Naeem et al 2020 [100]	3 kidney transplant recipients with COVID‐19 treated with CP (1 female 65 years of age admitted to the general medicine service and a female aged 35 years and a male 36 years of age in the ICU)	Collected from donors at local and regional blood centers	One or two units of CP were given on day 2, 4, or 7 after hospital admission, in addition to immunosuppressant/ antiviral/antibiotic	All showed clinical improvement and were discharged 9, 16, and 25 days after hospital admission with no evident infectious complications	1 patient experienced acute chest pain and dyspnea but improved over the following 12-24 h.
Olivares-Gazca et al 2020 [101]	10 male severe COVID-19 patients with a median age of 53 (range 27-72) years and comorbidities (diabetes, hypertension)	Obtained by apheresis from 5 donors (2 females) with a median age of 35 (range 24-52) years and two negative PCR tests in a 24-h interval 10 days after the resolution of COVID-19 symptoms	Each patient received 200 mL of ABO-compatible CP and other therapies (eg, steroids or hydroxychloroquine)	Improvement in overall respiratory function and clinical condition over a period of 8 days, with 6 discharged and 2 died	No side effects
Pal et al 2020 [102]	17 critically ill patients (mean age 56, range 24-81 years; 10 males) with COVID‐19 and most patients had multiple medical comorbidities, including 6 with hematological malignancies	Collected from donors 18-56 days following full recovery from COVID-19 with anti–SARS-CoV-2 spike protein IgG titers 1:400-1:6400 as measured by ELISA	A single unit of 200 mL CP was given at an average time of 12 (range 4‐41) days from illness; 3 patients received two units roughly 8 days apart in addition to other COVID-19 treatment and chemotherapy as required	All patients showed a decline in oxygen needs and ventilatory support with most effects seen in patients when CP was administered early in their disease course	No adverse events except a fever during transfusion in 1 patient, resulting in infusion of only 100 mL
Rahman et al 2020 [103]	13 SOT[q] recipients (median age 51, range 20‐75 years; 8 males) with severe COVID-19 and comorbidities (eg, hypertension and diabetes)	Collected from eligible blood donors with anti–SARS-CoV‐2 spike protein antibody titers ≥1:320 as measured by ELISA	All patients received two ABO-compatible units of CP, for a total of 500 mL, at a median time of 8 days from symptom onset and additional therapies (hydroxychloroquine alone or in combination with azithromycin, steroids, anticoagulation, and immunosuppression)	8 patients had de-escalating oxygenation support by day 7 post CP. 9 patients were discharged, 1 still hospitalized, and 3 patients died ~3 months after the CP transfusion.	No apparent transfusion-related adverse reactions

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Salazar et al 2020 [104]	25 patients (median age 51 years) with severe or life-threatening COVID-19 and one or more underlying chronic conditions	Obtained from donors eligible according to standard blood donor criteria, confirmed SARS-CoV-2 infection and symptom free for 14 days, and tested negative for SARS-CoV-2 by RT-PCR; ELISA IgG titer ranged from 0 to 1350	One 300-mL dose of CP at a median time of 10 days from symptom onset and concomitant anti-inflammatory and antiviral treatments, and 1 patient received a second dose 6 days after the initial transfusion	By day 14 of CP transfusion, 19 (76%) patients had clinical improvement and 11 were discharged	No adverse events within 24 h after transfusion. 1 patient developed a morbilliform rash 1 day after transfusion that lasted for several days.
Shen et al 2020 [105]	5 critically ill patients (age range 36-65 years; 2 female) with laboratory-confirmed COVID-19, rapid progression, and continuously high viral load despite antiviral treatment	Obtained from 5 patients who recovered from COVID-19; anti–SARS-CoV-2 IgG titer >1:1000 as determined by ELISA and a neutralization titer >40	ABO-compatible CP was administered at a dose of 200-250 twice (400 mL in total) between 10 and 22 days after admission	Improvement in their clinical status as indicated by declined viral load, body temperature reduction, improved Pa_{O2}/F_{iO2}, and chest imaging	Not reported
Tremblay et al 2020 [106]	24 patients with cancer and severe or life-threatening COVID-19 (median age 69, range 31-88 years; 14 males), some having other comorbidities (eg, hypertension in 15 patients)	Collected via plasmapheresis, spike protein-directed ELISA antibody titers ≥1:320	Two units (250 mL) of ABO-compatible CP were transfused at 3 (IQR 2-7) days from admission in addition to cancer - directed treatment and COVID-19–specific therapies (hydroxychloroquine, azithromycin, remdesivir, and tocilizumab)	Marked variability in both the timing and degree of improvement or worsening of oxygen requirement; 13 discharged; 10 deaths	3 patients experienced febrile nonhemolytic transfusion reactions
Wang et al 2020 [108]	5 critically ill COVID-19 patients (median age 56, IQR 50-62 years) admitted to ICU with a persistent (>30 days) positive nucleic acid test for SARS-CoV-2 and underlying chronic comorbidities, including hypertension and diabetes	Collected from the recently cured patients whose antibody titers were above 1:640	200 mL of cross-matching CP was transfused over 15 min initiated at a median of 37 (IQR 34-44) days from the onset of symptoms. In total, 3 patients received 400 mL and the other 2 received 1200 mL; all received antibiotics, antiviral, and anti-inflammatory agents.	Within 6 days after CP therapy, all patients became negative for two consecutive nucleic acid tests. Additionally, 4-9 days following the CP, 3 patients showed resolution of pulmonary lesion. 2 recovered and 3 died.	No adverse reactions
Wei et al 2020 [107]	2 COVID-19 patients (males aged 50 and 81 years, the latter with type 2 diabetes mellitus, hypertension, and aortic dissection) with long-term positive viral infection	Not reported	One or two 200-mL doses of CP were administered >8 weeks after symptom onset; other therapeutics: interferon, arbidol, chloroquine phosphate, and ritonavir-boosted danoprevir	Substantial improvement as confirmed by CT scan and discharged after three consecutive negative nucleic acid tests	Not reported

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Wu et al 2020 [109]	27 adult patients with prolonged infection for a median of 44 (IQR 30-47) days between symptom onset and last positive test of SARS-CoV-2 before CP therapy (median age 64, IQR 57-72 years; 55.5% males), some with chronic diseases	Collected from donors (without transfusion-related infectious diseases who recovered from COVID-19) >3 weeks after symptom onset and >10 days after discharge; neutralizing antibody titer >1:160	The patients were treated with a median of 400 (IQR 200-600) mL CP at a median of 45 (IQR 3549) days after symptom onset and other therapeutics: antivirals, antibiotics, corticoid, or immunoglobulin	The patients showed pulmonary imaging improvement (within 5-8 days) and viral clearance (18 patients) 15 days after the CP transfusion, and 3 died within 60 days	No transfusion-related adverse reactions
Xi et al 2020 [110]	3 severe COVID-19 patients with comorbidities (hypertension, liver injury, and hepatitis B)	Collected from 2 recovered patients with high levels of IgG (>30 AU/mL) and IgG titer >1:80	50 mL twice with a 2-day interval and other treatments with noninvasive mechanical ventilation and antiviral, antibacterial drugs, and traditional Chinese medicine	The CT images, blood gas analysis, and symptoms improved after CP therapy. All recovered after 16-18 days of hospitalization.	No adverse event
Ye et al 2020 [111]	6 laboratory‐confirmed critically ill COVID‐19 patients (mean age 58, SD 16.4 years; 3 male)	Collected from patients at least 3 weeks following disease onset, two consecutive negative RT-PCR tests, and seropositive for anti–SARS‐CoV-2 IgG and IgM	One to three doses of ABO-compatible CP (200 mL/dose) at 6-31 days after admission. Each transfusion was administered over a 30‐minute period.	A resolution of ground‐glass opacities and consolidation in 5 out of 6 patients and an elimination of the virus in 2 in the following days of CP therapy	No adverse events
Zhang et al 2020 [112]	4 critically ill patients infected with SARS-CoV-2 (age: 31-73 years; 2 male)	Prepared from recovered patients without details	One to eight doses of CP (200-2400 mL in total) 11-41 days after admission in addition to antiviral therapy	The time from transfusion to negative RT-PCR test results ranged from 3 to 22 days. 3 were discharged from the hospital, and 1 remained in ICU up to the time of this writing	No adverse events
Zeng et al 2020 [113]	8 patients (4 males, median age 65 years) with severe or critical COVID-19; 5 patients had coexisting chronic diseases	Collected from seven donors (median age of 37 years) who had mild or moderate COVID-19 with no comorbidities and were at a median day of 11 from discharge; neutralizing antibody titer 1:255-1:1576	ABO-compatible and cross-matched CP were administered at one (3 patients) or two doses of 100-200 mL of CP within 24 h between 9 and 34 days following the onset of symptoms	6 of 8 patients showed an improvement in oxygen support status within 5 days from CP treatment, partial resolution of pulmonary lesions, and decreased viral load	No adverse events
Observational (cohort, case-control) studies					

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Abolghasemi et al 2020 [114]	115 CP treatment group with an average age of 54.4 years, and 74 control group– matched by age, gender, underlying diseases (hypertension and diabetes), and COVID-19 severity	Selected from clinically and laboratory-confirmed recovered patients of COVID-19 who were between the ages of 18-60 years and had no remaining symptoms of COVID-19 infection for at least 14 days; ELISA antibody titer cutoff index >1.1	One unit of 500 mL was infused in <3 days of hospital admission (≤7 days since illness onset), followed by another unit if the patient did not show any improvement after 24 h	More discharged patients (98.2 % vs 78.7 %), shorter hospital stay (9.54 vs 12.88 days), and less requirement for intubation (7% vs 20%) in the CP group than the control group	No adverse effect
Duan et al 2020 [115]	10 severe COVID-19 patients (6 males and 4 females) with a median age of 52.5 years in comparison with a historic control group of 10 patients matched by age, gender, and severity of the diseases	Collected by apheresis using a Baxter CS 300 cell separator from 10 donor patients who recovered from COVID-19 at 3 weeks after illness and 4 days after discharge and two consecutively negative results of sputum SARS-CoV-2 by RT-PCR assay (1-day sampling interval) neutralization activity of >1:640	One dose (200 mL) of CP at the median time of 16 days from onset of illness in combination with antiviral, antibiotic or antifungal treatment, or glucocorticoid therapy	Improved clinical symptoms and paraclinical criteria within 3 days after CP, varying degrees of absorption of lung lesions for all patients within 7 days, as compared to 3 deaths, 6 cases in stabilized status, and 1 case of improvement in the control group (P<.001)	No SAEs or safety events; 1 patient showed an evanescent facial red spot
Hegerova et al 2020 [116]	20 patients (median age 60, range 29-95 years) with severe or critical COVID-19 treated with CP under an expanded access protocol, as compared with 20 matched controls with regard to age, number of comorbidities, and severity of illness	Collected from patients aged from 29 to 79 years who recovered from COVID-19 (symptom free) for >28 days without hospitalization, most showing anti–SARS-CoV-2 IgG	One unit of ABO-compatible CP was administered early at the median time of 2 (IQR 1-4.3) days from hospitalization and additional therapies (eg, azithromycin and hydroxychloroquine)	Improved laboratory and respiratory parameters in patients following CP infusion, similar to those in controls but with lower mortality (2 vs 6 deaths)	No adverse events
Liu et al 2020 [117]	39 hospitalized patients (mean age 55, SD 13 years; 25 males) with severe to life-threatening COVID-19 received CP transfusion in comparison with a cohort of retrospectively matched controls (n=156)	Collected by plasmapheresis from donors with antispike antibody titers ≥1:320 as measured by ELISA	Two units (250 mL each unit) of ABO-type matched were infused over 1-2 hours at the median time of 4 days after admission in addition to a variety of inpatient pharmacotherapies	More likely improvements in supplemental oxygen requirements by posttransfusion day 14, improved survival, compared to control patients, especially for nonintubated patients	No significant transfusion-related morbidity or mortality

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Perotti et al 2020 [118]	46 moderate to severe COVID-19 patients (mean age 63, SD 12 years), with 19 (41%) having two or more comorbidities, in comparison with a control cohort of 23 consecutive patients	Collected using a Trima Accel blood collection device from eligible COVID-19 recovered patients with 2 consecutive negative tests for SARS - CoV - 2, followed by pathogen reduction; neutralization titers ≥1:80	24 patients received one unit of plasma, 21 received two units, and 1 patient received 3 units after having symptoms for 2 weeks, with most having been treated with antibiotics, hydroxychloroquine, and anticoagulants	3 out of 46 patients (6.5%) died within 7 days (at 1, 4, and 6 days), lower than 30% in the control, and showed improved respiratory function (PaO_2/FiO_2), chest radiogram, laboratory parameters (CRP^r, Ferritin, LDH^s, viral load), and weaning from mechanical ventilation	Five serious adverse events occurred in 4 patients.
Rasheed et al 2020 [119]	49 early-stage (no more than 3 days in ICU) critically ill COVID-19 patients randomized to receive CP or not (21 and 28 patients, respectively, matched in terms of age, sex, and comorbidities)	Collected from healthy donors younger than 50 years who recovered from moderate COVID-19 and had a IgG index ≥1.25 as measured by ELISA	400 mL of CP were transfused over 2 hours in addition to standard of care in the control group	CP-treated patients showed reduced duration of infection in about 4 days, a lower death rate (1/21 vs 8/28), and higher levels of SARS-CoV-2 IgG and IgM 3 days after CP transfusion compared to the control group	No adverse events except that 1 patient developed mild skin redness and itching that lasted for 1 hour after CP; resolved by antihistamine injection
Roger et al 2020 [120]	64 patients with symptom onset ≤10 days prior to admission and supplemental oxygen (but not invasive ventilation) within 48 h of hospitalization versus a matched control group of 177 patients for all cause in-hospital mortality and rate of hospital discharge at day 28	The SARS-CoV-2 antibody content in CP was assessed retrospectively with 13% of the units below the cutoff for a positive antibody index	3 of 64 patients received one and the remainder received two units of CP at a median of 7 (IQR 5-9) days after symptom onset	No significant difference in the risk of in-hospital mortality or overall rate of hospital discharge between the two groups, except for a significantly increased hospital discharge rate among patients 65 years or older	2 patients had TRALI reactions associated with the first unit of CP, and 1 had TACO approximately 3 h after transfusion of the second unit of CP
Salazar et al 2020 [121]	136 severe or life-threatening COVID-19 patients treated with CP versus 215 propensity score-matched patients to assess the efficacy of CP transfusion compared to standard of care	Collected from donors who had been asymptomatic for more than 14 days and had negative SARS-CoV-2 RT-PCR tests at the time of plasmapheresis; antispike IgG antibody titers ≥1:1350 as measured by ELISA	The majority of patients received one and some patients reviewed two units of CP due to worsening COVID-19 conditions	Patients treated by CP with IgG titer ≥1:1350 within 72 h of hospital admission had decreased mortality within 28 days	Reported in Joyner et al 2020 [95]

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Xia et al 2020 [122]	1568 severe or critical COVID-19 patients, most with comorbidities, among whom 1430 patients (median age of 63 years; 50% male) only received standard treatment and 138 patients (median age of 65 years; 56% male) also received ABO-compatible CP	Not reported	200-1200 mL of CP were transfused at a median of 45 days of symptom onset (1 week to ≥8 weeks from symptom onset to CP therapy)	Compared to that in the standard treatment group, there was a reduced mortality rate (2.2% vs 4.1%), lower admission to ICU (2.4% vs 5.1%), and improved respiratory symptoms of severe patients as evaluated by SCSS[t]	No significant differences in cardiac, liver, and renal functions before and after CP therapy, except for a decrease in total bilirubin and 3 patients with minor allergic reactions (pruritus or erythema) during the transfusion
Xiao et al 2020 [123]	18 patients with severe and critical COVID-19 divided into two groups with no significant differences in age, gender, and basic clinical data: one with CP transfusion (n=6) and the other without CP transfusion (n=12)	Collected from donors between age 18-55 years who had fully recovered from COVID-19 without symptoms for 2 weeks and ≥4 weeks from symptom onset; anti–SARS-CoV-2 IgG titers >1:160	200~500 mL (4~5 mL/kg body weight) of CP were transfused	No difference between the two groups of patients in terms of ventilator and ECMO weaning time, time for viral clearance, and hospitalization	Not reported
Zeng et al 2020 [124]	21 critically ill patients with COVID-19 and respiratory failure: 6 patients (median age of 61.5 years; 5 males) in the CP group versus 15 patients (median age of 73 years; 11 males) in a control group with no significant differences in demographic and clinical features	200-400 mL obtained from each young adult individual who had recovered from COVID-19 for 1-2 weeks and was negative for SARS-CoV-2 RNA and IgM testing, and positive for IgG testing before donation	A median volume of 300 mL CP was transfused at a median of 21.5 days after viral shedding was first detected	All CP-treated patients tested negative for SARS-CoV-2 RNA within 3 days after infusion versus 26.7% in the control group, but 5 patients eventually died with a longer survival period, suggesting treatment should be initiated earlier	No immediate or noticeable adverse effects
RCT[u]					
Gharbharan et al 2020 [125]	86 hospitalized patients (median age of 63 years; 72% male) randomized at 1:1 for standard of care therapy with and without CP	Collected from donors confirmed with an RT-PCR SARS-CoV-2 infection and were asymptomatic for at least 14 days; neutralizing antibodies titer ≥1:80 determined by a SARS-CoV-2 plaque reduction neutralization test	One unit of 300 mL ABO-compatible CP was transfused on the day of inclusion followed with the second plasma unit after 5 days for patients with persistent positive RT-PCR tests	There was no difference in day-60 mortality, hospital stay (P=.68), or day-15 disease severity (P=.58) between CP-treated patients and patients on standard care. The study was discontinued due to high neutralizing antibody titers at hospital admission in the majority of the study population.	No plasma-related serious adverse events were observed

Study design and studies	Population	Details of CP[a]	Interventions and comparisons	Outcomes/main findings	Adverse events related to CP therapy
Li et al 2020 [126]	103 patients (median age 70 years; 60 males, 58.3%) with severe and life-threatening COVID-19 randomized to receive CP in addition to standard treatment (n=52) or standard treatment (antiviral medications, antibacterial medications, steroids, human immunoglobulin, Chinese herbal medicines, and other medications) alone (control; n = 51)	Collected based on routine plasma collection procedures via plasmapheresis from adults aged 18-55 years that were suitable for blood donation, initially diagnosed with COVID-19 but with 2 negative PCR results from nasopharyngeal swabs (at least 24 h apart) prior to hospital discharge, discharged for ≥2 weeks from the hospital, and had no persisting COVID-19 symptoms. CP S-RBD–specific IgG titer ≥1:640 correlating to serum neutralization titre of 1:80	ABO-compatible CP was transfused at approximately 4-13 mL/kg of recipient body weight and at approximately 10 mL for the first 15 minutes, which was then increased to approximately 100 mL per hour with close monitoring	More clinical improvement occurred within 28 days in the CP group than in the control group among those with severe disease (91.3% vs 68.2%; *P*=.03) but not for those with life-threatening disease (20.7% vs 24.1%; *P*=.83). There was a higher negative conversion rate of viral PCR at 72 hours in the CP group than in the control group (87.2% vs 37.5%; *P*<.001).	2 patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care

[a]CP: convalescent plasma.
[b]PCR: polymerase chain reaction.
[c]ICU: intensive care unit.
[d]ECMO: extracorporeal membranous oxygenation.
[e]ELISA: enzyme-linked immunosorbent assay.
[f]CT: computed tomography.
[g]ASCT: autologous stem cell transplantation.
[h]RT-PCR: real-time polymerase chain reaction.
[i]S-RBD: spike protein receptor-binding domain.
[j]XLA: X-linked agammagloblulinemia.
[k]qPCR: quantitative polymerase chain reaction.
[l]ARDS: acute respiratory distress syndrome.
[m]FDA: Food and Drug Administration.
[n]TRALI: transfusion-related acute lung injury.
[o]SAE: serious adverse event.
[p]TACO: transfusion-associated circulatory overload.
[q]SOT: solid organ transplant.
[r]CRP: C-reactive protein.
[s]LDH: lactate dehydrogenase.
[t]SCSS: six-category scale score.
[u]RCT: randomized controlled trial.

Patient Demographics

A total of 36,379 patients, with most patients (n=35,322) from a single study [97], have been treated with CP in all clinical studies included in this review. There is a patient heterogeneity across the clinical studies in terms of age (ranging from infant [81] and 6 [70] to 100 years [79]), gender, and different underlying diseases, in particular hypertension and diabetes [114,122,124,294]. Some case studies investigated CP therapy for COVID-19 in patients who were immune compromised or deficient [56,80,94,100,103,125].

A few studies reported the antibody titers of patients before CP transfusion, which varied from undetectable IgG RBD antibody levels (<1:50 serum dilution) to extremely high levels (1:25,600) [88]. Studies suggested that patients with low antibody levels may benefit more from CP therapy [88,125].

Donor Selection and CP Antibody Titer

Most individuals with previous laboratory-diagnosed SARS-CoV-2 infection developed measurable antibody responses and neutralizing antibodies. There is evidence for a significant decline in neutralizing antibody levels over time [280].

Studies suggest that the efficacy of CP depends on the antibody levels of the donor plasma and CP, with high antibody levels possibly conferring immediate immunity to recipients [122]. One key factor associated with CP therapy is the neutralizing antibody titer, and when the infused plasma has a high antibody titer, it may be of the greatest benefit [88,97,99,113]. Hence, it may be a prerequisite to find eligible donors who have high levels of neutralizing antibody.

Prior smaller studies have reported a variety of titer cut-offs [105,115]. The FDA has recommended that CP with a virus neutralizing antibody titer of ≥1:160 be used for therapeutic transfusion [295]. Recently, the FDA has updated its EUA to limit the authorization to the use of high titer CP for the treatment of hospitalized patients with COVID-19 early in the disease course and to those hospitalized who have impaired humoral immunity and cannot produce an adequate antibody response, and include additional tests to be used in the manufacture of COVID-19 CP [296]. Studies have reported the levels of CP antibody titer, ranging from no minimum neutralizing antibody titer level [96] to 1:640 [115], and an even wider range of RBD-specific IgG titer, from <1:160 to >1:6000 within the same study [88].

There was substantial heterogeneity in the antibody response among potential CP donors, but sex, age, and hospitalization emerged as factors that can be used to identify individuals with a high likelihood of having strong antiviral antibody levels [297]. In vitro testing of CP showed a tendency of higher neutralizing antibody titers from donors with increased disease severity, of advanced age, and of male sex; however, the clinical relevance of this difference needs to be investigated [109,270,276,277,283,284]. Moreover, pooling CP samples from many donors may prove more effective for increasing and standardizing anti–SARS-CoV-2 neutralizing antibody titers [19].

In addition, CP collection efforts should be organized around the temporal dynamics of the immune response to viral clearance and a rise in neutralizing antibody titer, with a recommended window for plasma collection beginning at 4 weeks after the resolution of symptoms and narrowing rapidly by 12 weeks [165].

Timing and Dose

One key factor associated with CP efficacy is the optimal treatment time point [115]. The phase of the disease that this treatment modality may be most beneficial is still a matter of some debate, with early versus intermediate-late stages of the cytokine storm reaction being associated with acute respiratory distress syndrome or other severe disease complications [298].

There was no therapeutic effect from CP treatment on severely or critically ill patients with COVID-19 more than 2 weeks after the onset of disease as reported by Liu et al [117]. However, CP therapy has been limited to patients with severe or critical COVID-19. The majority of patients were severe or critically ill with COVID-19, with only a few mild cases [79,90,109].

Similar to most viral illnesses, viremia in COVID-19 peaks in the first week of infection, and the primary immune response develops by days 10-14, which is followed by virus clearance. Therefore, transfusion of CP at the early stage of disease theoretically should be more effective [114,121,124]. CP appears to be of greater clinical benefit when administered early in the course of disease than delaying transfusion under the development of severe disease [63,108]; in principle, the course of disease does not exceed 3 weeks [67]. Studies have found that, regardless of COVID-19 severity at time of transfusion, patients that received CP earlier in their course of disease showed lower mortality, more rapid viral clearance, and shorter hospital stays [92,113].

Based on the current findings, CP treatment should be given to patients with COVID-19 at the right phase or severity of illness and at the right time point. It is known that most patients with mild COVID-19 can recover without treatment, and CP may be an improper therapy for those patients. For patients with end-stage COVID-19, treatment with CP may be unable to avert a poor outcome, as demonstrated by the current findings [108,124,294]. Therefore, CP treatment may be more beneficial if used in patients who are potentially critically ill with COVID-19 at an early stage of the disease. Thus, early recognition of patients with COVID-19 who are likely to become critically ill is important for timely treatment with CP [124].

This is in line with one of the first published RCTs of CP, in which Li and colleagues [126] found that clinical improvement was limited to those without life-threatening disease, with 91% improvement in the plasma group compared to 68% in the control arm [294]. A large multicenter study involving 35,322 patients found significant reductions in 7- and 30-day mortality with early use of CP containing high levels of SARS-CoV-2–specific IgG antibodies in a subset of patients [97].

Transfusion volume ranged from 2x50 mL [110] to 8x300 mL [112]. Total antibody dose could be calculated as the transfused volume of CP multiplied by SARS-CoV-2 neutralizing antibody titer. CP dose has also been recognized as a key characteristic that may influence CP-associated outcomes [187]. One study showed that patients transfused with 400 mL of CP tended to turn faster to viral clearance than those who received 200 mL of CP [113].

Safety

All studies that assessed adverse events have reported no or minimal adverse events [102,206]. Of major interest is one of the first large trials published so far—concerning the safety of 5000 recipients—that has identified only limited and nonunexpected transfusion complications [95]. The case series study focused on the safety of CP transfusion in COVID-19 reported that, out of 5000 patients, there were 7 transfusion-associated circulatory overload (TACO), 11 transfusion-related lung injury (TRALI), and 3 severe allergic

reactions. However, the reported low incidence of serious adverse effects might be due to an extremely short time frame of observation (4 hours) [194]. The latest update of the study involving 20,000 hospitalized adults with severe or life-threatening COVID-19 further demonstrated low adverse events because of the treatment, with 36 TACO, 21 TRALI, 21 severe allergic reactions, and 38 transfusion-related thromboembolic events [96]. Consistently, other studies reported no to minimal adverse events. Half of the case reports that assessed the safety of CP did not indicate any adverse events or complications related to its use. One case series study reported 5 serious adverse events in 4 out of 46 patients [118]. The controlled studies reported 15 adverse events out of 695 patients. Overall, among a total of 20,749 patients reported with safety data, the incidence of adverse events related to CP transfusion was less than 0.8%, comparable or even lower than the incidence of adverse events related to plasma transfusions in other clinical settings [299]. There has been no evidence so far of antibody-mediated enhancement of disease in patients with COVID-19 treated with CP despite the concern that this might be a possibility in the presence of reactive but nonneutralizing antibodies against SARS-CoV-2 [170].

Although it is not yet clear whether the SARS-CoV-2 virus is transmitted by blood [300], donor selection criteria in compliance with existing policies and routine procedures should be met and pathogens reduction by solvent- or detergent–based treatments or light-based methods (especially for noncovered or detected in screening tests) should be performed in each donated plasma product as a standard for any plasma production [157,230]. Ultraviolet light and riboflavin used in the pathogen reduction process could effectively reduce SARS-CoV-2 in plasma and blood products without decreasing the quality of the blood products [301]. More studies have shown that the pathogen reduction processes did not alter neutralizing antibodies [156,272].

Outcomes

These were measured by SARS-CoV-2 negative PCR tests, improvements of clinical symptoms assessed by respiratory distress and fever, computed tomography, time to death, length of hospital stay, and mortality at discharge.

All case reports showed either viral load decrease/clearance or different extents of improvements of clinical symptoms with no mortality. Preliminary evidence from case reports and case series is favorable, as significant clinical and biochemical improvement and hospital discharge have been reported.

COVID-19 severity and underlying diseases affected the outcome of CP treatment. A patient with lymphoma who underwent autologous stem cell transplantation showed persistent SARS-CoV-2 viral shedding for 74 days, even with the administration of CP [77]. On the other hand, 1 study reported that 2 patients with long-term positive viral infection for 8 weeks showed substantial improvement after treatment with CP and ritonavir-boosted danoprevir [107]. Similarly, another study showed that CP therapy could rapidly reduce viral loads in more than half of 27 patients with prolonged positivity of SARS-CoV-2 for a median of 44 days after symptom onset [109]. It should be noted that most of these patients had mild COVID-19 symptoms.

Studies demonstrated that CP could effectively improve the respiratory symptoms of severe patients and help them wean from oxygen support. However, patients in extremely critical or life-threatening conditions could not benefit from CP [63,122,124,294].

The case series reported a mortality rate of 24.4% in 35,666 patients, mainly from 1 study with 35,322 patients [97]. The case-control and randomized controlled studies included a total of 2289 patients in the control group and 695 patients in the CP group, and reported a total of 219 (9.6%) and 63 (9.1%) deaths in each group, respectively. The number of patients and the mortality rates varied remarkably among these studies, from 6 [124] to 1430 patients [122] and from 0% [115] to 93.3% [124], respectively. The mortality at discharge [114] or at 28-day posttransfusion [121,294] have been reported as a primary outcome. Some studies showed improved survival for the CP group compared to its control [115,117,122], more clinical improvements [115,117], and viral clearance [115,124]. The efficacy of CP on mortality, length of hospital stay, clinical improvement, and viral clearance was further analyzed by meta-analysis of controlled studies, as presented later.

Quality Assessment of Clinical Studies

As indicated in Table 3, 52 clinical studies showed overall weak quality, 9 had moderate quality, and 1 had strong quality. Patients often had underlying medical conditions (hypertension, diabetes). Case reports and series with limited number of patients were considered weak for selection of participants (high risk of selection bias). Some studies included only males with a total of 3 patients [117] or only pediatric patients with fewer than 4 children [70,88] and therefore were judged to be weak for sample selection. Studies that targeted a specific group (eg, older populations, median age >60 years) were rated with moderate selection bias [122,124,125,294], while studies that selected patients with a broad range of ages and balanced gender and comorbidities [114,121] were ranked as strong.

Table 3. Quality assessment components and their rankings for clinical studies evaluated using the Effective Public Health Practice Project tool.

Studies	Patient selection	Study design	Confounders	Blinding	Data collection methods	Withdraws/ dropouts	Overall
Al Helali et al 2020 [65]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Anderson et al 2020 [66]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Bao et al 2020 [67]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Cinar et al 2020 [68]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Clark et al 2020 [69]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Figlerowicz et al 2020 [70]	Weak	Weak	Weak	Moderate	Moderate	Strong	Weak
Grisolia et al 2020 [71]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Hahn et al 2020 [72]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Hartman et al 2020 [73]	Weak	Weak	Moderate	Weak	Weak	Moderate	Weak
Im et al 2020 [74]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Jafari et al 2020 [75]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Jiang et al 2020 [76]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Karataş et al 2020 [77]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Kong et al 2020 [79]	Weak	Weak	Weak	Moderate	Moderate	Strong	Weak
Mira et al 2020 [80]	Weak	Weak	Moderate	Weak	Moderate	Strong	Weak
Soleimani and Soleimani 2020 [82]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Xu et al 2020 [83]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Zhang et al 2020 [84]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Ahn et al 2020 [85]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Abdullah et al 2020 [86]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Bradfute et al 2020 [87]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Diorio et al 2020 [88]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Enzmann et al 2020 [89]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Erkurt et al 2020 [90]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Fung et al 2020 [56]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Gemici et al 2020 [91]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Hartman et al 2020 [63]	Moderate	Weak	Weak	Weak	Weak	Strong	Weak
Ibrahim et al 2020 [92]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak
Bobek et al 2020 [93]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Jin et al 2020 [94]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Joyner et al 2020 [95]	Strong	Weak	Weak	Weak	Weak	Strong	Weak
Joyner et al 2020 [96]	Strong	Weak	Weak	Weak	Moderate	Strong	Weak
Joyner et al 2020 [97]	Strong	Weak	Moderate	Weak	Strong	Strong	Weak
Liu et al 2020 [98]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Maor et al 2020 [99]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak
Naeem et al 2020 [100]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Olivares-Gazca et al 2020 [101]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Pal et al 2020 [102]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Rahman et al 2020 [103]	Weak	Weak	Weak	Weak	Moderate	Strong	Weak
Salazar et al 2020 [104]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Shen et al 2020 [105]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak

Studies	Patient selection	Study design	Confounders	Blinding	Data collection methods	Withdraws/ dropouts	Overall
Tremblay et al 2020 [106]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Wang et al 2020 [108]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Wei et al 2020 [107]	Weak	Weak	Weak	Weak	Weak	Strong	Weak
Wu et al 2020 [109]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak
Xi et al 2020 [110]	Weak	Weak	Weak	Weak	Weak	Moderate	Weak
Ye et al 2020 [111]	Moderate	Weak	Weak	Weak	Strong	Strong	Weak
Zhang et al 2020 [112]	Moderate	Weak	Weak	Weak	Moderate	Strong	Weak
Zeng et al 2020 [113]	Weak	Weak	Weak	Weak	Strong	Strong	Weak
Abolghasemi et al 2020 [114]	Strong	Moderate	Moderate	Weak	Strong	Strong	Moderate
Duan et al 2020 [115]	Moderate	Moderate	Weak	Weak	Strong	Strong	Weak
Hegerova et al 2020 [116]	Moderate	Moderate	Weak	Weak	Strong	Strong	Weak
Liu et al 2020 [117]	Moderate	Moderate	Moderate	Moderate	Strong	Strong	Moderate
Perotti et al 2020 [118]	Moderate	Moderate	Moderate	Weak	Strong	Moderate	Moderate
Rasheed et al 2020 [119]	Moderate	Strong	Strong	Weak	Moderate	Strong	Moderate
Roger et al 2020 [120]	Moderate	Moderate	Moderate	Weak	Strong	Strong	Moderate
Salazar et al 2020 [121]	Strong	Moderate	Moderate	Weak	Strong	Strong	Moderate
Xia et al 2020 [122]	Moderate	Moderate	Moderate	Weak	Moderate	Strong	Moderate
Xiao et al 2020 [123]	Weak	Moderate	Moderate	Weak	Moderate	Strong	Weak
Zeng et al 2020 [124]	Moderate	Moderate	Moderate	Weak	Moderate	Strong	Moderate
Gharbharan et al 2020 [125]	Moderate	Strong	Strong	Weak	Strong	Strong	Moderate
Li et al 2020 [126]	Moderate	Strong	Strong	Moderate	Strong	Strong	Strong

With respect to the study design, case reports and series were considered to be weak; case-control studies and RCTs were determined to be moderate and strong, respectively. The confounders for case reports and series studies were ranked weak given the uncontrolled nature of these studies involving other therapeutic treatments and supportive care and the use of other treatment regimens, including antiviral medications along with CP transfusion. Two different analytical methods were used to control for confounding in 1 case series study [97] subsequently determined to be of moderate risk for confounders. This component was ranked to be strong for RCTs and moderate for case-control studies, except for 1 study by Duan et al [115] given the uncertain characteristics of participants selected into the intervention group and the use of a historical control group.

As CP treatment was not blinded to either outcome assessors or study patients in most studies, the blinding component was judged to be weak except for the RCT by Li et al [126], where the evaluation of clinical outcomes was performed by an investigator who was blind to the treatment.

If there was no detailed CP therapy in terms of CP collection, neutralizing antibody or anti–SARS-CoV-2 IgG titers, timing and dose of the treatment, and valid measures of clinical outcomes, the data collection methods of the study were deemed to be weak. Some case reports did not provide any information for CP donators, antibody titers, and adverse events [66,67].

There were no dropouts in the case reports and case series. One case series study where all patients were followed up for only 7 days [118] was ranked as moderate. In the RCT reported by Gharbharan et al [125], all 86 patients had been followed for at least 15 days after inclusion, and 75 and 32 patients for at least 30 and 60 days, respectively.

Both RCTs were terminated prematurely due to the concerns over the potential benefit of CP in the study population with high neutralizing antibody titers (≥1:160) at baseline [125] and the lack of patients with COVID-19 to reach the planned recruitment target of 200 patients [294], resulting in an underpowered study sample size.

Meta-analyses

Figures 2-5 summarize the statistical analyses of pooled results from the controlled clinical studies addressing the efficacy of CP treatment for COVID-19. We found 13 controlled articles (2 RCTs and 11 cohort studies) assessing mortality, with a total of 695 and 2289 patients in the CP and control groups, respectively. CP reduced the mortality by half in COVID-19 (OR 0.48, 95% CI 0.34-0.67; I^2=0), as demonstrated in the forest plot (Figure 2).

However, fewer studies were available to assess the effects of CP treatment on the length of hospital stay, clinical improvement, and viral clearance. We identified only 6 studies (1 RCT and 5 cohort studies) reporting the length of hospital

stay, with a total of 366 and 1735 patients in the CP and control groups, respectively (Figure 3). These studies had significant heterogeneity (P<.001; I^2=95%) and, when combined, did not show any effects of CP treatment on the length of hospital stay (mean difference 0.84, 95% CI –3.35 to 5.02 days).

Similarly, 4 studies (2 RCTs and 2 cohort studies) assessed the clinical improvement with the number of patients in both CP and control groups. As depicted in Figure 4, a larger portion of the patients in the CP group showed improved clinical status compared to that in the control, but the difference was not statistically significant (OR 1.54, 95% CI 0.79-3.01; I^2=43%).

Based on the 3 studies (1 RCT and 2 cohort studies) with a total of 63 and 65 patients in the CP and control groups, respectively, we found that the use of CP increased the viral clearance significantly (OR 26.21, 95% CI 4.36-157.66; I^2=43%) as shown in Figure 5.

Figure 2. Efficacy of CP treatment on mortality in COVID-19 patients. Data from 13 controlled clinical trials were pooled using an inverse variance method and analyzed using a random-effects model. Odds ratios and 95% CIs were used as statistical measures for mortality as a dichotomous outcome. CP: convalescent plasma.

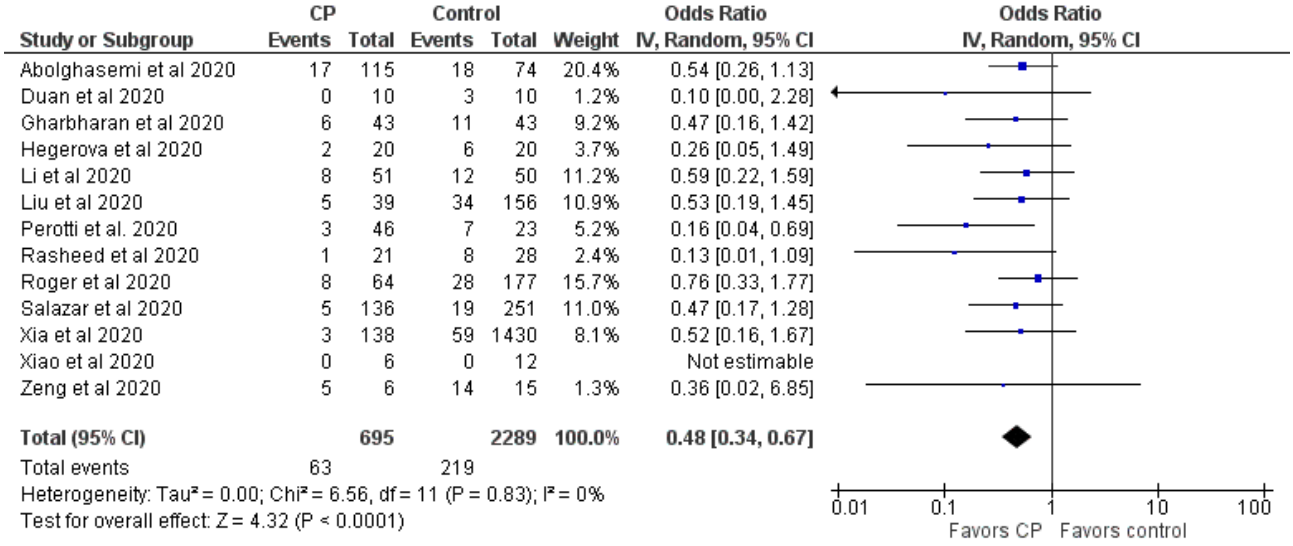


Figure 3. Efficacy of CP treatment on length of hospital stay in COVID-19 patients. Data from 6 controlled clinical trials were pooled using an inverse variance method and analyzed using a random-effects model. Means and SDs were the statistical measures used to describe the length of hospital stay. CP: convalescent plasma.

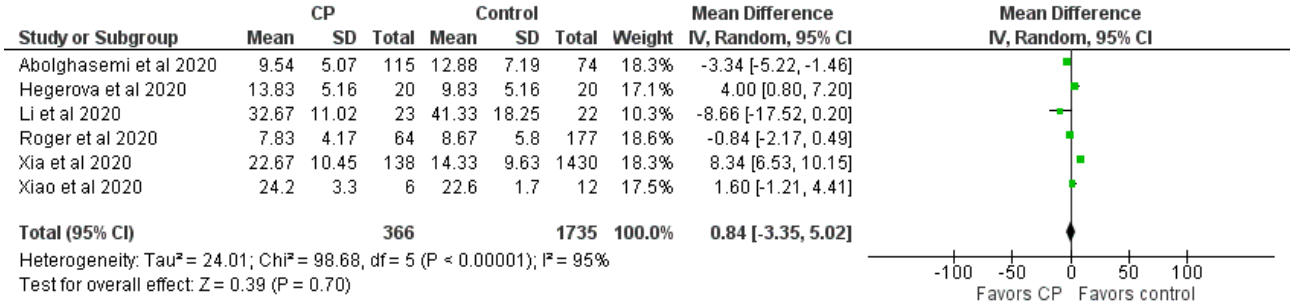


Figure 4. Efficacy of CP treatment on clinical improvement in COVID-19 patients. Data from 4 controlled clinical trials were pooled using an inverse variance method and analyzed using a random-effects model. Odds ratios and 95% CIs were used as statistical measures for clinical improvement as a dichotomous outcome. CP: convalescent plasma.

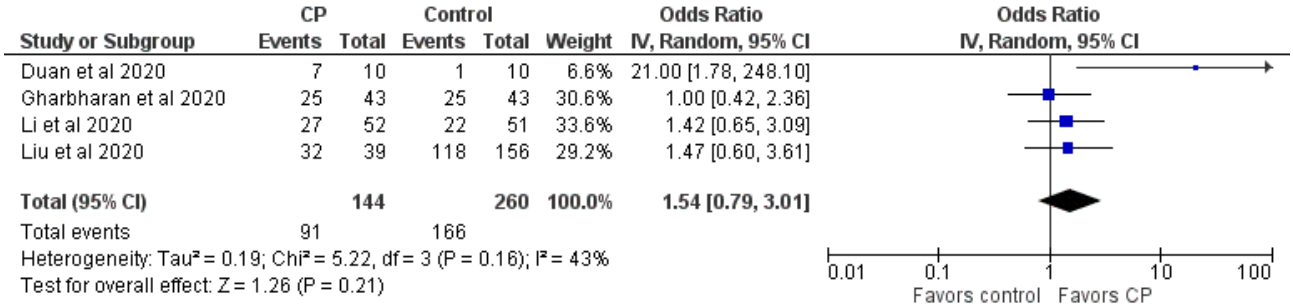
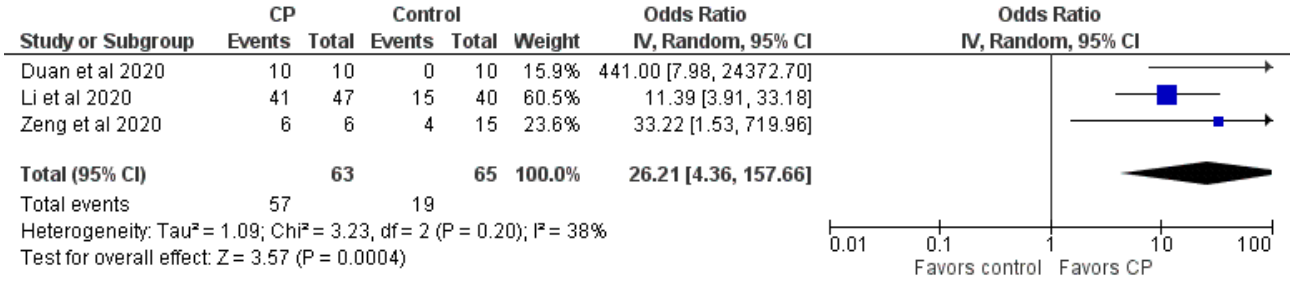


Figure 5. Efficacy of CP treatment on viral clearance in COVID-19 patients. Data from 3 controlled clinical trials were pooled using an inverse variance method and analyzed using a random-effects model. Odds ratios and 95% CIs were used as statistical measures for viral clearance as a dichotomous outcome. CP: convalescent plasma.



Except for the high heterogeneity among the studies on assessing the length of hospital stay (I^2=0.98; *P*<.001), the heterogeneity among the studies assessing the clinical improvement and viral clearance was mild (I^2=43%, *P*=.16 and I^2=38%, *P*=.20, respectively). Furthermore, since the included studies on the efficacy of CP treatment for mortality are homogenous (I^2=0; *P*=.99), the overall effect on the mortality from the meta-analysis seems to be conclusive.

Mechanisms of Action

The biological basis for efficacy of CP entails the transfer of specific antiviral immunoglobulins (antibodies) and other bioactive substances in the plasma of patients in the convalescent phase of COVID-19 infection [233,302]. In theory, administration of CP containing high levels of polyclonal neutralizing antibodies (comprised mainly of IgG, with smaller amounts of IgM, IgA) can confer immediate pathogen-specific protection by inhibiting viral infection in a susceptible person [303]. However, findings suggest considerable variation in antibody titers and the duration of protective anti–SARS-CoV-2 IgG and IgM immunity observed in recovered CP donors [304,305]. A recent population-based study of humoral immune responses to SARS-CoV-2 demonstrated that >90% of people who recovered from COVID-19 were seropositive on virus-specific pan-immunoglobulin assays by day 25, and hospitalized patients seroconverted more frequently than nonhospitalized people. Furthermore, anti–SARS-CoV-2 antibody titers remained stable in recovered patients for the next 2 months, suggesting a durable immunoglobulin response [306]. Aside from CP, pooled human immunoglobulins may also be prepared from plasma as a concentrated antibody-containing solution to be administered as intravenous, subcutaneous, or intramuscular immunoglobulin. These pooled plasma-derived immunoglobulin products benefit from the polyclonal response of each individual donor and from the interindividual variability in such responses [307]. In addition, purified, high-titer hyperimmune immunoglobulin formulations can be obtained from vaccinated or convalescing donors, which have known levels of plasma-derived neutralizing antibodies that may prove valuable against COVID-19 [33,207,225].

Although not fully elucidated, the protective mechanisms of CP are based on direct and indirect antiviral activities, including antibody neutralization of viral infectivity [233,307]. In the case of SARS-CoV-2 pathogenesis, the viral spike glycoprotein is critical to the dissemination and pathogenesis of the virus [308]. The spike protein mediates binding of SARS-CoV-2 to host cell ACE-2 surface receptors, thereby acting as the first step in cellular entry and infection. Several lines of evidence from studies of SARS-CoV and CoV-2 show that infected hosts produce neutralizing antibodies directed against the RBD of the homotrimeric spike protein and can block infection by preventing viral entry and subsequent replication [309]. Other beneficial immune effects of CP are thought to include enhanced antibody-dependent cellular cytotoxicity, complement activation, and phagocytosis, along with restoration of the vascular endothelial glycocalyx [34,200]. Moreover, a majority of convalescent patients display robust antiviral SARS-CoV-2–specific T cell responses, with enhanced in vivo priming and expansion of CD8+ cytotoxic T cells and a higher frequency of CD4+ memory T cells in those who recovered from severe COVID-19, which may provide long-term antiviral protection even if antibodies wane [310]. Therefore, T cells could help to control SARS-CoV-2 infection and serve as correlates of protective antiviral immunity [311].

As new strains of SARS-CoV-2 with several dominant mutations in the spike protein have been identified recently, crucial questions associated with the possible reinfection of recovered patients and the efficiencies of vaccines designed based on early epidemic strains have arisen [22]. Recent findings show that sera collected from convalescent COVID-19 patients in early 2020 vaccinated with RBD-based vaccines efficiently neutralize viral variants of D614G and B.1.1.7 but weakly neutralize those of 501Y.V2, suggesting a warning to recovered patients and developed vaccines [312]. These results show that, as mutations accumulate in the RBD, spike proteins may acquire an antigenic shift that enable SARS-CoV-2 variants with loss-of-neutralization potency in vitro against emerging variants and eventually resist the current vaccines. Therefore, intensive monitoring of virus mutations and timely adjustments to the spike sequences of designed vaccines and updated antibody cocktail therapies, targeting highly conserved regions, are required to control the viral pandemic [313].

Discussion

Main Findings

This systematic review summarizes a variety of evidence on the use of CP for treatment of COVID-19. Though the focus of this review was to identify and assess the quality of clinical studies reporting CP treatment for COVID-19, the broad search strategy identified a large number of studies related to various aspects of CP use, highlighting substantial research in this field.

The data on this topic is being rapidly generated and reported. Most are commentary and review articles and protocol or guidance descriptions on the theme of CP treatments for COVID-19. The main findings according to each group of articles dealing with COVID-19 CP were:

1. Clinical studies: Overall, there were significant variations among the studies regarding the study design and population, the timing of initiation of CP transfusion, dosage and neutralizing antibody titer, and concomitant therapy. The quality of the current evidence on the use of CP for COVID-19 was low. However, there is a widespread belief that CP should be used given that no other efficacious treatment is currently available.
2. Commentary articles: This category mainly consisted of commentary and letter to the editor in addition to a few editorials and perspectives that collectively supported the use of CP for COVID-19 and suggested further clinical trials.
3. Review: The volume and the pace of the clinical trials launched to evaluate the safety and efficacy of CP against COVID-19 reflects the need for high-quality evidence for the therapy to be practiced by clinicians.
4. Protocol and guideline: This category of literature showed the importance for establishment of a CP production and storage transfusion program in a public health care network and a decision-making framework; the requirements applicable to plasma donors; and the standards for preparation, qualification, storage, distribution, and control of product use.
5. In vitro testing of CP: A variety of tests have been developed to measure the levels of CP antibodies. Generally, two methods have been most used to determine antibody titers of CP: ELISA for IgG and IgM, and neutralization assay for neutralizing antibodies. ELISA-based antibody titers can correlate well with neutralizing titers.

Our meta-analysis of controlled studies showed significant reduction in mortality by CP therapy in comparison to controls. Similar meta-analysis of the efficacy of CP therapy on different types of infectious disease found a 44% reduction in the mortality of patients with COVID-19 [208]; a 25% reduction in other severe acute respiratory infections [33]; and a 32% reduction in SARS-CoV infection, severe influenza, and Ebola infection [209]. In contrast, the meta-analysis from 4 RCTs on CP treatment for influenza infection (n=572 patients) showed no convincing effects on deaths [206]. Another recent systematic review of 1 RCT and 3 controlled nonrandomized studies of CP therapy in patients with COVID-19 reported a potential reduction in mortality, time to death, and improvement of clinical symptoms but was unable to provide any opinion regarding the efficacy of CP treatment for COVID-19 due to paucity in quantitative synthesis [207].

Our meta-analysis showed no effect of CP on the length of hospital stay (mean difference), which is consistent with another meta-analysis of 3 RCTs for the effect of CP on the length of hospitalization in other severe respiratory viral infections, as reported by Devasenapathy et al [206]. Other systematic reviewers reported mixed results of both reduced length of hospital stay and no effects on the length of hospitalization in SARS-CoV infection, severe influenza, and Ebola infection [209], suggesting that the effectiveness of CP in reducing hospital length of stay might be dependent on early administration of the therapy, and its use as prophylaxis is more likely to be beneficial than treating severe disease [33]. However, the optimal timing and dosage of CP therapy remains to be defined.

The insignificant effect of CP on the improvements of clinical COVID-19 symptoms is comparable to another systematic review and meta-analysis of 5 studies with a total of 259 patients with COVID-19, showing more clinically improved patients treated with CP than no CP treatment but was not statistically significant (OR 2.06, 95% CI 0.8-4.9; I^2=44%) [208]. In contrast, the meta-analysis of 9 controlled and uncontrolled studies showed improved clinical status of patients with COVID-19 when compared to baseline (ROM 0.53, 95% CI 0.36-0.79; P<.01; n=149) [147].

The significant increase in the viral clearance is also consistent with the other meta-analysis of 2 studies with a total of 144 patients, suggesting that the use of CP helps in viral clearance significantly [208], and with the meta-analysis of 9 controlled and uncontrolled studies showing reduced viral loads [147].

Various tools have been developed for quality assessment involving slightly different components and ranking criteria [314]. We used the EPHPP tool as it can be used for all types of clinical studies. This is a generic tool used to evaluate a variety of intervention study designs such as RCTs, before-and-after, and case-control studies [62]. A study has shown differences in quality assessment for RCTs between the EPHPP and the Cochrane Collaboration Risk of Bias tool [315]. Overall, clinical studies and systematic reviews have confirmed that CP caused few or no serious adverse events with low-quality evidence.

Consistent with other reviews [207,208], our quality appraisal showed that the present studies on the efficacy of CP are generally of low quality, although there are certain agreements and discrepancies between our assessment and others on the overall quality of case and randomized controlled studies on the use of CP for COVID-19, as different assessment tools have been used. Only 1 high-quality (low risk of bias in the underlying study results) RCT by Li et al [126] was identified in our assessment using the EPHPP tool, which is in agreement with the assessment in the systematic review by Sarkar et al [208], but was rated to be unclear in another systematic review by Piechotta et al [207], even though both reviews used the same Cochrane risk-of-bias tool (RoB 2.0) for the RCT.

The overall quality of the case-control studies in our assessment lies in between the risk of bias assessed by other two systematic reviews conducted by Piechotta et al [207] and Sarkar et al [208]. Specifically, the study by Duan et al [115] was considered weak in our quality assessment but was critical as assessed by Piechotta et al [207] and moderate risk of bias by Sarkar et al [208] in their reviews. The case-control study reported by Liu et al [117] was of moderate quality in our assessment but was critical and had a low risk of bias as assessed by Piechotta et al

[207] and Sarkar et al [208], respectively, using the same Risk of Bias in Non-randomized Studies–of Interventions. The case-control study reported by Zeng et al [124] was moderate in our assessment, agreeing with the assessment in the systematic review by Sarkar et al [208], but was rated to be a critical risk of bias in the systematic review by Piechotta et al [207]. In addition to controlled and randomized studies, EPHPP could be used to assess the quality of case reports and series studies [62]. The overall quality of all case reports and series were weak based on our assessment.

Considering the promising evidence from existing clinical data, there is a clear need for RCTs on large patient numbers to evaluate the efficacy of CP therapy. Apart from sample size and the noncomparative, nonrandomized study design, numerous limitations hamper the interpretation of the aforementioned studies, such as the superimposition of effects mediated by other antiviral treatments, antibiotics, and glucocorticoids administered concomitantly with CP. As a whole, these studies indicate that patients receiving transfusions earlier than 14 days post infection may benefit from CP treatment [228,230].

Limitations

There are 2 systematic reviews and meta-analysis to appraise the literature on CP therapy for patients with COVID-19. However, this review covers the latest literature as of the date of our manuscript submission and provides insights about various aspects for the subject on the use of CP for COVID-19 that needs further investigation. The primary limitation of this review is that most data identified are nonrandomized (only 2 out of 64 clinical studies were randomized, with only 1 being of high quality), and therefore, confounding is highly inevitable. Furthermore, study populations, interventions, and measured outcomes have important clinical and methodological heterogeneity, which reflects an overall low to moderate quality of evidence identified by the appropriate quality assessment tool.

Publication bias may be another potential limitation given that the majority of early clinical studies on COVID-19 lacked original data, and those that did were rushed and did not include the appropriate measures to reduce bias [316]. Among the 243 papers included in this review, 32.5% (n=79) were commentaries, 18.9% (n=46) were reviews, and 7.8% (n=19) were protocols that did not contain any new data. We then evaluated the quality of the original clinical studies using the validated tool and found that more than 80% (52/64) were at risk of bias, mainly because of few participants, unrepresentative patient selection, poor study design, no control of confounders, and no blinding.

Future Directions

We summarized various aspects of the evidence on the use of CP in patients with COVID-19. However, important gaps in knowledge remain. Notably, the following areas require further investigation.

Well-designed prospective observational studies, preferentially RCTs, with well-defined characteristics for both CP donors and recipients are warranted to answer questions concerning the effects on mortality or other important clinical outcomes such as improvement in symptoms and respiratory status. The placebo or control should include standard-of-care or normal fresh frozen plasma. The plasma exchange has shown therapeutic effects for severe COVID-19 acute respiratory distress syndrome with multiple organ failure [317].

In vitro testing showed variable or diverse neutralizing antibody titers among individual donors, suggesting that an adequate pooling strategy of plasma units from different donors could reduce the variability of neutralizing antibody titers of CP and compensate deviations of individual antibody titers [289]. Clinical studies on the safety and efficacy of pooled CP should be conducted.

The COVID-19 pandemic has substantially reduced the national ability to provide blood products for medical care in an emergency [318], which further highlights the need to secure a stockpile of blood products with a long shelf life (eg, freeze-dried plasma) to be self-sufficient in a national crisis. Current CP protocols specify that, once thawed, CP may be stored for up to 5 days at 4 °C, similar to that of fresh frozen plasma. A recent study has demonstrated long-term stability of anti–SARS-CoV-2 spike antibodies in donor CP for 42 days when stored under refrigerated conditions [291]. There will be a need to stockpile freeze-dried CP for future waves of the pandemic for several years. Additionally, global concern over the potential for future waves of infection to occur before effective vaccines or drug therapies are available has many looking at other biological sources for large-scale production of neutralizing SARS-CoV-2 antibodies. Taking this into consideration, we are developing COVID-19 convalescent freeze-dried plasma. As this is a pooled plasma product of 10 donors, we also hypothesize that convalescent freeze-dried plasma will have higher anti–SARS-CoV-2 neutralizing antibody titers and activity than single donor CP. As well, this product may be administered in a hypertonic solution for those patients who cannot tolerate large volume CP transfusions.

Conclusions

There is still limited evidence but accumulating interest in CP treatment for COVID-19. The theoretical reasons for the likely efficacy of passive immunization, the urgent need felt by clinicians worldwide for effective treatment options for COVID-19, and the promising results offered mainly by retrospective clinical studies must be balanced against the lack of efficacy in the RCTs of CP and hyperimmune globulin therapy in severe influenza and COVID-19.

CP may be of greatest benefit for patients who are early in their illness and have not yet generated endogenous antibodies, and when the infused CP has a high antibody titer. Recurring observations suggested that treatment with CP within 4-5 days of symptom onset might be more effective than later treatment.

Our systematic review and analysis emphasizes the low quality of clinical studies. These studies could provide important lessons that should inform the planning of adequately powered and properly designed RCTs to evaluate the promise of CP therapy for patients with COVID-19.

Future research is necessary to fill the obvious knowledge gaps regarding CP treatment for patients with COVID-19. In brief,

we offered recommendations around the need for a large-scale properly designed RCT, the potential prophylactic use of CP, selection criteria for both CP donors and recipients, development of antibodies with higher potency than CP, and freeze-dried CP as a long-term strategy against the pandemic.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplemental Table 1.
[DOCX File , 486 KB - publichealth_v7i4e25500_app1.docx]

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Abbreviations

ACE-2: angiotensin-converting enzyme 2
CP: convalescent plasma
ELISA: enzyme-linked immunosorbent assay
EPHPP: Effective Public Health Practice Project
EUA: Emergency Use Authorization
FDA: Food and Drug Administration
Ig: immunoglobulin
MERS-CoV: Middle East respiratory syndrome–related coronavirus
OR: odds ratio
PCR: polymerase chain reaction
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RBD: receptor binding domain
RCT: randomized controlled trial
ROM: ratio of mean
SARS-CoV: severe acute respiratory syndrome–related coronavirus
TACO: transfusion-associated circulatory overload
TRALI: transfusion-related lung injury

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Original Paper

Physical Activity, Nutritional Habits, and Sleeping Behavior in Students and Employees of a Swiss University During the COVID-19 Lockdown Period: Questionnaire Survey Study

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Abstract

Background: The new coronavirus SARS-CoV-2 led to the COVID-19 pandemic starting in January 2020. The Swiss Federal Council prescribed a lockdown of nonessential businesses. Students and employees of higher education institutions had to install home offices and participate in online lectures.

Objective: The aim of this survey study was to evaluate lifestyle habits, such as physical activity (PA), sitting time, nutritional habits (expressed as median modified Mediterranean Diet Score [mMDS]), alcohol consumption habits, and sleeping behavior during a 2-month period of confinement and social distancing due to the COVID-19 pandemic. Survey participants were students and employees of a Swiss university of applied sciences.

Methods: All students and employees from Bern University of Applied Sciences, Department of Health Professions (ie, nursing, nutrition and dietetics, midwifery, and physiotherapy divisions) were invited to complete an anonymous online survey during the COVID-19 confinement period. Information on the lifestyle dimensions of PA, sitting time, nutritional and alcohol consumption habits, and sleep behavior was gathered using adaptations of validated questionnaires. Frequency analyses and nonparametric statistical methods were used for data analysis. Significance was set at 5% α level of error.

Results: Prevalence of non-health-enhancing PA was 37.1%, with participants of the division of physiotherapy showing the lowest prevalence. Prevalence of long sitting time (>8 hours/day) was 36.1%. The median mMDS was 9, where the maximal score was 15, with participants of the division of nutrition and dietetics being more adherent to a Mediterranean diet as compared to the other groups. Prevalence of nonadherence to the Swiss alcohol consumption recommendations was 8.3%. Prevalence of low sleeping quality was 44.7%, while the median sleeping duration was 8 hours, which is considered healthy for adult populations.

Conclusions: In the group analysis, differences in PA, sitting time, and mMDS were observed between different divisions of health professions as well as between Bachelor of Science students, Master of Science students, and employees. Therefore, public health messages regarding healthy lifestyle habits during home confinement should be more group specific. The results of this study may provide support for the implementation of group-specific health promotion interventions at universities in pandemic conditions.

Trial Registration: ClinicalTrials.gov NCT04502108; https://www.clinicaltrials.gov/ct2/show/NCT04502108

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KEYWORDS

COVID-19; healthy lifestyle; pandemics; public health; universities

Introduction

Background

The World Health Organization declared the new coronavirus SARS-CoV-2 leading to COVID-19 as a pandemic on March 11, 2020 [1]. Then 5 days later, the Swiss Federal Council declared an "extraordinary situation" in terms of the Epidemics Act. Stringent measures were put in place [2]. All nonvital businesses as well as schools of all levels, including universities and universities of applied sciences, had to be closed. To contain the pandemic, the Swiss Federal Council called on members of the public to remain at home in order to keep their distance from others.

This lockdown was immediately instituted by the president of Bern University of Applied Sciences (BFH). Classroom teaching was forbidden. Students and employees had to remain at home, continuing their study and work in home office settings. Lecturers were asked to switch to digitalization to guarantee the continuation of the different educational programs during this second part of the spring 2020 academic semester and upcoming fall 2020-2021 semester [3].

All sports infrastructure in Switzerland was forced to close during this nearly 2-month lockdown period. While regular access to fitness clubs or sports facilities was no longer possible, individual walking, jogging, and cycling, however, was still allowed. Food shops remained open during this period. Citizens were allowed to go outside for food supplies when adhering to the hygiene measures [2].

It can be hypothesized that such severe restrictions may have an influence on healthy lifestyles [4,5]. Some international studies reported on lifestyle changes during home confinement. In Italy, the perception of weight gain was observed in 48.6% of the population and a slight increase in physical activity (PA) has been reported [6]. Another study with data from Western Asia, North Africa, Europe, and other countries revealed that the COVID-19 home confinement has had a negative effect on all levels of PA and an increase in daily sitting time by more than 28% [7].

Hamer et al [8] suggested that an unhealthy lifestyle synonymous with an elevated risk of noncommunicable disease is also a risk factor for COVID-19 hospital admission.

There is limited knowledge on lifestyle habits, such as PA, physical inactivity (ie, sitting time), nutritional and alcohol consumption habits, and sleeping behavior, during an extraordinary period of 2 months' confinement and social distancing in university students [9-12], and information regarding university employees is even more scarce.

Because of their health profession–specific scholarly knowledge, differences in lifestyle habits between members of the different health profession divisions (eg, between the nutrition and dietetics division and physiotherapy) can be expected. Furthermore, in the Swiss context, Bachelor of Science (BSc) programs of the different health profession divisions are full time while most of the Master of Science (MSc) programs are scheduled as part time, allowing the latter students to combine study and work. Similar to the BSc students, most employees were also confined at home. Thus, it can be hypothesized that differences in lifestyle habits during a lockdown period can be observed between these three groups: BSc students, MSc students, and employees.

Because this pandemic is caused by a *new* coronavirus lacking vaccination and treatment possibilities, predictions on the development of the pandemic (eg, the rise of a *second wave* during winter) remains difficult. Increased knowledge about lifestyle habits of students and employees of the BFH, Department of Health Professions (BFH-DHP), during such an extreme confinement situation may help heads and deans of academic institutions as well as other decision makers to counsel students and employees during a similar situation or in case of another outbreak in the future. However, due to the uniqueness of this COVID-19 crisis and its societal impact, such knowledge is currently lacking.

Objective

This study evaluated differences in lifestyle habits, such as PA, sitting time, nutritional and alcohol consumption habits, and sleeping behavior, during COVID-19 home confinement (spring 2020) with social distancing between BSc students, MSc students, and employees as well as between the four health profession divisions (ie, nutrition and dietetics, midwifery, nursing, and physiotherapy) of BFH-DHP, Switzerland.

Delineated research questions were as follows: (1) Are there lifestyle differences between the four groups of health profession divisions (ie, nutrition and dietetics, midwifery, nursing, and physiotherapy) during lockdown home confinement? and (2) Are there lifestyle differences between BSc students, MSc students, and employees during lockdown home confinement?

Methods

This survey was conducted as an interdisciplinary collaboration between faculty members of the division of Physiotherapy and the division of Nutrition and Dietetics. A protocol of this observational study has been published elsewhere [13]. Here, a brief summary of the methods is presented.

Research Design

For this study, a self-reported electronic survey was conducted within the 2020 COVID-19 strict lockdown period assessing PA, sitting time, nutritional and alcohol consumption habits, and sleeping habits in students and employees of BFH-DHP, Switzerland.

Ethical issues were considered. Prior to the start of this survey, the dean of BFH-DHP was informed and approved this study. In the introductory section of the survey, eligible staff and students were informed that the survey was voluntary and anonymous, that no medical data will be asked for, and that they could contact the researchers for any information or further questions. Finally, it was explained that by filling out the survey and resubmitting it to the system, they explicitly gave their informed consent. The EvaSys software (Electric Paper Evaluationssysteme GmbH) does not allow for any personal tracing of the respondents. The study was submitted to the

Ethical Committee of Canton Bern. The Ethical Committee declared that this anonymous survey without medical data did not need to undergo a full approval procedure (KEK Bern, Req-2020-00909) because it does not fall under the regulations of the *Federal Act on Research involving Human Beings* in Switzerland. The survey has been registered at ClinicalTrials.gov (NCT04502108).

Study Participants

All students (n=1300; 88.0% [1144/1300] females and 12.0% [156/1300] males) enrolled in BSc or MSc study programs in the field of nursing, nutrition and dietetics, midwifery, and physiotherapy, as well as all academic and nonacademic employees (n=268) from BFH-DPH, were eligible and were invited to volunteer in this electronic survey.

Independent measures were BSc students, MSc students, and employees as well as the four health profession divisions.

Data Collection, Data Management, and Data Analysis

The survey was sent via the institute's email system to all staff and students on May 5, 2020, and remained open until May 15, 2020, to ensure a full COVID-19 confinement snapshot. A brief introduction section prior to the different questionnaires explained the objective of the survey. Automated reminders were sent two times during this time slot.

Data collection was performed anonymously using the *evaluation system software* of BFH-DPH, EvaSys. A standardized questionnaire was developed within the EvaSys framework, including validated tools to assess PA and sitting time (ie, the International Physical Activity Questionnaire–Short Form [IPAQ-SF]) [14] and to evaluate nutritional habits (ie, a Swiss adaptation of the brief Mediterranean Diet Screener [bMDSC]) [15]. Questions on alcohol consumption and sleeping behavior were added to the survey, while, for reasons of anonymity, questions on socioeconomic status were omitted. Lifestyle habits under evaluation were assessed during the 7 days prior to filling out the survey. A complete description of the data management, cleansing, and analysis can be consulted in Multimedia Appendix 1. A brief description follows.

The IPAQ-SF assesses PA undertaken across four domains, including leisure time PA, domestic and gardening activities, work-related PA, as well as transport-related PA. The IPAQ-SF evaluates three specific types of PA (ie, walking, moderate-intensity PA, and vigorous-intensity PA) undertaken in these four domains during the previous 7 days. Time spent in the three types of PA was calculated and expressed in minutes. The IPAQ-SF algorithm was used to transform the continuous data into categorical data (ie, *low*, *moderate*, and *high*, *health-enhancing* PA) [14]. A reliability study of the IPAQ-SF including 178 Swiss volunteers found fair to good reliability with Spearman correlation coefficients of 0.54 for total PA (MET [metabolic equivalent] min/week) and 0.60 for sitting [16].

The analysis of sitting time during the previous 7 days was also conducted following the IPAQ-SF guidelines.

A Swiss adaptation of the bMDSC was used to assess nutritional habits and adherence to the Mediterranean diet, which has been proposed as a healthy eating pattern because of its high content of antioxidant food items. Volunteers were asked to report their adherence to a recommended consumption frequency of 15 selected food items during the preceding 7 days. Answer categories were *yes* or *no*. Healthy items scored 1 if answered with *yes* and 0 otherwise, while unhealthy items were reverse coded. Scores were summed to calculate a modified Mediterranean Diet Score (mMDS). The maximal score is 15, with higher scores indicating better adherence to the Mediterranean diet. A validation study including 102 participants reported an intraclass correlation coefficient of 0.4 (P<.001) between the mMDS derived from the bMDSC and a 24-hour recall index. Reported limits of agreements were 59% and 144%. The authors concluded that the bMDSC is a valid tool for rapid assessment of dietary quality [15].

Daily wine, beer, and spirits (ie, liquor) consumption during the preceding 7 days was given in units (ie, glasses). While there is evidence that drinking patterns may matter more than the type of alcohol [17,18] consumption itself, it has also been proposed that adherence to a Mediterranean diet with a moderate wine intake during meals could explain the observed lower prevalence of cardiovascular disorders in Southern Europe as compared to Northern Europe. Furthermore, wine and spirits are more expensive than beer [19]. Therefore, in addition to alcohol intake frequency data, this study wanted to differentiate between the types of alcohol consumed.

Sleeping behavior during the preceding 7 days was given as time to go to bed and wake-up time. Sleeping duration was calculated as the difference between these two times. Quality of sleep was asked to be rated as *no sleeping problems*, *sleeping quality could be improved*, or *important sleeping problems*.

Data management was conducted on the institutional server while data cleansing was performed by one researcher (JT) to check for incompatibilities and to control plausibility of the data (eg, range checks). The IPAQ-SF data cleansing rules were followed: participants with incomplete data or who mentioned "don't know" were removed from the analysis [14].

Statistical Analyses

Frequency analyses and nonparametric statistics were used to report the results of this survey. For the descriptive analyses, central tendencies were expressed as medians, while variation was reported using the 25th and 75th percentiles and IQRs. Kruskal-Wallis tests and Whitney U tests with post hoc Bonferroni corrections were used to assess differences between independent groups (ie, between BSc and MSc students and employees as well as between members of the four divisions). Results are presented as frequency tables or as figures with box plots.

Data were prepared in Excel 2018 (Microsoft Corporation) but imported into SPSS Statistics for Windows, version 26.0 (IBM Corp), for statistical analyses. Statistical significance was set at the 5% level of error.

Results

Overview

A total of 821 participants (BSc students: 616/821, 75.0%; MSc students:100/821, 12.2%; employees: 105/821, 12.8%) volunteered for this online survey. Students' and employees' response rates were 55.1% and 39.2%, respectively. Respondents were affiliated with the divisions of nutrition and dietetics (119/821, 14.5%), midwifery (109/821, 13.3%), nursing (309/821, 37.6%), and physiotherapy (284/821, 34.6%).

Because incomplete files were excluded from the different analyses, the sample sizes were reduced to 650 out of 821 (79.2%) respondents for the PA analysis, 761 out of 821 (92.7%) for the sitting time analysis, 771 out of 821 (93.9%) for the nutritional habits analysis, 815 out of 821 (99.3%) for the alcohol consumption analysis, and 796 out of 821 (97.0%) for the sleeping time and quality analysis.

Physical Activity

In this sample of 650 respondents, never engaging in vigorous PA, moderate PA, or walking during the preceding 7 days was reported by 67 (10.3%), 44 (6.8%), and 18 (2.8%) participants, respectively. A total of 4 volunteers did not participate in any of the three PA types. The median MET minutes per week score was 3447 (IQR 2117-5396). Of the 650 volunteers, 30 (4.6%) were classified as *low*, 211 (32.5%) as *moderate*, and 409 (62.9%) as *high* for PA.

Figure 1 presents the box plot of the summed MET minutes per week scores for the four different health profession divisions (ie, nutrition and dietetics, midwifery, nursing, and physiotherapy). Participants of the division of nutrition and dietetics showed a lower median summed MET minutes per week score compared to that of the division of physiotherapy (P=.001). The other observed differences between divisions were not statistically significant (P>.05). Calculated values of the box and whisker plots are presented in Multimedia Appendix 2.

Figure 1. Box plots of the physical activity scores (summed metabolic equivalent [MET] min/week scores) per health profession division of a Swiss university of applied sciences during the spring 2020 COVID-19 lockdown. Whiskers indicate 1.5 × IQR unless truncated at the lowest score. Asterisks and circles represent values outside this range. E_D: nutrition and dietetics; HEB: midwifery; PFL: nursing; PHY: physiotherapy.

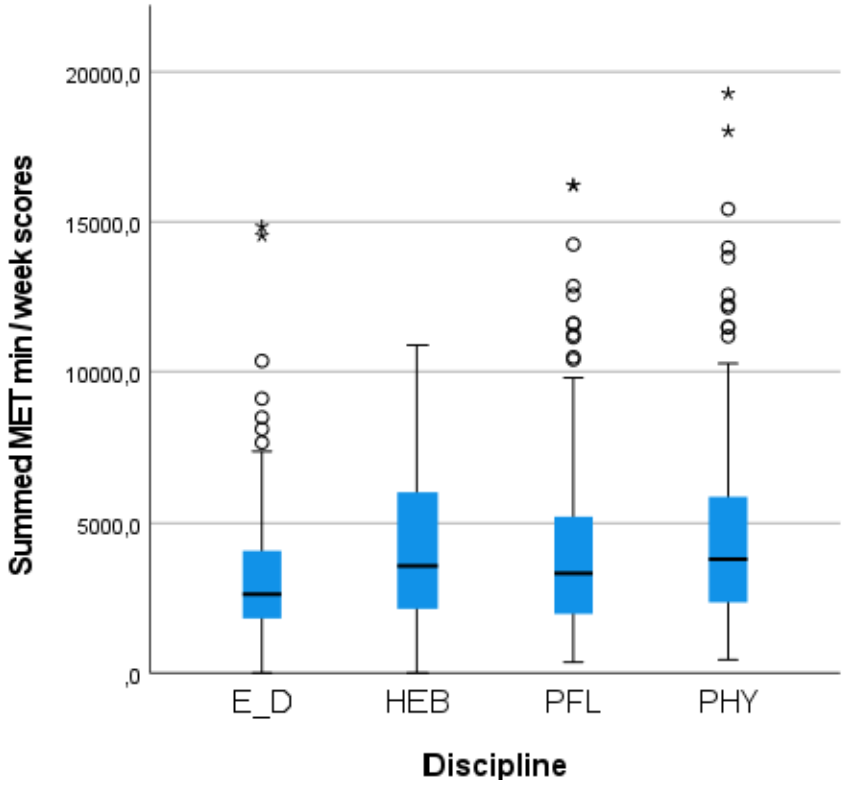


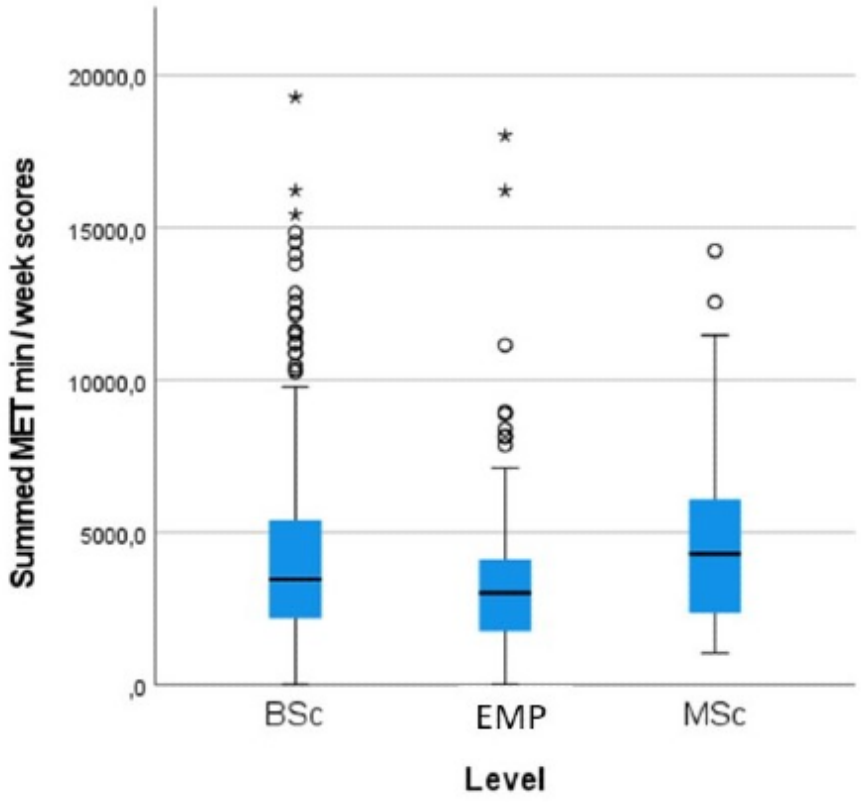
Table 1 shows the absolute and relative frequencies of the categories *low*, *moderate*, and *high*, *health-enhancing* PA in the groups of the four health profession divisions. The highest relative frequency of *high* PA was found in the participants from the division of physiotherapy (175/236, 74.2%), while the highest relative frequency of *low* PA was observed in the volunteers from the division of midwifery (8/79, 10.1%). Table 1 depicts the absolute and relative frequencies of the classifications in *low*, *moderate*, and *high* PA for the 650 participants of the two student groups (ie, BSc and MSc) and the employee group. The highest relative frequency of *high* PA was found in the group of MSc students (54/79, 68.4%), while the highest relative frequency of *low* PA was observed in the employee group (9/91, 9.9%)

Table 1. Categorized physical activity data of the preceding 7 days of 650 students and employees in four divisions of a Swiss university of applied sciences during the spring 2020 COVID-19 lockdown.

Participant group	Physical activity level per group, n (%)			
	High	Low	Moderate	Total
Division				
Nutrition and dietetics	49 (49)	3 (3)	47 (48)	99 (100)
Midwifery	47 (60)	8 (10)	24 (30)	79 (100)
Nursing	138 (58.5)	12 (5.1)	86 (36.4)	236 (100)
Physiotherapy	175 (74.2)	7 (3.0)	54 (22.9)	236 (100)
Students or employees				
Bachelor of Science students	307 (64.0)	20 (4.2)	143 (29.8)	480 (100)
Master of Science students	54 (68)	1 (1)	24 (30)	79 (100)
Employees	48 (53)	9 (10)	34 (37)	91 (100)

Figure 2 shows the box plot of the summed MET minutes per week scores for the BSc student, MSc student, and employee groups. The employee group showed a lower median summed MET minutes per week score compared to the group of MSc students (P=.002) and the group of BSc students (P=.04). There was no difference in the median MET minutes per week scores between the BSc and MSc student groups (P=.12). Calculated values of box and whisker plots are presented in Multimedia Appendix 2.

Figure 2. Box plots of the physical activity scores (summed metabolic equivalent [MET] min/week scores) for students and employees (n=650) of a Swiss university of applied sciences (health professions) during the spring 2020 COVID-19 lockdown. Whiskers indicate 1.5 × IQR unless truncated at the lowest score. Asterisks and circles represent values outside this range. BSc: Bachelor of Science students; EMP: employees; MSc: Master of Science students.

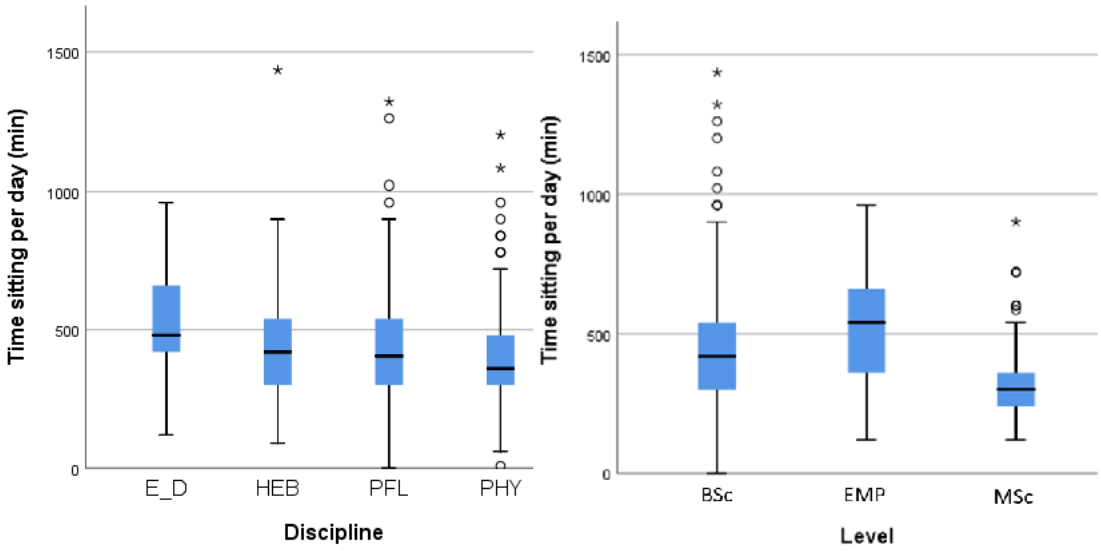


Sitting Time

A total of 761 out of the 821 respondents (92.7%) were included in this analysis. Median sitting time was 420 minutes per day (IQR 300-540). Figure 3 (left) depicts the box plot of the daily sitting time for members of the four different health profession divisions. Participants from the nutrition and dietetics division had higher median daily sitting time values compared to those from the other health profession divisions (all comparisons P<.001). Figure 3 (right) presents the box plot of daily sitting time values for the BSc student, MSc student, and employee

groups. Employees had a higher median daily sitting time value compared to values of the BSc and MSc students (all comparisons *P*<.001). BSc students showed a higher median daily sitting time value compared to that of the MSc students (*P*<.001). Calculated values of the box and whisker plots are presented in Multimedia Appendix 2.

Figure 3. Box plots showing the daily sitting times (in minutes) among students and employees (n=761) from four divisions of a Swiss university of applied sciences during the spring 2020 COVID-19 lockdown. Left: daily sitting times per health profession division. Right: daily sitting times per group of students and employees. Whiskers indicate 1.5 × IQR unless truncated at the lowest score. Asterisks and circles represent values outside this range. BSc: Bachelor of Science students; E_D: nutrition and dietetics; EMP: employees; HEB: midwifery; MSc: Master of Science students; PFL: nursing; PHY: physiotherapy.



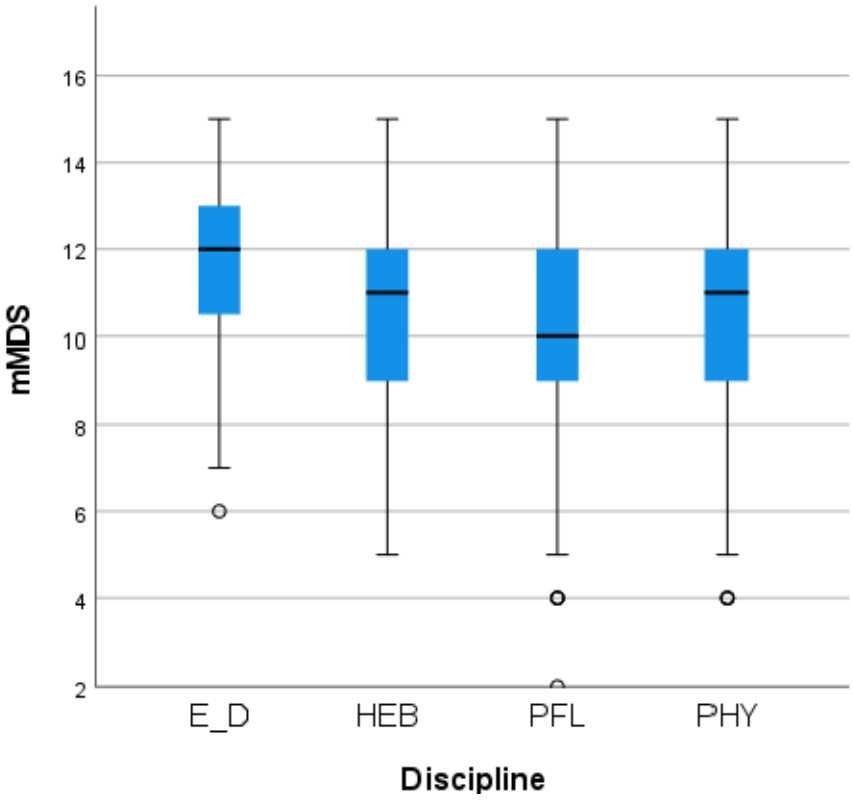
Nutritional Habits

A total of 771 out of the 821 respondents (93.9%) could be included in this analysis. The median mMDS in this sample was 11 (IQR 9-12). The lowest mMDS observed in this sample was 2 (n=1), while 8 persons were fully adherent to the Mediterranean diet (mMDS=15).

Figure 4 depicts the box plot of the mMDS values for members of the four different health profession divisions. Participants from the division of nutrition and dietetics had a higher median mMDS compared to those from the divisions of nursing and physiotherapy (both comparisons *P*<.001) or the division of midwifery (*P*=.03). The median mMDS of the participants from the division of midwifery was higher compared to that of the participants from the division of nursing (*P*=.047). Calculated values of the box and whisker plots are presented in Multimedia Appendix 2.

No differences were found between BSc students, MSc students, and employees (*P*=.17).

Figure 4. Box plots of the eating habits, measured using the modified Mediterranean Diet Score (mMDS), of students and employees (n=771) in each health profession division of a Swiss university of applied sciences during the spring 2020 COVID-19 lockdown. Whiskers indicate 1.5 × IQR unless truncated at the lowest score. Circles represent values outside this range. E_D: nutrition and dietetics; HEB: midwifery; PFL: nursing; PHY: physiotherapy.



Alcohol Consumption

A total of 815 out of the 821 respondents (99.3%) were included in this analysis. Table 2 shows the absolute and relative frequencies of the different types of alcohol consumption among these 815 participants. Over 80% of the volunteers reported no wine or beer consumption over the preceding 7 days, while nearly 97% reported no liquor or spirits consumption over the same period. Around 18% of the respondents adhered to the Mediterranean diet guideline of 2 units of wine per day. Out of 815 participants, 23 (2.8%) reported daily combinations of the different types of alcohol consumption above 3 units per day. Out of 815 participants, 2 (0.2%) reported an excessive alcohol consumption of more than 7 units of all types of drinks per day.

Table 2. Different types of alcohol consumption over the preceding 7 days by 815 students and employees in four divisions of a Swiss university of applied sciences during the spring 2020 COVID-19 lockdown.

Type of alcohol	Units of drinks consumed per day by participants (N=815), n (%)					
	0	1	2	3	4-7	>7
Wine	651 (79.9)	134 (16.4)	12 (1.5)	0 (0)	11 (1.3)	7 (0.9)
Beer	685 (84.0)	109 (13.4)	14 (1.7)	4 (0.5)	1 (0.1)	2 (0.2)
Liquor or spirits	788 (96.7)	20 (2.5)	3 (0.4)	2 (0.2)	0 (0)	2 (0.2)

No differences in alcohol consumption were observed between the four health profession division groups (P>.05). Similarly, no group differences between the BSc student, MSc student, and employee groups were found (P>.05).

Sleeping Behavior

A total of 796 out of the 821 respondents (97.0%) were included in this analysis. Of those, 44 (5.5%) reported poor sleeping quality, 312 (39.2%) found that sleeping quality could be improved, while 440 (55.3%) reported good sleeping quality.

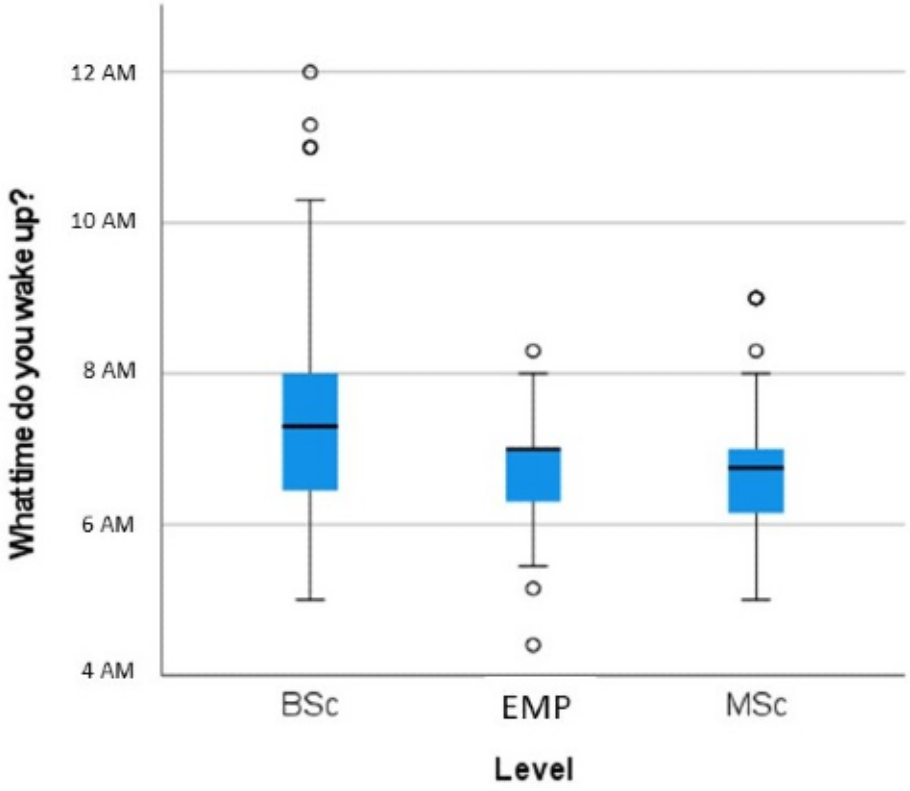
No differences in sleeping quality were observed between the four health profession division groups (P>.05). Similarly, no group differences between the BSc student, MSc student, and employee groups were found (P>.05).

In this sample, 253 out of 796 respondents (31.8%) reported going to bed at 11 PM. Only 1 volunteer (0.1%) mentioned that their bedtime was at 7:30 PM, while another respondent (0.1%) went to bed at 3:30 AM. A total of 176 persons (22.1%) reported waking up at 7 AM. Only 1 participant (0.1%) mentioned a wake-up time of 4 AM, while another (0.1%) mentioned not getting out of bed before noon. Median sleep duration in this sample was 8 hours (IQR 7.8-9.0).

No group differences for bedtime, wake-up time, and sleep duration between the four different health profession division groups were found (all comparisons $P>.05$).

No group differences between BSc students, MSc students, and employees were found for bedtime ($P=.15$). Figure 5 presents the box plot of the wake-up times for those three groups. Median wake-up time was later in the BSc student group compared to the MSc student and employee groups (both $P<.001$). Calculated values of the box and whisker plots are presented in Multimedia Appendix 2.

Figure 5. Box plots of wake-up time of students and employees (n=796) from the Bern University of Applied Sciences, Department of Health Professions during the spring 2020 COVID-19 lockdown. Whiskers indicate 1.5 × IQR unless truncated at the lowest score. Circles represent values outside this range. BSc: Bachelor of Science students; EMP: employees; MSc: Master of Science students.



Availability of Data and Material

The data set used during this study is available from the corresponding author on reasonable request.

Discussion

Principal Findings

This study found differences in PA, sitting time, nutritional and alcohol consumption habits, and sleeping behavior between BSc students, MSc students, and employees as well as between the four health profession divisions (ie, nutrition and dietetics, midwifery, nursing, and physiotherapy) of a university of applied sciences in Switzerland during COVID-19 home confinement (spring 2020) with social distancing.

In the same period, similar initiatives in the general population were launched by other institutions. For example, an Italian survey including 398 university students used the International Physical Activity Questionnaire to assess PA and sedentary behavior during COVID-19 lockdown in spring 2020. Lockdown sedentary behavior was greater than before lockdown ($P=.003$). While closure of the university increased sedentary behavior across the sample, it only decreased PA in participants who were the most active before lockdown [20].

In this study, response rates of students (55.1%) and employees (39.2%) were higher than expected in the study protocol (30%) [13]. Participants from the nursing and physiotherapy divisions together represented 72.2% of the total respondents (593/821). Both divisions also contribute the largest numbers of students and employees in the total BFH-DHP population. BSc students were 6 times more represented in this study sample than MSc students or employees. Undergraduate students also represent the highest number in the total BFH-DHP population.

During the 2020 COVID-19 confinement period, about 90% of the 650 respondents that could be included in the PA analysis were engaging in one of the three types of PA (ie, vigorous PA, moderate PA, or walking) during the preceding 7 days before filling out the survey questionnaires. On an individual level, 4 participants reported never having participated in such activities over the previous 7 days. The median summed MET minutes per week score was 3447 but with large variation (IQR 2117-5396). The IPAQ-SF interpreted the results from the perspective of health-enhancing effects: 4.6% of the respondents were classified as *inactive*, 32.5% as *minimally active*, and 62.9% as *health-enhancing physically active*. Persons classified as belonging to the latter group participated in PA bouts with evidence of health-enhancing effects [14]. These results are lower than those from the data from the Swiss Health Survey

2017, where the proportion of trained and sufficiently active people who met the PA recommendations was 76% [21]. Only participants from the division of physiotherapy (74.2%) met these criteria of health-enhancing PA during confinement. Participants from the division of nutrition and dietetics showed the lowest median PA level. The proportion of inactive or insufficiently active persons in this study is comparable with the Swiss Health Survey. The observed difference between these two groups was 85 MET minutes representing a short walking tour of 15 minutes for 5 days a week. When summed up over time, even small differences may become clinically relevant. The importance of PA is known. Active muscles produce chemicals that improve immune functioning, which in turn reduces the extent of infections and decreases inflammation, and these are the main causes of the lung damage from SARS-CoV-2 infection [22].

Students had a higher median PA level compared to employees. It is interesting to note that in this specific sample of health profession students and employees, 37.1% were not participating at a health-enhancing PA level. Being a health profession student or health professional may not always have a protective effect against unhealthy lifestyle habits [23-25]. It is encouraging to observe that participants from the division of physiotherapy—those who are, or have been, trained to become movement science experts—showed the highest median PA levels. It can be argued that participants in this specific sample have, on average, a higher health literacy than their peers from other faculties and, thus, an underestimation of the number of participants not adhering to a health-enhancing PA level cannot be excluded at the total population level of the university of applied sciences.

Results of this survey suggest that incentives organized by universities may be needed to empower students and employees more specifically. For example, action plans for workplace health promotions may be developed with a special focus on digital dissemination paths to reach students and employees in their home office settings.

Median sitting time in this sample during the preceding 7 days was 7 hours per day, with a prevalence of long sitting time (>8 hours/day) of 36.1%, which is higher compared to the Swiss data, where 25% of the employed persons sat for more than 8 hours a day [21]. The prevalence of long sitting time in university students under normal, nonconfinement conditions is high and its effect on cognition and academic performance is not well studied yet. A Spanish study including 372 undergraduate university students concluded that introducing health promotion programs into university settings to replace leisure sitting time with moderate PA may contribute to enhanced student performance [26]. Participants from the nutrition and dietetics division showed the highest median sitting time (8 hours/day) compared to their peers from the other health disciplines. The median sitting time for employees during the COVID-19 confinement period was more than 8 hours. The observed higher sitting time for BSc students as compared to their peers at the MSc level can be, at least partially, explained by the type of study program. While most BSc programs are full time, most MSc programs at BFH-DHP are part time. Even under strict confinement conditions, most graduate students were still working in the health care sector and, hence, this might have resulted in less sitting time as compared to their undergraduate peers.

The findings for PA and sitting time may have important public health implications. For example, health promotion campaigns to increase PA and reduce physical inactivity should focus on employees and students, especially those in the nutrition and dietetics division. They should be empowered to participate in health-enhancing PAs and to reduce daily sitting time in periods with strict confinement conditions when fitness centers and other sports facilities are closed. This study gives an opportunity to implement a module on healthy PA in the curriculum of the nutrition and dietetics division, and possibly in those for nursing and midwifery, of BFH-DHP. Furthermore, the BFH-DHP team for workplace health promotion might plan a similar module specifically for employees. Measures should be instigated to detect the very small group of physically inactive students and employees and to increase their health literacy on the negative effects of a totally sedentary lifestyle. Notwithstanding regular modifications of the curriculum, ad hoc action plans for an acute pandemic situation consisting of mainly digital distribution pathways may help and empower students and employees during similar lockdown situations.

Adherence to the Mediterranean diet during the preceding 7 days, as a reference for a healthy eating pattern [15] in this study, yielded a median mMDS of 11 (IQR 9-12) where the maximal score was 15. A total of 142 out of the 771 respondents (18.4%) included in the nutritional analyses showed low adherence (25^{th} percentile <9) to a healthy eating pattern during the confinement period. Undesirable changes to diet patterns have the potential to persist for some time, even after isolation measures are eased [27]. Participants from the nutrition and dietetics division adhered best to the healthy eating pattern, while participants from the nursing division adhered least well to the Mediterranean diet. It is encouraging to observe that participants from the nutrition and dietetics division—those who are, or have been, trained to become expert dietitians—showed the highest median mMDS. This indicates that they are adhering to a healthy eating pattern even under strict confinement conditions.

In this sample 96.3%, 97.4%, and 99.1% of the volunteers reported being abstinent or not drinking more than 1 unit of wine, beer, or liquor and spirits daily during the preceding 7 days. They adhered to the guidelines of the Swiss Federal Commission on Alcohol Issues for healthy adult females [28]. Following those Swiss guidelines, healthy adult males would be allowed to drink 2 units of alcoholic beverages daily. Alcohol consumption was evenly distributed across the participants of the different health profession divisions and between student study level and employee groups. The prevalence of moderate and high-risk alcohol drinkers in this study was much lower than in the German study of Keller et al [24], who reported 65% binge drinking in first-year university students. It is encouraging to observe the high prevalence of alcohol abstinence and healthy alcohol consumption habits in participants of the different health profession divisions of BFH-DHP, even under strict confinement conditions. However, on the individual level, 68 out of the 815

volunteers (8.3%) included in the alcohol consumption analysis reported daily alcohol intake of more than 1 unit, while 0.9% reported drinking more than 3 units per day of combinations of the different types of alcohol. These participants did not adhere to the Swiss healthy alcohol drinking guidelines for adult females [28]. It is impossible to check if the same 2 persons who reported a daily alcohol intake of more than 7 units of three types of alcohol are binge drinkers or simply reported their true consumption inaccurately.

Results of this study on nutritional habits and alcohol consumption may have important public health implications. When preparing health promotion campaigns to improve adherence to a more healthy eating pattern, the leaders of universities with different health profession divisions should primarily focus on those students and employees who are not enrolled at the division of nutrition and dietetics to empower them to practice healthier eating patterns, especially during a confinement period. This could be achieved by implementing a module on healthy eating habits in the curriculum of the divisions of midwifery, nursing, and physiotherapy. Furthermore, the team for workplace health promotion of such universities might plan such a module specifically for employees. Measures should be installed to detect the small group of students and employees with low to very low adherence to the Mediterranean diet and to increase their health literacy on the negative effects of an unhealthy eating pattern. Health promotion campaigns to strengthen the observed healthy attitude toward alcohol consumption in the majority of participants should focus on all students and employees; in addition, measures should be put in place to detect the small group of students and employees with unhealthy drinking behavior to increase their health literacy on the negative health and social effects of alcohol abuse, especially during such a confinement period.

During the confinement period and during the 7 days that preceded participation in this survey, the prevalence of poor sleeping quality or sleeping quality that could be improved was 44.7%. This is consistent with a study by Salehinejad et al [29] that showed that participants reported significantly poorer sleep quality in home quarantine during the COVID-19 crisis compared to the prequarantine time. For sleeping quality, no group differences between the participants of the different health profession divisions or between the students at different study levels and employees were found. The median sleeping duration in this sample was 8 hours, which represents adherence to healthy sleep guidelines [30]. Again, no group differences were observed. Prevalence of short sleep duration, defined as less than 7 hours of sleep in a 24-hour period [31], was 5.5%. This number is low compared to the prevalence of short sleep duration of 57.8% observed in 52,256 middle and high school students in the United States [32]. There is evidence that short sleep duration is associated with risk factors such as obesity, diabetes, mental health, and poor academic performance [32].

The observed later median wake-up time in the BSc students as compared to the MSc student group and the employee group could, at least partially, be explained by the fact that most BSc programs are full time while most MSc programs at BFH-DHP are part time, allowing MSc students to go to work.

Limitations

This study was conducted in a highly specific sample of members of the four divisions of different health professions at BFH-DHP in Switzerland. Generalizability to other universities or faculties may be hampered. Furthermore, this study evaluated the prevalence of risk factors in this population of university students and employees during the confinement period only. Therefore, a comparison with the preconfinement period cannot be made. To keep the questionnaire short and to guarantee anonymity, other important risk factors (eg, smoking status and stress status), demographic data (eg, age, sex, and living situation), and socioeconomic status data were omitted, making it impossible to correct for potential confounding factors. Socioeconomic status is indeed an important risk factor. Gallo et al [27] found that university students who had at least one graduate parent were more likely to achieve recommended levels of PA even during the lockdown as compared to their peers who had no graduate parent [10]. In self-reported surveys, a social desirability bias cannot be excluded. This is a special type of response bias describing a tendency of survey respondents to answer questions in a manner that will be viewed favorably by others and may lead to underreporting of unhealthy lifestyle habits and overreporting of healthy lifestyle habits [33]. This bias makes comparisons and interpretation of average tendencies difficult and has been well described in students of nutrition and dietetics [34]. It can be assumed that the issue of social desirability bias applies also for students and employees of other health professions. Another limitation of this study may be the lack of information about the current health status of the participants. Acute illness around the time of the survey may have interfered with usual PA levels or with nutritional and sleeping habits. Finally, a recently published meta-analysis on the validity of the IPAQ-SF concluded that there is but weak evidence to support the IPAQ-SF for the measurement of absolute or relative PA, yet only one of the 23 included studies compared the IPAQ-SF with the doubly labeled water technique as “criterion gold-standard” [35].

Conclusions

This survey described PA, sitting time, nutritional and alcohol consumption habits, and sleeping behavior of students and employees of a university of applied sciences during the 2020 COVID-19 confinement in Switzerland.

Results of this survey may help to make leaders of universities aware of the burden and the clustering of unhealthy lifestyle habits in students and employees during such a confinement period. Action plans are needed for health promotion campaigns for students and employees to be better prepared if a similar confinement period is imposed in the future. The findings of this study allow group-specific recommendations to be made: health promotion campaigns to increase PA and reduce physical inactivity should focus on students and employees, especially those in the nutrition and dietetics division, while healthy eating campaigns should primarily focus on those students and employees who are not enrolled in the division of nutrition and dietetics to empower them to practice healthier eating patterns, especially during a confinement period.

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Authors' Contributions

JT had the idea for and was project manager of this study. HB is the principal investigator of the research group. SR, JT, KH, EL, and HB designed the study protocol. SR and EL performed data collection and JT conducted the analyses and drafted the manuscript. SR, EL, JT, KH, and HB further edited the manuscript and all gave final approval.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data collection, data management, and data analysis.
[DOCX File , 23 KB - publichealth_v7i4e26330_app1.docx]

Multimedia Appendix 2
Calculated values for box and whisker plots for Figures 1 to 5 of the manuscript.
[DOCX File , 36 KB - publichealth_v7i4e26330_app2.docx]

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Abbreviations

BFH: Bern University of Applied Sciences
BFH-DHP: Bern University of Applied Sciences, Department of Health Professions
bMDSC: brief Mediterranean Diet Screener
BSc: Bachelor of Science
IPAQ-SF: International Physical Activity Questionnaire–Short Form
MET: metabolic equivalent
mMDS: modified Mediterranean Diet Score
MSc: Master of Science
PA: physical activity

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Short Paper

Assessment of the Effectiveness of Identity-Based Public Health Announcements in Increasing the Likelihood of Complying With COVID-19 Guidelines: Randomized Controlled Cross-sectional Web-Based Study

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Abstract

Background: Public health campaigns aimed at curbing the spread of COVID-19 are important in reducing disease transmission, but traditional information-based campaigns have received unexpectedly extreme backlash.

Objective: This study aimed to investigate whether customizing of public service announcements (PSAs) providing health guidelines to match individuals' identities increases their compliance.

Methods: We conducted a within- and between-subjects, randomized controlled cross-sectional, web-based study in July 2020. Participants viewed two PSAs: one advocating wearing a mask in public settings and one advocating staying at home. The control PSA only provided information, and the treatment PSAs were designed to appeal to the identities held by individuals; that is, either a Christian identity or an economically motivated identity. Participants were asked about their identity and then provided a control PSA and treatment PSA matching their identity, in random order. The PSAs were of approximately 100 words.

Results: We recruited 300 social media users from Amazon Mechanical Turk in accordance with usual protocols to ensure data quality. In total, 8 failed the data quality checks, and the remaining 292 were included in the analysis. In the identity-based PSA, the source of the PSA was changed, and a phrase of approximately 12 words relevant to the individual's identity was inserted. A PSA tailored for Christians, when matched with a Christian identity, increased the likelihood of compliance by 12 percentage points. A PSA that focused on economic values, when shown to individuals who identified as economically motivated, increased the likelihood of compliance by 6 points.

Conclusions: Using social media to deliver COVID-19 public health announcements customized to individuals' identities is a promising measure to increase compliance with public health guidelines.

Trial Registration: ISRCTN Registry 22331899; https://www.isrctn.com/ISRCTN22331899.

(JMIR Public Health Surveill 2021;7(4):e25762) doi:10.2196/25762

KEYWORDS

Amazon Mechanical Turk; compliance; COVID-19; custom; effectiveness; guideline; identity; public health; public health announcement; public service announcement; social media; web-based health information

Introduction

Public compliance with recommended guidelines to limit the spread of SARS-CoV-2 and COVID-19 is an important component in combating the disease [1]. Current guidelines suggest several measures, such as wearing a mask and staying at home [2]; nonetheless, a large number of individuals fail to follow the guidelines provided by public health officials [3]. Public compliance to guidelines remains an issue [3-5].

Public service announcements (PSAs) have long been used to promote public health behaviors, although their success and the success of PSAs in general have been inconsistent [6]. Information-based PSAs are often successful because they present facts about the nature of a threat, explain the benefits of a response, and provide a clear call to action [7]. However, it remains unclear whether presenting information is sufficient in a posttruth era as the world battles the COVID-19 pandemic. There has been strong backlash against wearing masks and staying at home [3,5] and "irrational behavior" in noncompliance with COVID-19 policies [8]. Psychological reactance occurs when individuals feel that previously permitted behaviors are constrained by an external agent, which impugns their freedom [9,10]. In such situations, individuals resist the constraint and attempt to regain their lost freedom [9,10]. Thus, rather than helping, a PSA could backfire by sparking reactance, which triggers individuals to eschew the recommended behavior and even actively impair compliance [11].

The likelihood of reactance may also be increased by the divisions among people in the United States along ideological lines, with stark differences in the extent to which those on the political left and right wings believe that COVID-19 is a legitimate threat [1,12-14]. In the era of tribalism and distrust toward experts, identity has become as central to many arguments as scientific information [14-16]. The interaction of an individual's identity with the source and content of the message can shape responses as much as the information that the message contains [17,18].

Individuals' identities determine how they answer the question of "who am I?" [19-21]. According to the social identity theory, these answers are dependent upon both social and personal identities [19-22]. Social identities derive from the social groups to which individuals belong [22], such as race, nationality, and organizational or religious affiliations [23-25]. Personal identities derive from values that individuals consider important [20,25,26], such as volunteering [27], environmentalism [28], or the economy and economic values [29-31]. Both social and personal identities can be potent influences on behavior because people are motivated to act in ways that align with their identity in order to maintain a sense of self-consistency [22,25,32,33].

Persuasive messages such as PSAs can take advantage of this desire for identity-consistent actions by framing a proposed action as being consistent with individuals' social or personal identity [34]. Speaking the language of an identity by using terms and arguments associated with that identity may render a more persuasive message [35]. Framing the advocated action as identity-consistent can further encourage individuals to adopt the desired behavior [34] because once an individual knows how others with the same identity act, it is easier to convince oneself to act in that same manner [1]. Thus, identity-framed messages are more persuasive than general messages [35].

This study aimed to investigate whether customizing PSAs in accordance with the source and language of a social identity (specifically Christian) or a personal identity (specifically economically motivated) increases the intention of individuals who identify with those identities to comply with the behaviors advocated by a PSA. We selected these identities because individuals who resist public health guidelines frequently provide religious [36,37] and economic [38] excuses. If individuals with these identities could be persuaded to follow public health guidelines, the benefits could be substantial [39]. We sought to investigate whether framing a PSA in accordance with a Christian social identity or an economically motivated personal identity increases the likelihood of compliance with COVID-19 guidelines among individuals who hold those identities.

Methods

Study Overview

We conducted a within- and between-subjects, randomized controlled cross-sectional, web-based study. All data were collected on the internet and no identifying information was collected in order to protect participants' privacy and confidentiality. The study was reviewed by the institutional review board of Indiana University (protocol# 2004499544) and was determined to be an exempt study. The study was initiated with the institutional review board approving the study data and if participants consented to participate, they were enrolled in the study.

Participants

In July, 2020, we recruited 300 participants from Amazon Mechanical Turk in accordance with the usual protocols to ensure data quality [40]. We recruited participants only from the United States who held an Amazon Masters classification and included a captcha to preclude nonhuman responses. Participants were paid US $1.25 and spent an average of about 13 minutes participating in the study (minimum: 3.6 minutes, maximum 11 hours). In total, 8 subjects failed 1 or more of the 3 attention checks (that asked participants to select specific answers), thus yielding 292 participants. All participants received both the control and treatment conditions; hence, demographics are described at the study level. Approximately 49% of participants were female, and 82% were White, 8% were Asian, 7% were Black, and 3% were of other racial backgrounds. The median age of the study participants was 30

years (24%: 18-24 years, 33%: 25-34 years, 19%: 35-44 years, 16%: 45-54 years, 6%: 55-64 years, and 1%: ≥65 years).

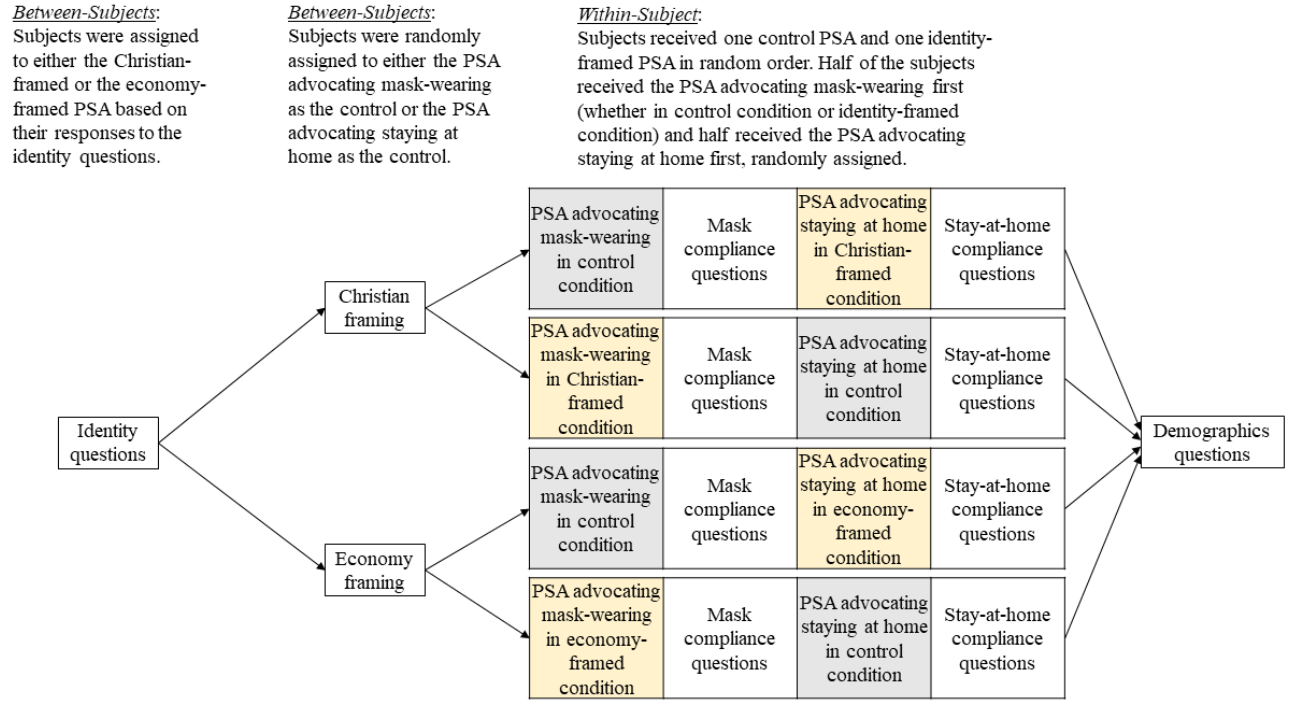
Study Design and Interventions

At the beginning of the survey, subjects were asked a series of questions to ascertain their identification with Christianity and with the economic health of the country (our selected identities). Participants were provided either the Christian-framed treatment or economy-framed PSAs depending on which identity they identified with more. If subjects identified with both identities equally, they were randomly assigned to 1 of the 2 treatments. The experimental design is presented in Figure 1.

Participants then received two COVID-19 PSAs in random order: 1 advocating wearing a mask and 1 calling on people to stay at home. One was a control PSA with information purportedly from the US Public Health Service and the other was an identity-framed PSA (either Christian-framed or economy-framed). After reading each PSA, participants reported the extent to which they would engage in the advocated behavior. Each subject received 1 identity-framed PSA and 1 control PSA; thus, we could examine the within-person effects of PSA framing and could control for differences in compliance between mask-wearing and staying at home.

The PSAs were of approximately 100 words. The treatments changed the source of the PSA and 1 sentence of their content. The identity-framed PSA contained a single short, substituted phrase designed to appeal either to people who held a Christian social identity (purportedly written by the Chaplain of the US Senate) or to those for whom protecting the country's economy was a central feature of their personal identity (purportedly written by the US Chamber of Commerce). For example, the control PSA for wearing a mask stated, "You should wear a mask whenever you are in public and see other people," which was replaced by, "We have a Christian duty to love our neighbors, and wearing a mask whenever you are in public and see other people is a way you can do this" in the Christian-framed PSA and by, "We now know how you can do your part to help us safely reopen our economy: wearing a mask whenever you are in public and see other people" in the economy-framed PSA. All PSAs are provided in Multimedia Appendix 1.

Figure 1. Experimental design. PSA: public service announcement.



Measurements

In accordance with previous studies, Christian identity, economically motivated identity, and trust in the 3 PSA sources were measured with single-item 7-point Likert scales [41-43]. Identity-framed PSAs were deemed to be aligned with the participant's identity when the participant's identity scores were 6 or 7 and the participant did not distrust the source (ie, trust in the source was ≥4). The likelihood of compliance was measured using 7 items adapted from previous studies [44,45]. The outcome compliance items were measured using scales of 0-100, not the same 7-point scales as those used for the independent variables to classify participants, to reduce the risk of a common method bias [46]. The likelihood of compliance proved reliable (Cronbach α=.94), thus indicating convergent validity. An exploratory factor analysis was performed to assess the discriminant validity among the constructs, which was satisfactory. The results of the items and factor analysis are presented in Multimedia Appendix 1.

Statistical Analysis

A power analysis using G*Power [47] determined that a sample of 300 participants with this design would provide a power of .93 to detect a small effect size (Cohen *f*=0.10). We analyzed the data using hierarchical linear modeling (HLM) [48] with robust standard errors using HLM for Windows (version 6.00,

Scientific Software International, Inc). HLM accounts for the correlation among the repeated within-subject observations and facilitates the assessment of the alignment or nonalignment of the identity-framed treatment condition with the participant's identity. All tests were 2-tailed with a significance level of α=.05 α=.05. We used the formula of Snijders and Bosker [49] to calculate R^2. The likelihood of complying was nonnormally distributed. For the PSA advocating mask-wearing, the mean likelihood of compliance was 78.75 (SD 29.79), and the median likelihood was 92.93; for the PAS advocating staying at home, the mean likelihood of compliance was 74.51 (SD 29.67), and the median likelihood was 86.75. HLM is robust to departures from the normality assumption for large samples such as this one [48].

Results

Table 1 shows the mean (SD) values of the likelihood of compliance under different experimental conditions. Overall, participants displayed more willingness to wear a mask than to stay at home. Furthermore, we observed higher means for identity-aligned PSAs than for non–identity-aligned PSAs. Table 2 shows the results of statistical analysis. The overall model has a large effect size, with an R^2 of 41.6%.

When participants received an identity-framed PSA that was aligned with their identity, they were more likely to comply with it rather than a purely information-based PSA in the control treatment (Christian-framed PSA: *P*=.01; economy-framed PSA: *P*=.01). The effects were significant, increasing compliance by almost 13% to the Christian-framed PSA (95% CI 2.9-22.6) and almost 7% to the economy-framed PSA (95% CI 1.5-12.1) compared to the control non–identity-framed PSA. The average effect sizes (Cohen *d*) for the Christian-framed and economy-framed PSAs were 0.30 and 0.24, respectively, which are between small and medium. This is congruent with our predictions that providing individuals with customized PSAs that align with their identities will increase their intention to comply with the advocated behaviors including staying at home or wearing a mask in public.

When participants received an identity-framed PSA that was not aligned with their identity, it did not significantly influence their likelihood of complying, although both nonaligned PSAs approached significance with negative coefficients (Christian-framed PSA: *P*=.10; economy-framed PSA: *P*=.10), which suggests that a nonaligned PSA may potentially be more damaging to compliance than a control PSA. Compliance was significantly greater for PSAs advocating mask-wearing than for those advocating staying at home (*P*=.001), which suggests that our participants were more likely to comply with the practice of wearing a mask than staying at home. Likewise, the main effects of some of the other control variables that we used to assess alignment (ie, trust and identity) were significant and some were not.

Table 1. Means for the likelihood of complying with public service announcements (PSAs). Data were collected in July 2020 from 292 participants from Amazon Mechanical Turk, who viewed two PSAs: 1 advocating wearing a mask and 1 advocating staying at home. One PSA was an information-based control PSA and the other was a Christian or economically motivated identity–framed PSA.

PSA type	Likelihood of staying at home		Likelihood of wearing a mask	
	Mean (SD)	Number of participants	Mean (SD)	Number of participants
Economy-framed PSA when aligned	78.94 (21.54)	65	84.26 (19.68)	78
Christian-framed PSA when aligned	81.99 (26.29)	31	84.62 (27.97)	24
Nonaligned PSA	68.09 (34.59)	51	63.35 (37.76)	43
Control PSA	71.09 (31.11)	145	77.85 (30.85)	147

Table 2. Analysis results with beta coefficients (β) for identity-framed public service announcements (PSAs) and information-based control PSAs (584 observations; 292 participants; R^2=41.6%).

Parameter	Likelihood of complying with PSAs	
	β (SE)	*P* value
Economy-framed PSA	−3.60 (2.19)	.10
PSA aligned with an economically motivated identity	6.77 (2.65)	.01
Christian-framed PSA	−6.86 (4.11)	.10
PSA aligned with a Christian identity	12.74 (4.94)	.01
PSA advocating mask-wearing	4.06 (1.23)	.001
Christian identity	−1.60 (0.64)	.01
Economically-motivated identity	−2.56 (1.41)	.07
Measure of trust		
Trust in the US Public Health Service	12.40 (1.12)	.00
Trust in the Senate Chaplain	−0.12 (0.64)	.92
Trust in the Chamber of Commerce	−1.42 (1.21)	.24
Constant	74.02 (1.61)	.00

Discussion

Principal Findings

Our study shows that modifying PSAs to leverage social and personal identities can promote increased compliance with public health guidelines for individuals who hold these identities. The Christian-framed PSA increased compliance by approximately 12.74 points (out of 100) when viewed by those with a Christian identity, and the economy-framed PSA increased compliance by approximately 6.77 points when viewed by those with an economically motivated identity. One might conclude that the Christian framing is more powerful, but this only applies to individuals who hold that identity. Hence, we believe that it is better to compare the 2 different identity-framed PSAs to their own controls, not to each other, as the differences in the coefficients between the 2 identity-aligned PSAs may have resulted from various subject-level factors that influence their different identities. For example, those with a Christian identity were slightly less likely to comply (*P*=.01) with any PSA, possibly because those with conservative beliefs are less likely to believe that COVID-19 is a legitimate threat [1,14].

Based on the social identity theory, we hypothesized that messages designed to activate an identity by using inclusive language and a consistent message source would be more effective in increasing compliance to PSAs rather than those without consistent identity-framing. Identity-framing was intended to emphasize commonalities between the individual and like-group members and to encourage users to act in accordance with those in their group [1]. Identity-framing harnesses the relevant identity that the individual holds and appeals to those relevant traits. This simple act of creating identity-aligned targeted PSAs significantly increased compliance with the behavior advocated in the PSAs. We decided to examine a Christian identity and an economically motivated identity on the basis of excuses that are commonly invoked to justify noncompliance [36-38]. We found both to be effective in increasing compliance. Various other social or personal identities may also be effective in increasing the compliance to PSAs.

The promise of identity-framed PSAs is noteworthy in view of the myriad of rampant rumors, misinformation, and disinformation regarding COVID-19 [12-14]. Rapidly developing situations, uncertainty, and fear foster the spread of false information (created with or without the deliberate intention to mislead people). It is unfortunate that individuals' responses to COVID-19 have implied that the provision of simple, information-based PSAs sometimes triggered psychological reactance and led to actions that disrupt public health efforts [1,13]. Our results show that designing PSAs to appeal to specific target demographics can increase their effectiveness beyond that of a message that simply provides correct information.

The vast amount of information about individuals available on social media platforms makes it practical to create multiple versions of a PSA and share the most individually relevant version with people, thereby making the message more persuasive [50]. Social media is an attractive channel to rapidly reach many people as it has more than 2 billion active users [50]. Identity-framed PSAs could facilitate public health goals by enabling the PSA to influence people who would otherwise ignore the message, capturing their attention by speaking their language, activating relevant identities, and reducing psychological reactance by framing the actions as being consistent with their identity [25,35]. By encouraging people to view a situation through the lens of a supportive identity, the effects of countervailing identities that dissuade people from the desired outcome can be reduced. Public Health agencies and nonprofits should take advantage of these tools when designing future public awareness campaigns. By leveraging readily available identity information to make minor adjustments to the framing of PSAs, such groups could facilitate higher

compliance with public health guidelines, thus enabling better outcomes. With increasing ease of accessing personal data, the small cost of targeting a PSA toward those individuals that would best respond (similar to targeted advertising) has the potential to yield enormous benefits with increased nationwide health outcomes.

We examined 1 social identity (Christian) and 1 personal identity (economically motivated) linked to noncompliance [36-38]. Many other identities may also be leveraged to enhance the effectiveness of PSAs. By reminding people of a role identity as a parent or grandchild, leveraging social group identities such as sport team loyalty, or by appealing to their self-identity as caring individuals, many opportunities are available to use identities to help persuade people to follow public health guidelines. Our use of 2 identities shows that this method can be successful; however, it is unclear which other identities may also be used. Future studies are required to investigate why some identities may be effective when used to increase compliance while others may not be effective. Furthermore, it remains unclear whether compliance is affected more by the relationship between the identity and the target behavior or that between the identity and the individual, or whether both relationships are equally important.

While we control for trust toward the source of the PSA, a potentially interesting question is one regarding the mediating influence of variables (eg, perceived similarity to the identity used in the PSA). While we did not assess perceived similarity, we controlled for the strength of the identity. Since our study suggests that identity-framed PSAs can be used to influence compliance, more studies are needed to investigate the potential mediating and moderating variables that could strengthen or weaken the effectiveness of identity-framed PSAs. For example, our identity-framed PSA contained only 1 modified sentence; however, it remains unclear whether adding more identity-related framing would increase its effectiveness, or whether it is sufficient to simply invoke the identity as in our PSAs. Moreover, it remains unclear whether the source of the message is a critical factor, or whether the message more important than the source.

Limitations

This study has the usual limitations of randomized controlled cross-sectional study. We assessed self-reported perceptions at one point in time, not actual behavior over several periods of time. Our participants were those who participate in research studies and thus may differ from those who decline to participate in research studies.

Conclusions

Compliance with public health measures designed to mitigate the COVID-19 pandemic has unfortunately become intertwined with identity, and individuals with certain social and personal identities are less likely to comply with the behaviors advocated in the PSAs. Our study shows that identity can also be an effective factor to induce compliance. The development of identity-framed PSAs may be effective in contexts beyond the COVID-19 pandemic. The most important factors to consider when developing effective PSAs are that the identities in question are deeply held and can be associated with recommended actions when coordinated efforts across society are needed.

Authors' Contributions

ARD had full access to all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. Furthermore, ARD supervised the study and performed the statistical analysis. AK acquired the data. All authors conceived and designed the study, drafted the manuscript, and provided administrative, technical, and material support.

Conflicts of Interest

None declared.

Editorial Notice

This randomized study was only retrospectively registered as, according to the authors, their field has not adopted pre-registration as convention. The editor granted an exception from ICMJE rules mandating prospective registration of randomized trials because the risk of bias appears low. However, readers are advised to carefully assess the validity of any potential explicit or implicit claims related to primary outcomes or effectiveness, as retrospective registration does not prevent authors from changing their outcome measures retrospectively.

Multimedia Appendix 1
Experimental Materials.
[PPTX File , 189 KB - publichealth_v7i4e25762_app1.pptx]

Multimedia Appendix 2
CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 499 KB - publichealth_v7i4e25762_app2.pdf]

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Abbreviations

HLM: hierarchical linear modeling
PSA: public service announcement

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Original Paper

“Thought I’d Share First” and Other Conspiracy Theory Tweets from the COVID-19 Infodemic: Exploratory Study

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Abstract

Background: The COVID-19 outbreak has left many people isolated within their homes; these people are turning to social media for news and social connection, which leaves them vulnerable to believing and sharing misinformation. Health-related misinformation threatens adherence to public health messaging, and monitoring its spread on social media is critical to understanding the evolution of ideas that have potentially negative public health impacts.

Objective: The aim of this study is to use Twitter data to explore methods to characterize and classify four COVID-19 conspiracy theories and to provide context for each of these conspiracy theories through the first 5 months of the pandemic.

Methods: We began with a corpus of COVID-19 tweets (approximately 120 million) spanning late January to early May 2020. We first filtered tweets using regular expressions (n=1.8 million) and used random forest classification models to identify tweets related to four conspiracy theories. Our classified data sets were then used in downstream sentiment analysis and dynamic topic modeling to characterize the linguistic features of COVID-19 conspiracy theories as they evolve over time.

Results: Analysis using model-labeled data was beneficial for increasing the proportion of data matching misinformation indicators. Random forest classifier metrics varied across the four conspiracy theories considered (F1 scores between 0.347 and 0.857); this performance increased as the given conspiracy theory was more narrowly defined. We showed that misinformation tweets demonstrate more negative sentiment when compared to nonmisinformation tweets and that theories evolve over time, incorporating details from unrelated conspiracy theories as well as real-world events.

Conclusions: Although we focus here on health-related misinformation, this combination of approaches is not specific to public health and is valuable for characterizing misinformation in general, which is an important first step in creating targeted messaging to counteract its spread. Initial messaging should aim to preempt generalized misinformation before it becomes widespread, while later messaging will need to target evolving conspiracy theories and the new facets of each as they become incorporated.

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KEYWORDS

COVID-19; coronavirus; social media; misinformation; health communication; Twitter; infodemic; infodemiology; conspiracy theories; vaccine hesitancy; 5G; unsupervised learning; random forest; active learning; supervised learning; machine learning; conspiracy; communication; vaccine; public health

Introduction

Background

On December 31, 2019, the World Health Organization (WHO) was made aware of a cluster of cases of viral pneumonia of unknown origin in Wuhan, Hubei Province, China [1]. The WHO reported this cluster via Twitter on January 4, 2020, saying, "#China has reported to WHO a cluster of #pneumonia cases —with no deaths— in Wuhan, Hubei Province. Investigations are underway to identify the cause of this illness [2]." On January 19, the WHO Western Pacific Regional Office tweeted evidence of human-to-human transmission, saying, "According to the latest information received and @WHO analysis, there is evidence of limited human-to-human transmission of #nCOV. This is in line with experience with other respiratory illnesses and in particular with other coronavirus outbreaks [3]." The first case in the United States was reported the next day. Five days later, on January 26, 2020, *GreatGameIndia* published the article "Coronavirus Bioweapon–How China Stole Coronavirus From Canada And Weaponized It," which claimed that the coronavirus was leaked into China from a Canadian laboratory [4]. The original article received 1600 likes on its first day of publication; it was then reposted verbatim but with the more provocative headline "Did China Steal Coronavirus From Canada And Weaponize It" on the website *ZeroHedge* [5]. This version was reposted by the website RedStateWatcher.com, one of the 140 most popular sites in the United States, with more than 4 million followers on Facebook; from there, the story quickly went viral [6].

Misinformation surrounding pandemics is not unique to SARS-CoV-2, the virus that causes COVID-19. At least as far back as the Russian flu pandemic of 1889, pandemic spread of *misinformation*, claims of fact that are either demonstrably false or unverifiable [7], has been concomitant with disease spread [8]. People are susceptible to misinformation when trust in authoritative sources is low, which can occur when officials provide conflicting information and guidance [9]. Misinformation will also include *conspiracy theories*, which posit explanations of events or circumstances based primarily on a conspiracy [10] (ie, an agreement between a small group of people to commit an illegal act). Although some conspiracies, such as Watergate or the Tuskegee experiments, may eventually be proven to be true criminal acts, the vast majority of conspiracy theories are not true, and their spread can undermine public health efforts [11]. Some conspiracy theories may be better classified as *disinformation*—false or misleading information that is intentionally passed to a target group [12] with its true source concealed [13].

The COVID-19 outbreak has left many people isolated within their homes, and these people are turning to social media for news and social connection. Thus, they are especially vulnerable to believing and sharing conspiracy theories [14]. This study examines four oft-repeated and long-lived conspiracy theories surrounding COVID-19: 5G technology is somehow associated with the disease; Bill Gates or the Bill & Melinda Gates Foundation created or patented the virus; the virus is human-made and was released from a laboratory; and a COVID-19 vaccine will be harmful. None of these conspiracy theories are unique, nor are they entirely distinct.

5G Cell Towers Spread COVID-19

Cellular carriers began a limited rollout of 5G cellular service in 2018 [15], which required the installation of new cell towers [16]. These new towers were already the source of a more general conspiracy theory that the signal is harmful to humans and that its dangers were being "covered up" by "powerful forces in the telecommunications industry" [17]. Wireless technology has consistently been blamed for causing immune damage in humans, and similar theories were seen with the rollouts of 2G, 3G, 4G, and Wi-Fi service [17]. Even the 1889 Russian flu was purported to be caused by the then-new technology of electric light [8]. The COVID-19–related 5G conspiracy theory emerged in the first week of January, and it may not have evolved past a fringe view into a trending hashtag without being shared by websites with the primary aim of spreading conspiracy theories on Twitter or by people aiming to denounce the theory [18].

Bill Gates and the Bill & Melinda Gates Foundation

J Uscinski stated that conspiracy theories often "are about accusing powerful people of doing terrible things" [19]. The Bill & Melinda Gates Foundation is arguably the largest philanthropic venture ever attempted, and it has proven to be fertile ground for the development of conspiracy theories, ranging from misinterpretations of a "patent on COVID-19" [20] to incorporation of vaccine-averse concerns. For example, the Bill & Melinda Gates Foundation funded research to develop injectable invisible ink to serve as a permanent record of vaccination in developing countries [21,22]. This technology was announced in December 2019, the same month that SARS-CoV-2 emerged in Wuhan, China, and a conspiracy theory emerged suggesting that the COVID-19 vaccine would be used to microchip individuals with the goal of population control [20].

Laboratory Origins

Associations between HIV and other infectious diseases consistently re-emerge, including associations with polio [23], Ebola virus [24], and COVID-19. The COVID-19–related HIV conspiracy theory began on January 31, 2020, with the preprint publication of "Uncanny similarity of unique inserts in the 2019-nCoV spike protein to HIV-1 gp120 and Gag" ([25], withdrawn paper), which was quickly retweeted by Anand Ranganathan, a molecular biologist with over 200,000 followers on Twitter. He cited the preprint as evidence of a potential laboratory origin with a now-deleted Tweet: "Oh my god. Indian scientists have just found HIV (AIDS) virus-like insertions in the 2019-nCoV virus that are not found in any other coronavirus. They hint at the possibility that this Chinese virus was designed…" Within two hours, Ross Douthat, a prominent *New York Times* opinion columnist, retweeted Ranganathan to his >140,000 followers, further legitimizing the theory through a reputable news outlet and greatly furthering the reach of the story outside the scientific community [26]. Three days after the initial release of the preprint, the original paper was retracted.

Laboratory origin theories have also garnered political attention; then-US President Donald Trump claimed to have evidence of a Chinese laboratory origin of SARS-CoV-2 [27], prompting a Twitter response from a Chinese government account [28] that was flagged by Twitter as misinformation [29]. Additional laboratory-related conspiracy theories quickly emerged, including theories that the virus was created to achieve global population reduction or to impose quarantines, travel bans, and martial law, all of which were previously seen during the 2014 Ebola virus outbreak [24] and the 2015-2016 Zika virus outbreak [30].

Vaccines

Vaccine-related social media articles are often shared by people who are relatively knowledge-deficient and vaccine-averse compared to nonsharers [31], with content consisting of debunked associations with autism and general mistrust of government or the pharmaceutical industry. With newly emergent diseases such as HIV and Ebola, conspiracy theories quickly followed regarding the ability to profit off of vaccines while conspiring with American pharmaceutical companies [24].

In the past year, substantial work has emerged investigating the onslaught of misinformation related to COVID-19. Multiple studies have found that misinformation is common; both social media platforms [32-34] and web pages returned results for common COVID-19 queries at the beginning of the pandemic [35], including scientific journals without sufficiently rigorous review processes [36].

Social media studies have so far indicated that original tweets present false information more often than evidence-based information, but that evidence-based information is more often retweeted [32]; therefore, during the first three months of the outbreak, the volume of misinformation tweets was small compared to that of the overall conversation [37]. The amount of Twitter data related to COVID-19 dwarfed that of other health-related content, but proportionally more of the data originated from credible websites [33].

Researchers have also attempted to characterize the people who are likely to believe misinformation. One nationally representative study in the United States found that some myths (eg, that the virus was created or spread on purpose) were believed by over 30% of respondents [38]. Evidence across several countries shows that people who believe misinformation are more likely to obtain information from social media or have a self-perceived minority status [39], and characteristics such as "trusting scientists" and obtaining information from the WHO had a negative relationship with belief in misinformation [40].

With the above framing in mind, this paper seeks to answer the following research questions:

1. *Can conspiracy theories identified a priori be automatically identified using supervised learning techniques?*

We used a large corpus of Twitter data (120 million initial tweets and 1.8 million tweets after our initial regular expression filtering step) and random forest models to classify tweets associated with the four conspiracy theories described above.

2. *Can identified tweets about defined conspiracy theories be characterized by existing methodologies?*

We used tweet sentiment to assess the emotional valence in conspiracy theory tweets compared to their non–conspiracy theory counterparts. We used dynamic topic modeling, an unsupervised learning approach, to explore the changes in word importance among the topics within each theory.

3. *Can our findings inform public health messaging to reduce the effects of misinformation found on social media?*

We compared the results of the preceding research questions to identify commonalities and connections between early conspiracy theories that can be addressed by initial public health messaging to prevent further misinformation spread. We additionally showed that theories evolve to include real-world events and incorporate details from unrelated conspiracy theories; therefore, later public health messaging will also need to evolve.

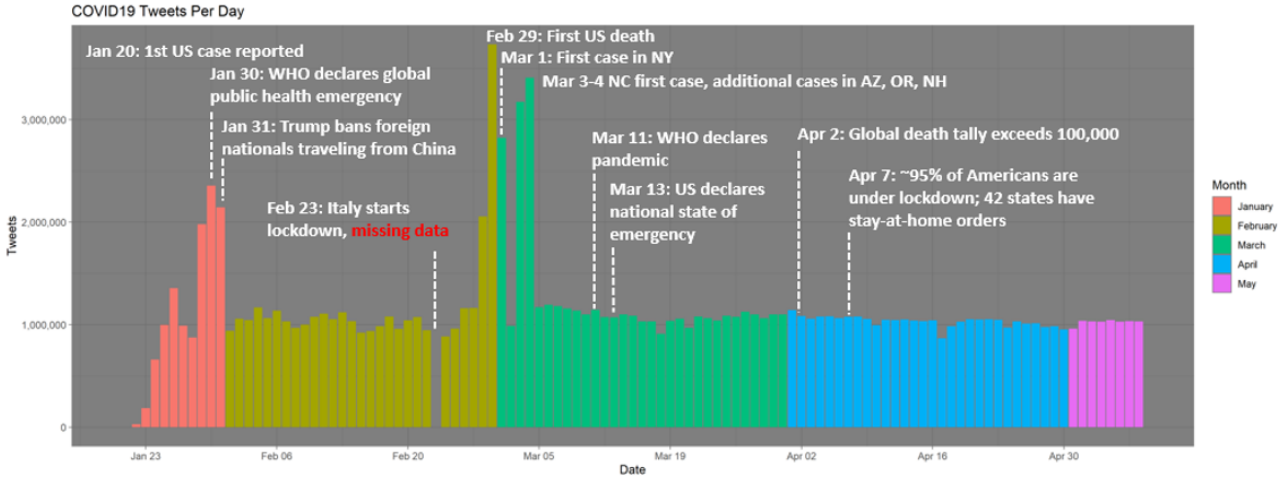
Methods

Data

Twitter Data

The Twitter data used for this study were derived from Chen et al (2020) [41], who constructed the tweet IDs of tweets that include COVID-19 keywords and health-related Twitter accounts and made them publicly available. Due to limitations in the Twitter application programming interface (API), these data represent a 1% sample of tweets that included these keywords or tracked accounts. We gathered these data from the Twitter API using the released IDs, identifying approximately 120 million tweets from January 21 to May 8, 2020 (see Figure 1). Although the initial repository includes tweets in a variety of languages [41], we restricted our analysis to tweets in English.

Figure 1. Volume of Twitter data collected during the study period. Twitter data were collected from January 21 to May 8, 2020, representing the first five months of the COVID-19 pandemic. We have annotated this timeline with major events to provide context during this early period of the pandemic. AZ: Arizona; NC: North Carolina; NH: New Hampshire; NY: New York; OR: Oregon; Trump: US President Donald Trump; US: United States; WHO: World Health Organization.



NewsGuard

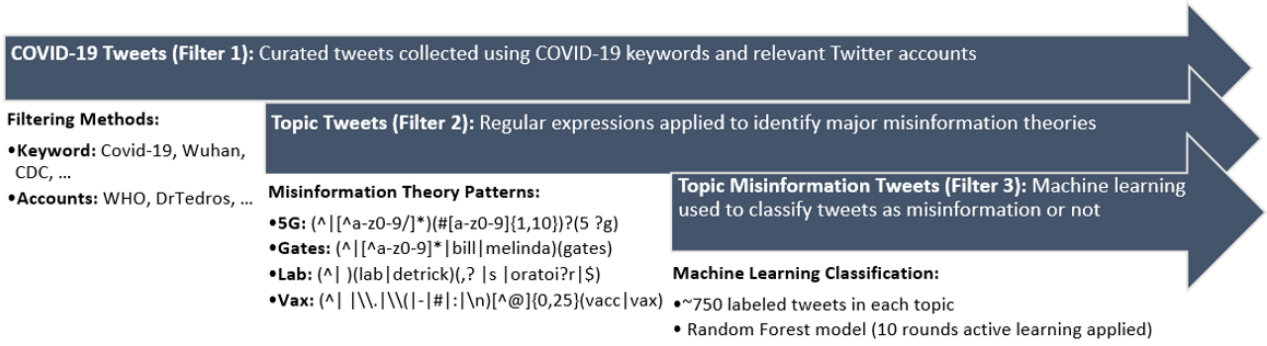
NewsGuard provides evaluations of thousands of websites based on criteria including funding transparency, journalistic integrity, and editorial track record [42]. Since the emergence of COVID-19, NewsGuard has also provided a summary of major myths and conspiracy theories associated with the pandemic, the earliest documented claims, major events that caused significant spread, and detailed reports of major sources of COVID-19 misinformation in their "Special Report: COVID-19 Myths" [20]. From this list, we identified four theories that were especially prominent in our Twitter data set and that were commonly discussed in mainstream news media. In addition, we used the domains classified as "not credible" and related to COVID-19 myths, as identified by NewsGuard, as features in our classification models described below.

Filtering and Supervised Classification

We filtered the data into four data sets using regular expressions (see Figure 2) to increase the number of relevant tweets in each category of interest [43-47]. The four data sets are hereafter referred to using the following terms:

- 5G: 5G technology is somehow associated with COVID-19.
- Gates: Bill and Melinda Gates or the Bill & Melinda Gates Foundation funded, patented, or otherwise economically benefited from SARS-CoV-2.
- Lab: SARS-CoV-2 is human-made or bioengineered and was released (intentionally or accidentally) from a laboratory.
- Vax: A COVID-19 vaccine would be harmful in a way not supported by science (eg, it could contain a microchip).

Figure 2. Tweet-filtering flow. The initial tweet corpus was obtained from Chen et al [41], who used keywords and known accounts to provide a sample of COVID-19–related Twitter data (Filter 1). We then used regular expressions to create four conspiracy theory data sets (Filter 2) and machine learning classifiers to identify misinformation tweets within each data set (Filter 3). 5G: conspiracy theories related to 5G technology; CDC: US Centers for Disease Control and Prevention; Gates: conspiracy theories related to Bill Gates or the Bill & Melinda Gates Foundation, Lab: conspiracy theories related to the virus being laboratory-released or human-made; Vax: conspiracy theories related to vaccines; WHO: World Health Organization.



Within each regular expression-filtered conspiracy theory data set, we randomly sampled 1000 tweets to create the training data. After sampling, duplicate tweets were removed. Two authors coded each set of tweets and established agreement by jointly coding a subset of tweets (see Table 1). Any tweet promoting or engaging with misinformation, even to refute it, was labeled as COVID-19 misinformation. This labeling was performed with the rationale that tweeting about misinformation, even in the context of a correction, increases the size of the audience exposed to that misinformation. In prior work on COVID-19 conspiracy theories, it was found that engaging with a theory to correct it can indeed increase the overall visibility

of the theory [18]. Interrater analysis found relatively high agreement and reasonable Cohen κ scores (mean 0.759, Table 1). However, the effort demonstrated the difficulty of reliably identifying misinformation; in many cases, oblique references and jokes fell in a gray area that raters labeled "uncertain" (~6.1% of the coded tweets). A second pass was made over tweets labeled "uncertain" by comparing rater assessments and marking these tweets as "COVID-19 misinformation" or "not COVID-19 misinformation" based on rater agreement. For example, if annotators 1 and 2 had high agreement when labeling 5G tweets, a tweet labeled by annotator 1 as "uncertain" could be relabeled as "COVID-19 misinformation". Using this approach, we were able to avoid removing data and thus shrinking the amount of available training data.

Table 1. Interrater results from the creation of the training data. Tweets were randomly sampled from the regular expression-filtered data sets and duplicates were removed. Each rater was assigned a portion of overlapping tweets to allow for interrater evaluation.

Theory	Unique tweets labeled (n)	Tweets labeled by multiple authors (n)	Agreement	Cohen κ
5G[a]	725	146	0.852	0.708
Gates[b]	711	143	0.893	0.782
Lab[c]	735	146	0.901	0.796
Vax[d]	775	199	0.915	0.751

[a]5G: conspiracy theories related to 5G technology.

[b]Gates: conspiracy theories related to Bill Gates or the Bill & Melinda Gates Foundation.

[c]Lab: conspiracy theories related to SARS-CoV-2 being laboratory-released or human-made.

[d]Vax: conspiracy theories related to vaccines.

The tweets were tokenized, and both URLs and stop words were removed. Unigrams and bigrams were used as features in a document-term matrix, and the most sparse (<0.05% populated) terms were removed. Additionally, we added Boolean features describing relationships to domains identified by NewsGuard as sources of misinformation. This was achieved by linking associated Twitter accounts to tracked websites. Features included (1) a tweet originating from a misinformation-identified domain, (2) a tweet replying to an originating tweet, (3) a tweet retweeting an originating tweet, or (4) a tweet that was otherwise linked (eg, replying to a retweet of a tweet from a misinformation source). As noted elsewhere, only English tweets were used in this analysis.

The data were partitioned into a two-thirds/one-third training-test split. Data were sampled so that the training data had an equal sample distribution (50% misinformation, 50% nonmisinformation). The testing data used the remaining available data; thus, the sample distribution was uneven.

Classifiers were built using R, version 3.6.3 (R Project); the randomForest package, version 4.6-14, was used to train random forest models with 150 trees up to 25 terminal nodes (and at least 3 terminal nodes), and 25 variables were randomly sampled at each split. Case sampling was performed with replacement. We used an active learning approach in which after each run of the random forest classifier, the calculated posterior entropy was used to select the three unlabeled tweets that caused the most uncertainty in the model. These were then hand-labeled by an author (DG) and applied to the next run of the model. We applied 9 cycles of active learning to each model. Additionally, for each hand-labeled tweet, highly similar tweets (string similarity ≥0.95) were identified and given the same label. This approach was implemented using the R activelearning package, version 0.1.2. The models that performed the best (measured by F1 score) were used to assign labels to the regular expression-filtered tweets.

Sentiment Analysis

Two well-documented sentiment dictionaries were used to label the tokenized tweets. The first, AFINN [48], provided an integer score ranging from –5 (negative sentiment) to +5 (positive sentiment) for each word in the dictionary. The second dictionary, the National Research Council (NRC) Word-Emotion Association Lexicon [49], was used to tag words with categories of emotion, providing labels for 8 emotions of anger, anticipation, disgust, fear, joy, sadness, surprise, and trust in addition to an overall "positive" or "negative" sentiment. We then compared the sentiment for each classified data set over time. For each tweet, aggregate sentiment metrics were calculated, including the sum of integer scores and the counts for each emotion label.

Dynamic Topic Modeling

Dynamic topic modeling (DTM) was used to characterize themes and analyze temporal changes in word importance [50]. DTM divides tweets into weekly time slices based on the time they were generated. The set of topics at each time slice is then assumed to evolve from the set of topics at the previous time slice using a state space model. The result is an evolving probability distribution of words for each topic that shows how certain words become more or less important over time for the same topic. Traditional topic models, such as latent Dirichlet allocation [51], assume that all the documents (which are here equivalent to tweets) are drawn exchangeably from the same topic distribution, irrespective of the time when they were generated. However, a set of documents generated at different times may reflect evolving topics.

Dynamic topic models were trained for each conspiracy theory, with the number of topics ranging from 2-5. Small numbers of topics were chosen because these tweets were already classified to be relevant for individual misinformation topics, and because our goal was to identify potential subtopics that evolved over time. The optimal number of topics was assessed qualitatively

by reviewing the topic modeling results. DTM was implemented in Python using the gensim [52] wrapper ("ldaseqmodel") for the DTM model [50,53].

Results

Filtering and Supervised Classification

After filtering using regular expressions, our corpus included roughly 1.8 million unique tweets across the four conspiracy theories (Table 2). The relative volume of tweets in each data set is shown in Figure 3. The number of tweets appearing in multiple data sets corresponds to the edge thickness. All the data sets showed some degree of overlap between categories, with Gates showing the most overlap and 5G showing the least. 5G additionally had a low volume of tweets compared to the other theories.

Table 2. Results of the regular expression filtering step. After filtering using regular expressions on tweets spanning January 21 to May 8, 2020, the number of tweets per conspiracy theory and the number of tweets that were included in multiple theories are shown. The number of tweets within each filtered data set that were later classified as COVID-19 misinformation and the number of classified tweets that appear in multiple theories are also provided.

Conspiracy theory	Tweets after regular expression filtering (n=1,901,108), n (%)	Tweets after regular expression filtering found in multiple theories, n (%)	Tweets classified as COVID-19 misinformation, n (%)	Tweets classified as COVID-19 misinformation found in multiple theories, n (%)
5G[a]	127,209 (6.69)	6300 (4.95)	51,049 (40.13)	1984 (1.56)
Gates[b]	278,130 (14.63)	69,566 (25.01)	147,657 (53.09)	35,880 (12.90)
Lab[c]	526,115 (27.64)	44,198 (8.40)	224,052 (42.59)	20,001 (3.80)
Vax[d]	969,654 (51.00)	82,380 (8.50)	206,046 (21.25)	34,435 (3.55)

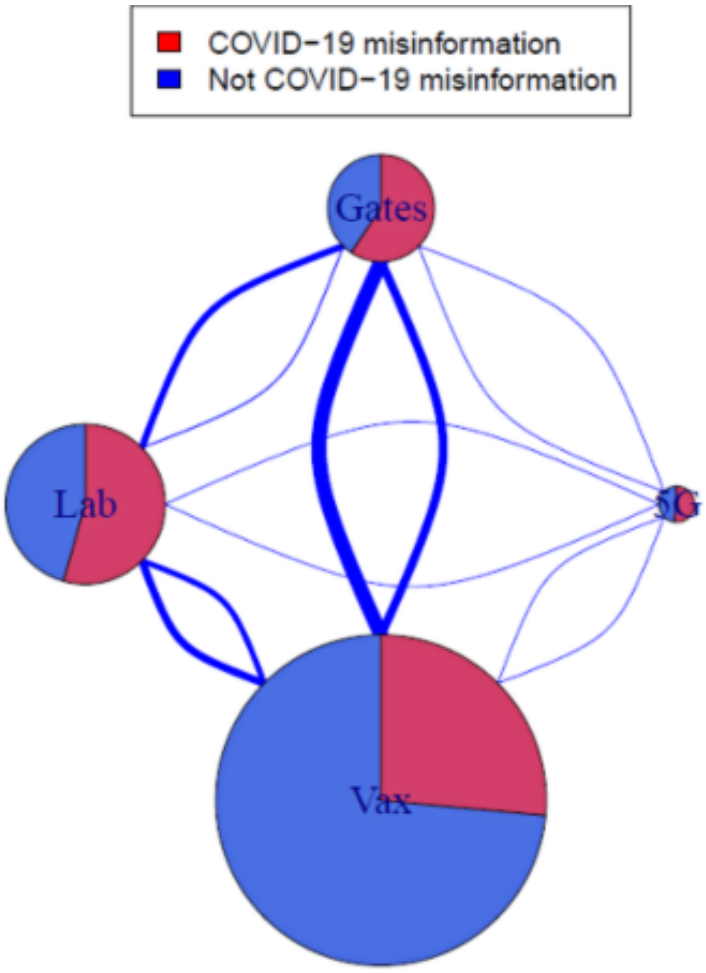
[a]5G: conspiracy theories related to 5G technology.

[b]Gates: conspiracy theories related to Bill Gates or the Bill & Melinda Gates Foundation.

[c]Lab: conspiracy theories related to SARS-CoV-2 being laboratory-released or human-made.

[d]Vax: conspiracy theories related to vaccines.

Figure 3. Data set volumes and overlap by theory. The node size indicates the total number of tweets discussing each conspiracy theory, while the edge thickness corresponds to the number of tweets discussing any pair of conspiracy theories simultaneously. 5G: conspiracy theories related to 5G technology; Gates: conspiracy theories related to Bill Gates or the Bill & Melinda Gates Foundation; Lab: conspiracy theories related to SARS-CoV-2 being laboratory-released or human-made; Vax: conspiracy theories related to vaccines.



The model performance metrics for each theory are presented in Tables 3 and 4. Class proportions were roughly balanced in the 5G, Gates, and Lab theories. The Vax tweets were heavily imbalanced, with only ~18% labeled as COVID-19 misinformation (Table 3). The best performing models were the 5G and Lab theories, with F1 scores of 0.804 and 0.857, respectively (Table 4). Although the results for the Gates theory were weaker (F1 score=0.654), Vax scored the lowest (F1 score=0.347). This could be due to the imbalanced nature of the data set.

Table 3. Distributions of labels for the four COVID-19 conspiracy theories.

Conspiracy theory	Label distribution		
	COVID-19 misinformation, n	Not COVID-19 misinformation, n	Proportion of COVID-19 misinformation, %
5G[a]	367	356	50.8
Gates[b]	354	356	49.9
Lab[c]	407	327	55.4
Vax[d]	142	632	18.3

[a]5G: conspiracy theories related to 5G technology.

[b]Gates: conspiracy theories related to Bill Gates or the Bill & Melinda Gates Foundation.

[c]Lab: conspiracy theories related to SARS-CoV-2 being laboratory-released or human-made.

[d]Vax: conspiracy theories related to vaccines.

Table 4. Random forest model results. Random forest with active learning often, although not universally, shows improved performance compared to generic random forest models. The change between these two approaches is noted in the Change column.

Conspiracy theory and metrics	Random forest	Random forest with active learning	Change
5G[a]			
Accuracy	0.779	0.783	0.004
Recall	0.908	0.872	–0.036
Precision	0.728	0.744	0.016
F1 Score	0.808	0.804	–0.004
Gates[b]			
Accuracy	0.622	0.5819	–0.04
Recall	0.675	0.793	0.118
Precision	0.608	0.556	-0.052
F1 Score	0.64	0.654	0.014
Lab[c]			
Accuracy	0.782	0.84	0.058
Recall	0.699	0.833	0.134
Precision	0.9	0.883	–0.017
F1 Score	0.787	0.857	0.070
Vax[d]			
Accuracy	0.507	0.751	0.244
Recall	0.653	0.474	–0.1786
Precision	0.170	0.274	0.104
F1 Score	0.270	0.347	0.077

[a]5G: conspiracy theories related to 5G technology.

[b]Gates: conspiracy theories related to Bill Gates or the Bill & Melinda Gates Foundation.

[c]Lab: conspiracy theories related to SARS-CoV-2 being laboratory-released or human-made.

[d]Vax: conspiracy theories related to vaccines.

Sentiment Analysis

The range in sentiment was significantly greater for COVID-19 misinformation, with tweets more consistently showing increased negative sentiment, especially in April and May 2020. Figure 4 shows Gates-related tweets by net sentiment score over time. See Multimedia Appendix 1 for additional figures related to other conspiracy theories (Figures S1-S3).

Figure 4. Sentiment comparison for data from tweets about COVID-19 conspiracy theories related to Bill Gates and the Bill & Melinda Gates Foundation by label. Tweets are plotted over time and stratified by misinformation status. Sentiment varies from highly negative to highly positive. Loess smoothing was used to draw the blue line indicating general trend over time.

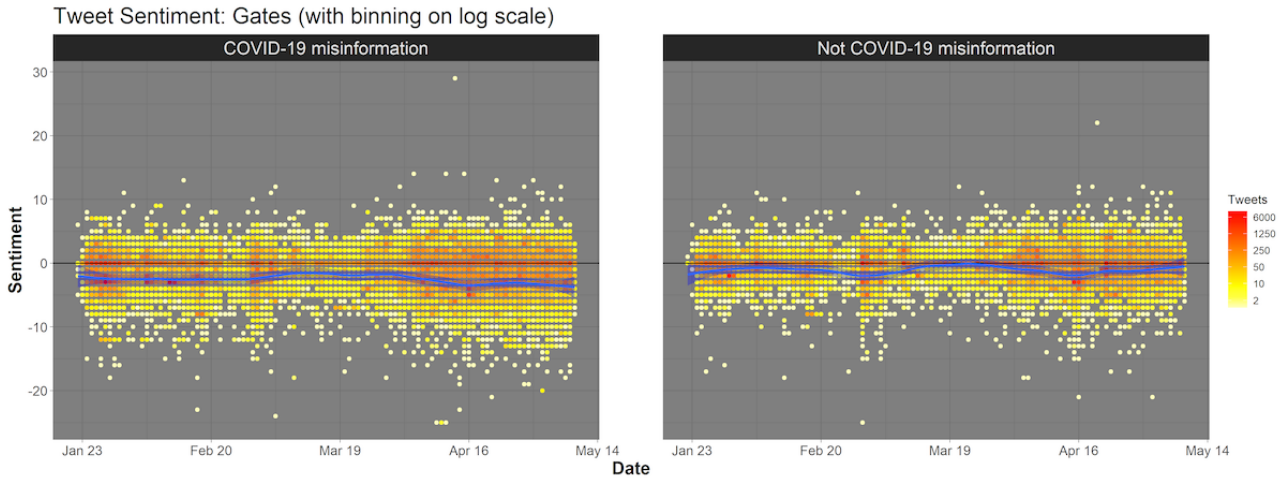
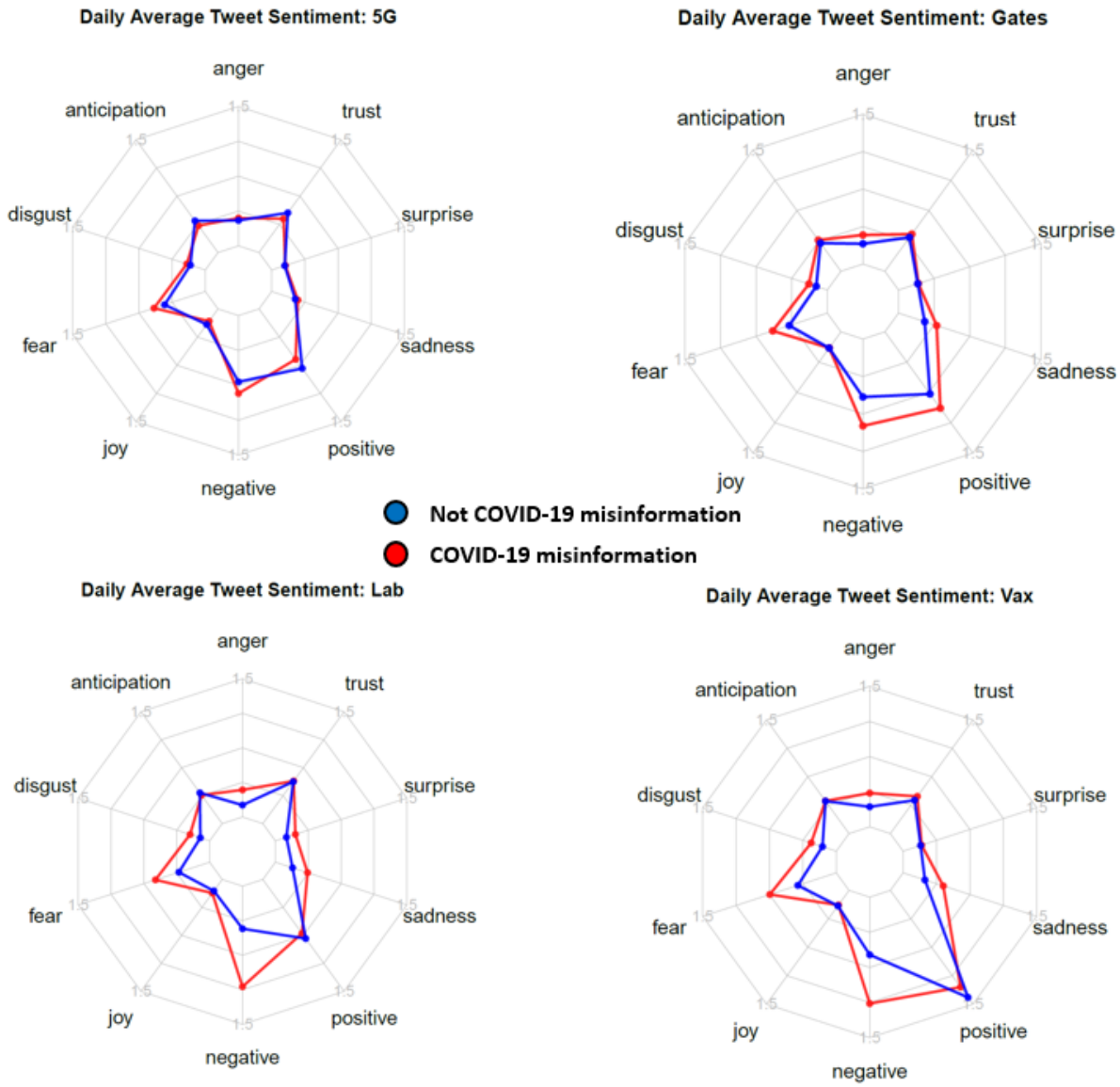


Figure 5 shows the sentiments of tweets (with daily average sentiment scores for each category averaged across all dates in the study range) in each conspiracy theory subset across eight emotions and the general negative or positive sentiment. Although tweets related to 5G conspiracies show similar results for misinformation and nonmisinformation, there are clear differences in the other four conspiracy theories. In general, tweets classified as misinformation tend to rate higher on negative sentiment, fear, anger, and disgust compared to tweets not classified as misinformation.

Figure 5. Sentiment comparison for each conspiracy theory by classification. The average numbers of words per tweet flagged for each sentiment category are plotted. 5G: conspiracy theories related to 5G technology; Gates: conspiracy theories related to Bill Gates or the Bill & Melinda Gates Foundation; Lab: conspiracy theories related to SARS-CoV-2 being laboratory-released or human-made; Vax: conspiracy theories related to vaccines.



DTM Analysis

For each conspiracy theory data set, DTM was used to identify 2-5 potential subtopics and understand their evolution over time. The optimal model was assessed qualitatively by reviewing the results. Models with 2 topics led to optimal results (qualitatively coherent topics with the least amount of overlap) for Gates, 5G, and Lab theories, while the model with 3 topics qualitatively led to optimal results for Vax theories. The results for the Gates theory are visualized here, and the remaining theories are visualized in Multimedia Appendix 1.

The Gates theory was optimally represented by 2 topics. Both topics showed peaks of increased Twitter discussion in mid-January to mid-February and a second peak in April (Figure 6). The initial peaks in Topic 1 corresponded to high weighting of the words *predicted*, *kill_65m*, *event*, and *simulation*, while the later spike in April showed higher weights for words such as *fauci* and *buttar* (Figure 7). The model identified a second topic that referred to several conspiracy theories about Bill Gates, SARS-CoV-2, and vaccines. This second topic initially focused on theories about the origins of the virus, with highly weighted words including *pirbright* and *patent*. In late April, higher-weighted words included *kennedy*, *jr*, and *fauci*.

The Vax data showed high weighting for the word *bakker* in Topic 1 and a brief increase in the word *microchip* in early April

within Topic 2 (Multimedia Appendix 1, Figure S6). The term *bakker* refers to the tele-evangelist Jim Bakker, who promoted myths about possible COVID-19 cures, including the use of colloidal silver, on his show [54]. A linguistic shift in referring to the virus was also observable within the vaccine theory, with *coronavirus* highly weighted until mid-March, when *COVID* became more frequently used.

In the Lab data, words such as *biosafety*, *biowarfare*, *warned*, and *laboratory* were more highly weighted early in the outbreak, suggesting that people were discussing a malicious laboratory release [63] (Multimedia Appendix 1, Figure S5, topic 2*)*. The weight of words such as *escaped*, *evidence*, and *originated* increased as the theory evolved over time. Overlap was seen between the Lab theory and the Gates theory, including words such as *kill*, *kill_65m*, and *kill_forget*. In addition, we observed terms related to other, older theories, such as *ebola* in Topic 2 in mid-January, and terms related to Jeffrey Epstein and conspiracy theories associated with his death (*epstein*, *forget_epstein*) [40].

Figure 6. Topic distribution over time for the 2-topic dynamic topic model for tweets related to the conspiracy topic of Bill Gates and the Bill & Melinda Gates Foundation. Tweets belonging to Topic 1 are more common in the conversation in January, while Topic 2 becomes more prominent in the spring. Additionally, distinct peaks show the popularity of tweets related to this conspiracy theory category overall.

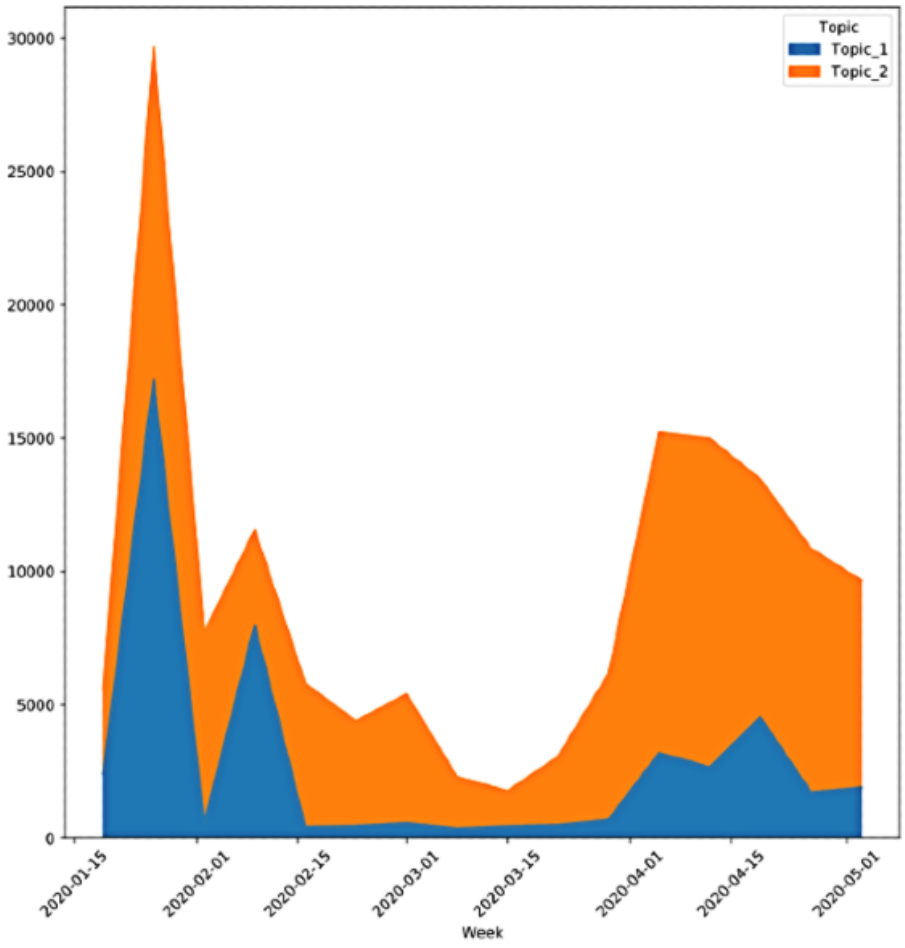
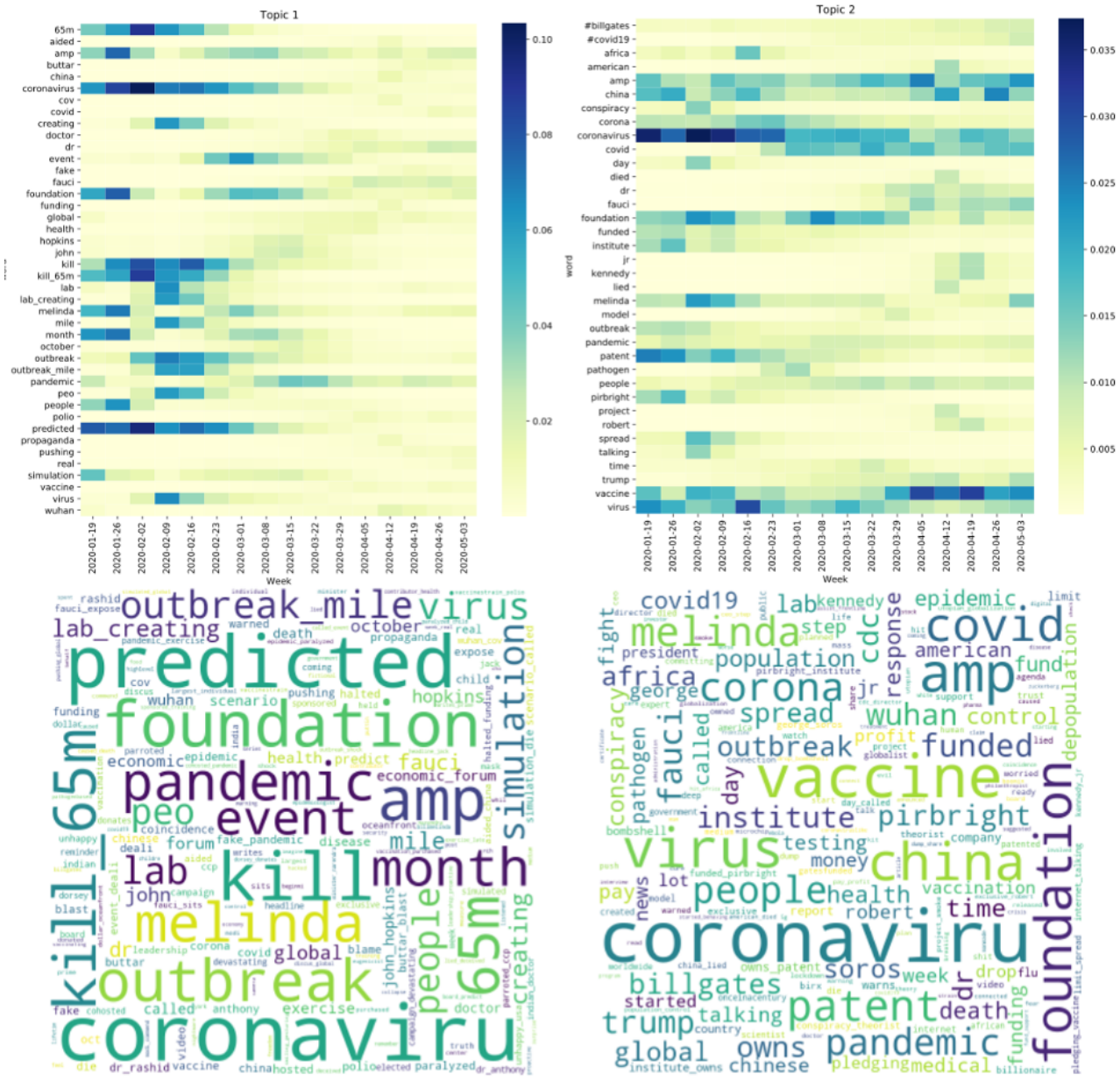


Figure 7. Topic evolutions and word clouds for COVID-19 conspiracy theories related to Bill Gates and the Bill & Melinda Gates Foundation. Top panel: word evolution in the 2-topic dynamic topic model. Color represents the importance of the words, with a darker color denoting higher importance. Bottom panel: word clouds for each topic. The size of each word corresponds to its weight (higher-weighted words are larger in size).



Discussion

Principal Findings

The ongoing COVID-19 pandemic clearly illustrates the need to identify health-related misinformation, especially with a lens toward improving communication strategies to combat it. We focused on four specific conspiracy theories and fused existing methods to identify relevant tweets and characterize the language used over time. This is especially important in the context of COVID-19 as an emerging infectious disease, when much of the scientific knowledge about its risks, transmission, and mitigation may be quickly evolving [56]. With this context in mind, we address our findings with respect to each research question below.

Can Conspiracy Theories Identified A Priori Be Automatically Identified Using Supervised Learning Techniques?

In prior work, it was found that misinformation, defined more broadly than just conspiracy theories, is relatively common on social media [32-34], with some caveats. For example, although original tweets were found to present false information more often than evidence-based information, evidence-based information was retweeted more often [32]. In another analysis, it was found that although a greater proportion of data on Twitter originated from credible websites than from noncredible websites, there were instances in which low-quality content was boosted by credible websites; it was also found that website credibility may be a poor marker of the quality of information being presented [33]. Overall, we classified 582,290 tweets (32% of the regular expression–filtered corpus) as relating to

at least one of the four specific conspiracy theories considered. Using regular expression–based filtering and supervised learning, we identified tweets associated with these conspiracy theories. Classification models performed quite well for the 5G and Lab theories because the focus of these conspiracy theories was well defined. Classifiers for the Gates conspiracy theory performed more moderately, likely because the theory was broad and its content overlapped with that of the other three theories. The Vax theory performed the worst, likely due to class imbalance.

Can Identified Tweets About Defined Conspiracy Theories Be Characterized by Existing Methodologies?

We used sentiment analysis to assess the affective states of tweets classified as misinformation. Overall, misinformation-classified tweets showed more negative sentiment over time, both on a scale from negative to positive sentiment and when discretized into specific emotions. Within specific conspiracy theories, these differences were the smallest when comparing misinformation and nonmisinformation in the 5G data. This could be a result of the intense political polarization surrounding the rollout of 5G in Europe, even when discussed outside the context of COVID-19. Importantly, in prior work, it was found that individuals who believe conspiracy theories have personality characteristics aligned with the emotions that were most strongly identified in our tweets. For example, research has found that individuals who subscribe to conspiracy theories tend to be suspicious of others, uncertain, and anxious [57].

We used dynamic topic modeling to find evidence of conspiracy theory evolution over time and to identify overlaps between theories. In Gates-classified tweets, early terms such as *predicted*, *kill_65m*, *event*, and *simulation* all refer to the simulation of a novel zoonotic coronavirus outbreak at Event 201, a global pandemic exercise that was co-hosted by several organizations, including the Bill & Melinda Gates Foundation [58]. The simulation predicted that a disease outbreak would spread to multiple countries and result in 65 million deaths. However, in April, the high-importance words shifted to include *fauci* and *buttar*, which corresponded to news coverage in which Dr Rashid Buttar stated that SARS-CoV-2 was manufactured to hurt the economy and that Dr Anthony Fauci and Bill Gates were using the pandemic to drive hidden agendas [59].

Similar morphing in the second topic of the Gates theory shows a shift in focus from funding the virus to vaccine-averse theories. Early terms such as *pirbright* and *patent* correspond to theories that the Gates Foundation funded or patented the virus through the Pirbright Institute, a UK-based company. Later, this topic morphed to include several words associated with vaccine hesitancy, such as *kennedy*, *jr*, and *fauci*, corresponding to claims by Robert Kennedy Jr that a COVID-19 vaccine would personally benefit Dr Anthony Fauci or Bill Gates. This shift in words from focusing on SARS-CoV-2 as a manufactured virus to vaccine-averse conspiracy theories highlights the importance of real-world events. Bill Gates participated in an "Ask Me Anything" on Reddit in March 2020, which highlighted Gates-funded research to develop injectable invisible ink that could be used to record vaccinations [21,22]. Immediately after this event, the prominence of words associated with vaccine-averse conspiracy theories increased, with tweets suggesting that the COVID-19 vaccine would be used to secretly microchip individuals for population control [20].

Finally, we assessed connections between conspiracy theories. Connections were most frequently identified in the Gates theory, for which nearly 13% of tweets classified as "COVID-19 misinformation" were identified in one or more of the other tracked theories. This was consistent with identified conspiracy theories connecting the Bill & Melinda Gates Foundation to work in disease research and vaccination technology. Although the Gates, Vax, and Lab theories had demonstrable overlap, only approximately 1.5% of tweets associated with 5G were found to have overlap. This may be due to the previously noted controversies surrounding the rollout of 5G in Europe.

Frequent overlap with conspiracies unrelated to COVID-19 was also observed. The Lab category showed an overlap with prior conspiracy theories about other disease outbreaks. For example, the word *ebola* was highly weighted, corresponding to the 2014-2016 Ebola outbreak, which also sparked conspiracy theories around its bioengineering or laboratory origins [11]. Other unrelated conspiracy theories were noted, including terms related to Jeffrey Epstein and his death. These observations are consistent with prior studies that showed that people who believe in one conspiracy theory are more likely to also believe in others or are more broadly prone to conspiratorial thinking [60,61].

Can Our Findings Inform Public Health Messaging to Reduce the Effects of Misinformation Found on Social Media?

In exploring these four conspiracy theories, we found a clear distinction between the 5G theory and the other conspiracy theories. The 5G theory was specific and narrow in scope, while the other conspiracy theories were substantially broader, could include numerous variations on the precise actor, location, or perceived threat, and had more overlap with the other conspiracy theories overall.

It is likely that the clear scope of the 5G theory contributed to its exceptionally high classification metrics. Additionally, these distinctions in the context of public health are valuable for contextualizing any public health messaging efforts that seek to address misinformation. When determining whether to address a spreading conspiracy theory, the degree to which an emerging theory becomes entwined with existing information should determine whether the conspiracy theory should be addressed with targeted messaging versus more generalized public health information. For instance, attempts to debunk the isolated 5G connection theory were seen to elevate the exposure of the theory to a wider audience [18], while messaging regarding vaccine development and safety could both inform the public more generally and address several conspiracy theories simultaneously without promoting any particular theory.

We additionally show that conspiracy theories evolve over time by changing in focus and scope. This theory evolution will likely necessitate public health messaging, which also evolves to address a changing landscape. Our work demonstrates that off-the-shelf methods can be combined to track conspiracy

theories, both in the moment and through time, to provide public health professionals with better insight into when and how to address health-related conspiracy theories. These same methods can also track public reaction to messaging to assess its impact.

Limitations

A major limitation of any work on misinformation is that we obviously cannot examine all relevant theories, or even all of the nuance in our four identified public health-related theories, in any single study. Conspiracy theories are continuous in nature, as demonstrated here, whereas we can only observe a discrete sample within any single study. Because of this, we must aim for internal validity within any single, well-defined study and hope that many such studies will contribute to a "big picture" of social media misinformation and its effects. Not only has COVID-19 misinformation continued to spread past the end of our analysis in May 2020, but emerging conspiracy theories and topics continue to relate back to the conspiracy theories presented here. For instance, our research into claims about a laboratory origin of SARS-CoV-2 focused on popular conspiracy theories around a Chinese laboratory in Wuhan, a Canadian laboratory, and Fort Detrick in the United States. However, even at the time of this writing, two additional theories have gained traction. One indicates that the virus originated from the French Pasteur Institute; another suggests that it originated in a laboratory at the University of North Carolina [20]. We hope that results captured at the time of this analysis can inform subsequent investigations.

Second, our labeled training data explicitly labeled attempts to correct or refute misinformation as misinformation. Although this approach more accurately captured the exposure a given conspiracy might have in social media, it likely led to overestimation of the number of individuals supporting any particular theory. Excluding corrections could also have produced subtly different sentiment and dynamic topic model results, as people promoting conspiracy theories will likely differ in sentiment and word usage from those attempting to refute them. We chose to include corrections to avoid attempting to infer tweet context (eg, sarcasm is difficult to distinguish in an individual tweet) and because retweeting inaccurate information, even to correct it, still increases the number of individuals who see inaccurate content [18]. Prior work has identified both rumor-correcting and rumor-promoting tweets during crises using Twitter data [62]. Future work would benefit from considering these separately.

Additionally, our exclusive use of Twitter data fails to capture the entirety of the spread of misinformation. Social media platforms have broadly faced significant challenges in identifying and containing the spread of misinformation throughout the course of the COVID-19 pandemic [7]. Twitter users are also known to be a demographically biased sample of the US population [63-65]. Future research would benefit from analysis of misinformation on other social media platforms. Our findings are thus not generalizable to the US population as a whole. However, we emphasize that the goal of this study is not to achieve generalizability but rather to achieve internal validity by accurately categorizing sentiment and describing misinformation patterns within this population.

Conclusions

Characterizing misinformation that poses concerns to public health is a necessary first step to developing methods to combat it. The ability to assess conspiracy theories before they become widespread would enable public health professionals to craft effective messaging to preempt misperceptions rather than to react to established false beliefs. Health officials too often fail to craft effective messaging campaigns because they target what they want to promote rather than addressing the recipients' existing misperceptions [66]. Misinformation can spread rapidly and without clear direction; this is evidenced by one tweet we uncovered while conducting this research, which shared an article promoting a conspiracy theory with the commentary that the user had not established credibility but rather "thought I'd share first" (tweet anonymized for privacy). An understanding of the appearance, transmission, and evolution of COVID-19 conspiracy theories can enable public health officials to better craft outreach messaging and to adjust those messages if public perceptions measurably shift. This study demonstrates that identifying and characterizing common and long-lived COVID-related conspiracy theories using Twitter data is possible, even when those messages shift in content and tone over time.

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Authors' Contributions

DG, NP, ARD, CWR, GF, and NYVC collected and analyzed the data. DG and ARD labeled the data for supervised learning classifiers. NP ran the dynamic topic models, which NP, DG, CDS and ARD analyzed. TP performed geospatial analyses. DG ran the sentiment analysis and built the supervised models. CDS and DG wrote the initial manuscript. All authors contributed critical revisions of the manuscript. ARD led the project.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary figures.
[DOCX File , 2876 KB - publichealth_v7i4e26527_app1.docx]

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Abbreviations

API: application programming interface
DTM: dynamic topic modeling
NRC: National Research Council
WHO: World Health Organization

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Original Paper

A Recursive Model of the Spread of COVID-19: Modelling Study

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Abstract

Background: The major medical and social challenge of the 21st century is COVID-19, caused by the novel coronavirus SARS-CoV-2. Critical issues include the rate at which the coronavirus spreads and the effect of quarantine measures and population vaccination on this rate. Knowledge of the laws of the spread of COVID-19 will enable assessment of the effectiveness and reasonableness of the quarantine measures used, as well as determination of the necessary level of vaccination needed to overcome this crisis.

Objective: This study aims to establish the laws of the spread of COVID-19 and to use them to develop a mathematical model to predict changes in the number of active cases over time, possible human losses, and the rate of recovery of patients, to make informed decisions about the number of necessary beds in hospitals, the introduction and type of quarantine measures, and the required threshold of vaccination of the population.

Methods: This study analyzed the onset of COVID-19 spread in countries such as China, Italy, Spain, the United States, the United Kingdom, Japan, France, and Germany based on publicly available statistical data. The change in the number of COVID-19 cases, deaths, and recovered persons over time was examined, considering the possible introduction of quarantine measures and isolation of infected people in these countries. Based on the data, the virus transmissibility and the average duration of the disease at different stages were evaluated, and a model based on the principle of recursion was developed. Its key features are the separation of active (nonisolated) infected persons into a distinct category and the prediction of their number based on the average duration of the disease in the inactive phase and the concentration of these persons in the population in the preceding days.

Results: Specific values for SARS-CoV-2 transmissibility and COVID-19 duration were estimated for different countries. In China, the viral transmissibility was 3.12 before quarantine measures were implemented and 0.36 after these measures were lifted. For the other countries, the viral transmissibility was 2.28-2.76 initially, and it then decreased to 0.87-1.29 as a result of quarantine measures. Therefore, it can be expected that the spread of SARS-CoV-2 will be suppressed if 56%-64% of the total population becomes vaccinated or survives COVID-19.

Conclusions: The quarantine measures adopted in most countries are too weak compared to those previously used in China. Therefore, it is not expected that the spread of COVID-19 will stop and the disease will cease to exist naturally or owing to quarantine measures. Active vaccination of the population is needed to prevent the spread of COVID-19. Furthermore, the required specific percentage of vaccinated individuals depends on the magnitude of viral transmissibility, which can be evaluated using the proposed model and statistical data for the country of interest.

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KEYWORDS

epidemiology; COVID-19; model; modelling; prediction; spread; infection; effective; contagious; transmission

Introduction

The first mathematical models to predict the development of infectious diseases were used in the early 20th century [1,2]. In 1927, Kermack and McKendrick [3] proposed the use of differential equations for calculations, dividing the human population into people susceptible to disease (S) and those who had already recovered (R). The susceptible persons became infected (I) at some rate of transmission and then recovered at

a different rate. Their model became known by the acronym SIR, which means that the model simultaneously calculates the number of susceptible, infected, and recovered persons. This model served as a basis for the development of subsequent models—by modifying the equations and adding to the calculation other persons not belonging to the three specified basic categories, which allowed consideration of the features of particular diseases. Since then, various models have been created that consider the possibility of re-infection (SIS model) [4] and death (SIRD model) [5], the existence of an incubation period (SEIR model) [6], and temporary immunity of infants (MSIR model) [7], among others.

When a new infection appears, neither the set of population categories to be considered in the model nor the rate of transition of people from one category to another is known. Current information about the features of the COVID-19 infection caused by the novel coronavirus (SARS-CoV-2) and the manner in which people perceive it and act should serve as a basis for building a model to describe the spread of this virus. These features can be described as follows: first, the presence of a long incubation period, during which the infected persons are contagious to others, and second, the isolation of discovered infected persons, which as a result become conditionally noncontagious. The combination of these two factors makes this novel coronavirus infection unique. In general, the opposite is true—infected people are not dangerous to others during the incubation period and become contagious after its expiry. For this reason, a new model that considers these circumstances is needed to predict the spread of COVID-19. However, the duration of the immunity produced after recovery from COVID-19 is currently unknown. In addition, there is also very little information available to accurately calculate the rate of recovery among patients with COVID-19: a small percentage of the population recovers within just a week after contracting infection, whereas the majority of people experience the illness for a long time. Therefore, the proposed model cannot be final, but it is necessary for forecasting and management decisions.

Methods

The model for COVID-19 spread is based on a set of parameters whose values are unique for each country due to differences in population density, human behavior, date of virus penetration, and government actions. The set includes the following parameters:

- d_0 is the date of the initiation of the epidemic; it is not the date of detection of the first infected person but the date of appearance of the first undetected (or detected too late) person.
- d_1, d_2, and d_3 are dates of change in the behavior of the population, for example, due to the awareness of the reality of what is happening and the introduction of quarantine and its tightening.
- t_D is the average time from infection to isolation of the infected person, which is equal to the incubation period assumed to be 6 days (ranging from 5.2 to 6.4 days according to different sources [8,9]); theoretically, this parameter can be reduced by testing of the entire population, but it is feasible only for small communities.
- R_0, R_1, R_2, and R_3 are the viral transmissibilities that are equal to the average number of people who will be infected by one person before he or she is isolated and depend on the behavior of the population at different stages of the epidemic; when R is less than 1.0, the epidemic fades, and vice versa.
- r_0, r_1, r_2, and r_3 are the reduced viral transmissibilities that are equal to the average number of people who will be infected by one person per day: $r = R/t_D$; to suppress the spread of COVID-19, r should be less than 0.167.

The evaluation of the spread of the virus is based on the calculation of the following data:

- $N_D(d_i)$ is the number of infected persons detected on d_i date, which equals the total number of infected persons 6 days earlier:

$$N_D(d_i) = N_T(d_i\text{-}t_D)$$

- $N_T(d_i)$ is the total number of infected persons on date d_i, which is the sum of the total number of infected persons the day before and the number of new infected persons that, in turn, is equal to the product of the reduced transmissibility and the number of active infected persons the day before (taking into account that those who have been previously infected cannot be reinfected):

$$N_T(d_i) = N_T(d_i\text{-}1)+r_0\times N_A(d_i\text{-}1)\times[1\text{-}N_T(d_i\text{-}1)/N_P],$$

where N_P is the total population.

In the case of vaccination of the population and considering the temporary nature of the immunity received due to SARS-CoV-2 infection or vaccination, the above expression will be as follows:

$$N_T(d_i) = N_T(d_i\text{-}1)+r_0\times N_A(d_i\text{-}1)\times[1\text{-}[N_T(d_i\text{-}1)+ N_V(d_i\text{-}1)\text{-}N_T(d_i\text{-}1\text{-}t_{im})\text{-}N_V(d_i\text{-}1\text{-}t_{im})]/N_P],$$

where t_{im} is the average duration of preserving full immunity against the virus after vaccination or disease, whereas $N_V(d_i)$ is the total number of vaccinated persons on date d_i who have not had COVID-19 in the last t_{im} days;

- $N_A(d_i)$ is the total number of active (undetected) infected persons on date d_i, which equals the difference between the total number of infected persons and the number of infected persons detected on the same day:

$$N_A(d_i) = N_T(d_i)\text{-}N_D(d_i).$$

At the start of the epidemic (date d_0), $N_A(d_0) = 1$, $N_T(d_0) = 1$, and $N_D(d_0) = 0$.

Thus, in order to calculate the virus spread dynamics, it is necessary to know the values of only two parameters—d_0 and r_0. In the case of changing the behavior of the population from the date d_1, parameter r_0 changes its value from this date to become r_1. If the behavior changes again, a pair of d_2 and r_2 will appear, and so on.

However, it is more difficult to model human losses correctly. Two more parameters need to be considered:

- L is the apparent lethality rate that is equal to the ratio of the number of deaths to the sum of those who died or recovered;
- t_L is the average time from infection to death.

These two parameters depend on the efficacy of treatment and may vary as physicians gain experience and as hospitals overflow. The number of deaths on date d_i equals the total number of people infected t_L days earlier multiplied by the lethality rate:

$$N_L(d_i) = N_T(d_i\text{-}t_L)\times L$$

Because of the presence of two parameters (t_L and L) in the equation, which have the same effect on the resulting value, the precision of their evaluation is lower than that for viral transmissibility. It should be understood that the fewer the number of asymptomatic and mild cases of the disease have been detected, the more the lethality rate is overestimated. The average time from infection to death was found to be about 8 days, and this duration will be used to make calculations for all countries.

The situation with predicting the number of recovered persons is even worse due to the appearance of an even greater number of independent parameters:

$$N_R(d_i) = N_T(d_i\text{-}t_M)\times k_M + N_T(d_i\text{-}t_S)\times k_S$$

where k_M and k_S are the shares of mildly and seriously ill patients ($k_M+k_S+L = 1$), and t_M and t_S are the corresponding times from infection to healing:

$$k_M+k_S+L = 1$$

The model equations are presented in the discrete form (instead of differential one), so that the model can be easily reproduced for calculations in any spreadsheet editor. At first glance, it seems that the model does not take into account the existence of asymptomatic carriers of infection, but this is not true: since the share of asymptomatic carriers in the population does not change over time, their presence is taken into account implicitly by the value of the transmissibility. This model can be denoted by the abbreviation SILRD, which means that it takes into account Susceptible, Infected, Isolated, Recovered, and Dead persons.

Results

Based on historical data on disease development in eight countries (China, Italy, Spain, the United States, the United Kingdom, Japan, France, and Germany [10]), the model was tested (Figure 1) and most of its parameters were found (Table 1). For all the countries, the viral transmissibility at the start of the epidemic was between 2.28 and 3.12. The highest viral transmissibility was found in China, wherein one person infected three others, probably because of higher population density. The introduction and progressive strengthening of quarantine measures resulted in a decrease in the viral transmissibility, which was noticeable 6 days later in the decline in the rate of new cases. All the countries had introduced quarantine measures gradually. The initial restrictions reduced the viral transmissibility to 1.20-1.74, which was not adequate (it was necessary to achieve a transmissibility of less than 1.0), and the virus continued to spread with acceleration. As a result, all the countries, with the exception of Japan, initiated stricter measures, thus reducing the transmissibility to 0.87-1.14. Japan focused on timely detection and isolation of infected persons. It can be concluded that this strategy does not work, as can be observed from the curve of the total number of cases in Japan that alternately slows down and then accelerates again. This is the result of the fact that Japan has been successfully isolating most of the infected persons, but a few infected people remain nonisolated and they can cause another outbreak to occur. By contrast, China further strengthened its containment measures, which resulted in a reduction of the transmissibility to 0.36 and a quick win over the epidemic (in 6 weeks according to the model).

Figure 1. Time dependences of the total number of COVID-19 cases, deaths, and recovered cases. Dots show actual data, whereas lines represent the result of calculations using the model.

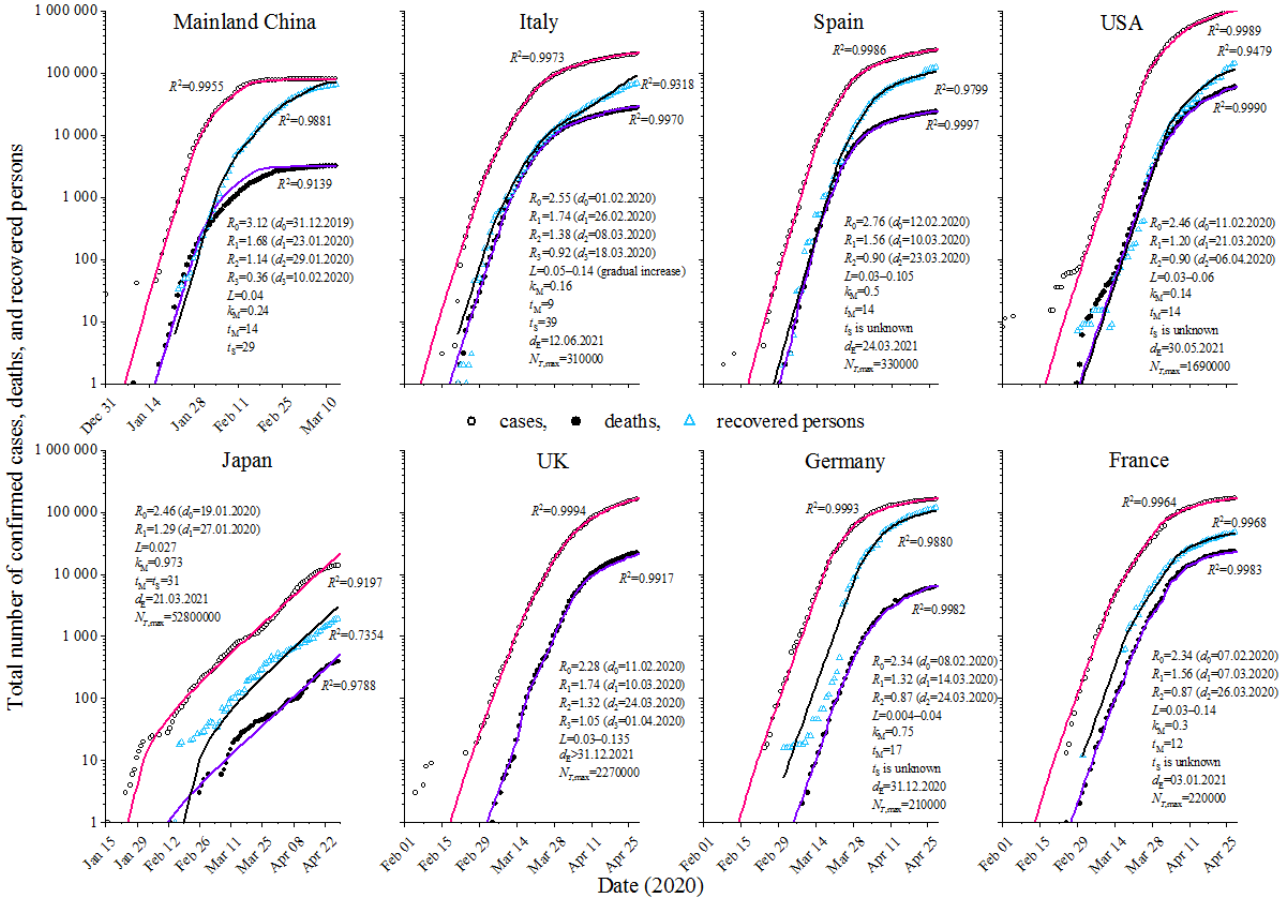

Table 1. Parameters identified from the models used in different countries.

Parameter	China	Italy	Spain	USA	Japan	UK	Germany	France
R_0	3.12	2.55	2.76	2.46	2.46	2.28	2.34	2.34
d_0	31.12.19	01.02.20	12.02.20	11.02.20	19.01.20	11.02.20	08.02.20	07.02.20
R_1	1.68	1.74	1.56	1.20	1.29	1.74	1.32	1.56
d_1	23.01.20	26.02.20	10.03.20	21.03.20	27.01.20	10.03.20	14.03.20	07.03.20
R_2	1.14	1.38	0.90	0.90	N/A[a]	1.32	0.87	0.87
d_2	29.01.20	08.03.20	23.03.20	06.04.20	N/A	24.03.20	24.03.20	26.03.20
R_3	0.36	0.92	N/A	N/A	N/A	1.05	N/A	N/A
d_3	10.02.20	18.03.20	N/A	N/A	N/A	01.04.20	N/A	N/A
L[b]	0.04	0.05–0.14	0.03–0.105	0.03–0.06	0.027	0.03–0.135	0.004–0.04	0.03–0.14
k_M	0.24	0.16	0.5	0.14	0.973	N/A	0.75	0.3
t_M	14	9	14	14	31	N/A	17	12
t_S	29	39	unknown	unknown	31	N/A	unknown	unknown
d_E	N/A	12.06.21	24.03.21	30.05.21	21.03.21	>31.12.21	31.12.20	03.01.21
$N_{T,max}$	N/A	310000	330000	1690000	52800000	2270000	210000	220000

[a]Not applicable.

[b]If an interval is indicated, it means gradual growth.

Discussion

On the date on which the analyzed data set ends, all European countries (except the United Kingdom) only managed to reduce the transmissibility slightly below 1.0. From a practical point of view, this means that the number of people falling ill on a daily basis in these countries was gradually decreasing, but it was at such a slow pace that the end date of the epidemic in these countries could not have been before, at best, the end of 2020. In reality, these countries have partially canceled quarantine measures, causing an increase in viral transmissibility and, consequently, a new rise in the number of infected persons and a shift in the date of a possible end of the epidemic to the future. It should be understood that any alleviation of quarantine measures would lead to increased transmissibility and resumption of an accelerated spread of the virus. To prevent this from happening after the quarantine restrictions have been removed, the viral transmissibility must remain below 1.0. By way of example, the original transmissibility was 2.55 in the case of Italy; therefore, it is necessary that 61% of the Italian population be either infected and then recovered (provided the immunity produced is durable and strong) or vaccinated against SARS-CoV-2 so that when quarantine measures are lifted, the transmissibility remains less than 1.0. At the time of writing this manuscript, 0.33% of the Italian population had been infected according to official statistics [10]. Statistics may not take into account asymptomatic and mild cases of the disease, numbers of which may be 4-50 times higher (for the time being, only by rumor) than that of the officially recorded cases. Even if this were true, the percentage of infected and recovered persons is still significantly lower than necessary, and the removal of quarantine measures will inevitably lead to a return of the growth rate of the number of infected people to almost their original level. In other words, the rapid development, production, and subsequent application of a vaccine are vital to overcoming the COVID-19 crisis in the near future.

Thus, the model allows forecasting of the situation development and concluding about the effectiveness of quarantine measures. By way of example, it helps determine the current number of active infected persons ($N_A(d_i)$), the approximate date of isolation of the last infected person (d_E), and the number of people that could eventually be infected under the current quarantine ($N_{T,max}$). According to the calculations, the efforts made by many European countries, the United States, and Japan to stop the spread of COVID-19 are not as effective as those implemented previously in China. Most countries have been able to achieve a daily reduction in the number of infected people, but even in these cases, the viral transmissibility remains high enough, which does not allow the country to overcome the epidemic crisis within a reasonable time. At the same time, suppressing the epidemic, albeit slowly, allows time for vaccine development and launch into mass production.

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Conflicts of Interest

None declared.

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Original Paper

The Impact of COVID-19 Management Policies Tailored to Airborne SARS-CoV-2 Transmission: Policy Analysis

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Abstract

Background: Daily new COVID-19 cases from January to April 2020 demonstrate varying patterns of SARS-CoV-2 transmission across different geographical regions. Constant infection rates were observed in some countries, whereas China and South Korea had a very low number of daily new cases. In fact, China and South Korea successfully and quickly flattened their COVID-19 curve. To understand why this was the case, this paper investigated possible aerosol-forming patterns in the atmosphere and their relationship to the policy measures adopted by select countries.

Objective: The main research objective was to compare the outcomes of policies adopted by countries between January and April 2020. Policies included physical distancing measures that in some cases were associated with mask use and city disinfection. We investigated whether the type of social distancing framework adopted by some countries (ie, without mask use and city disinfection) led to the continual dissemination of SARS-CoV-2 (daily new cases) in the community during the study period.

Methods: We examined the policies used as a preventive framework for virus community transmission in some countries and compared them to the policies adopted by China and South Korea. Countries that used a policy of social distancing by 1-2 m were divided into two groups. The first group consisted of countries that implemented social distancing (1-2 m) only, and the second comprised China and South Korea, which implemented distancing with additional transmission/isolation measures using masks and city disinfection. Global daily case maps from Johns Hopkins University were used to provide time-series data for the analysis.

Results: The results showed that virus transmission was reduced due to policies affecting SARS-CoV-2 propagation over time. Remarkably, China and South Korea obtained substantially better results than other countries at the beginning of the epidemic

due to their adoption of social distancing (1-2 m) with the additional use of masks and sanitization (city disinfection). These measures proved to be effective due to the atmosphere carrier potential of SARS-CoV-2 transmission.

Conclusions: Our findings confirm that social distancing by 1-2 m with mask use and city disinfection yields positive outcomes. These strategies should be incorporated into prevention and control policies and be adopted both globally and by individuals as a method to fight the COVID-19 pandemic.

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KEYWORDS

social distancing policies; COVID-19; airborne transmission; convergence and stability properties

Introduction

Unexpected Forms of Transmission and the Role of Policy

The COVID-19 pandemic consistently demonstrated a pattern of growing community transmission worldwide, even with the adoption of social distancing measures (lockdown or voluntarily shelter in place) in January and early May 2020. The continuing transmission of the virus despite the policy measures adopted in some countries was an important point of debate and investigation in the scientific community and among authorities. Unexpected forms of transmission (atmospheric [1-3]) associated with the social distancing policy became the central question for the infectious transmission modeling of SARS-CoV-2 and predictive methods.

This research considers the advanced phases of community transmission observed in some countries [4] in a select period. Due to the increasing numbers of new infections and deaths, monitored by the World Health Organization [4] and Johns Hopkins University, this research is mainly focused on the nonlinear epidemic properties of SARS-CoV-2 transmission. These nonlinear epidemic properties of transmission can be understood through the highly random forms of virus transmission associated with human social behavior and with environmental conditions (physical or aerosol long-range transmission, airborne transmission). In this research, nonlinearity refers mainly to the unpredictability of the epidemiologic framework of the SIR (susceptible, infected, removed) stochastic models used to track the possible rate of infection in the population, even with some policy measures implemented by countries [5-8]. This limited ability to predict future rates of contagion was noted during the spread of the pandemic. It was suggested that the qualitative theory of differential equations may be appropriate for identifying the variables, policies, or environmental conditions that influence the constant propagation of the virus. The random patterns of virus reproduction suggest that transmission happens through the air. Other dimensions of research must be considered—the social behavior of individuals and the aerosol fluid dynamic behavior. This direction of research has yielded unresolved mathematical equations that simulate the daily growth of new cases. This study defined the aerosol, or biosol, or ground form of transmission as spreading patterns of infection. The policy measure adopted by a country may or may not address these spreading patterns adequately, which then may sustain (or not) dissemination patterns of the virus worldwide. In this way, the spreading pattern is related to the forms of virus transmission. At the same time, the dissemination of the virus, regardless of how it can be transmitted, depends on the cultural, personal, and policy aspects of managing societal and individual behaviors.

In this study, geographical regions in Asia, South America, North America, the Middle East, Africa, and Europe were analyzed to confirm whether the policies adopted by China and South Korea during the outbreak were the most effective ones in the period of January to April 2020. During this period, only these two countries had adopted specific policy measures addressing the airborne framework of SARS-CoV-2 transmission beyond social distancing (mask wearing and city disinfection). These countries also had the lowest daily new case counts of COVID-19. The relationship between mask wearing, city disinfection, and the airborne form of transmission during the period of interest will be used to test the hypothesis that the virus can be transmitted through the air.

Theoretical Analysis of the Nonlinear Properties of SARS-CoV-2 Dissemination Patterns

SARS-CoV-2 follows different patterns of transmission among humans [5-7]. These patterns are being investigated not only using clinical trials, statistical tools [5-11], and medical interviews with patients [9,10], but also from a mathematical point of view, using SIR compartmental models with a high degree of uncertainty. Concerning mathematical predictions of SARS-CoV-2 reproductive patterns within a complex network of human behavior [5], the maximum possible rate of infection with the virus in daily human life [5-8,12,13] consists of a community dissemination pattern with an increasing margin of statistically unpredictable outcomes. The models were still being developed due to predictive failures. One specific unpredictable pattern [14] of the virus spread and dissemination from January to April 2020 is visible in the numbers of new infections over time in countries where the input and output (which is the number of people who could be infected from an initial number, resulting in maximum and minimum margins of dissemination of the virus fluctuation) expressed unpredictability. This observation was initially and briefly modeled by Koerth et al [15].

Regarding these nonlinear aspects of infection within countries, this study points out that there is evidence for long-range airborne transmission [16-18] of SARS-CoV-2. The evidence consists of the type of policies adopted in China and South Korea from January to April 2020, where a significant reduction in infection cases occurred, with distinct patterns found in other countries during all epidemic contagion phases. China and South

Korea instituted social or physical distancing measures along with additional methods, such as mask use and city disinfection. It was one of the main causes of the nontrivial frequency of daily new COVID-19 case distribution during the early stage of the pandemic, up to late April and early May. Physical distancing with an air preventive framework was revealed to be an urgent need for any country at that time, and, along with social distancing and testing policies, is now one of the main preventive methods used.

Recent studies reported that the transmission of SARS-CoV-2 occurs due to proximity to other humans and to social interactions within a set of empirical variables, including the most basic forms of human behavior, such as coughing, sneezing, handshakes, sharing clothes, sharing cups, general touching, and general object-sharing behaviors [19,20]. This set of variables influences transmission, together with the environmental factors associated with the virus's possible transmission on the ground (surfaces) and in the air (not only aerosols in medical facilities but aerosol and biosol formed under atmospheric conditions outdoors). This leads to new patterns for course epidemiology [12]. Between January and April 2020, the World Health Organization confirmed aerosol transmission only at medical facilities [21], not in outdoor urban spaces. However, van Doremalen et al [22] stated early on that human upper and lower respiratory tracts cause the nearby atmosphere to become infected, propagating the virus through the air. They measured this effect for about 3 hours during an experiment and observed low infection reduction over time, with infectious titer changing from $10^{3.5}$ to $10^{2.7}$ $TCID_{50}$ (50% tissue culture infective dose) for SARS-CoV-2 [22]. An alternative scientific hypothesis and further probabilistic and statistical frameworks were needed to establish new policies and guide individual preventive actions. Although a scientific breakthrough occurred early in the pandemic, no policy measure was announced as definitive, and each country was searching for preventive methods independently. This is why it is worthwhile to compare how some countries reduced SARS-CoV-2 transmission with specific social distancing measures.

The analysis of the nonlinear properties of the mathematical models and nonpharmaceutical interventions for the COVID-19 epidemiological framework is important not only for medical facilities but also for public policies and health care infrastructure. It can help to estimate the disease patterns of community transmission in a pandemic scenario that affect the economy and threaten people's health and survival. This research is also relevant due to the large active workforce trying to maintain essential services and sectors necessary for survival, such as electrical, water, garbage disposal, energy, food supply/production, commerce, and industry.

COVID-19 Transmission Instability

Policy that consists of physical distance between individuals may fail because the virus may continue to be transmitted in other unexpected ways. This instability becomes visible when countries that adopt this policy still fail to contain virus spread due to asymptotic instability between the virus's potential to infect individuals in spite of the policy measures and methodology. The unbalancing of this equation is found in a wide variety of probability distributions of daily new cases, with distinct patterns [6-9,12,13,15,19,23] observed in many countries [4]. This may be why new cases continued to occur between January and April 2020, even with preventive methods such as social distancing (lockdown or shelter in place) and COVID-19 testing.

Causes beyond the traditional transmission analysis [5-9,13,24-26] need to be considered to explain the continued growth of new cases. Other factors for transmission and modeling patterns should be considered and constructed [12,13,15,27-30] using mathematical counterproof predictions for countries that had already adopted social distancing and had COVID-19 testing available but adopted social physical distancing measures with distinct parameters such as using or not using masks and city disinfection.

Statistical Uncertainty and COVID-19 Prevention

Many variables affect virus transmission rates, such as the type of health policies adopted by each country, public health infrastructure, population genetics, human variance in biological resistance, local epidemic outbreaks, globalization aspects, COVID-19 testing availability, virus mutation, and citizens' adherence to social physical distancing. The influence of these factors is visible on the Our World in Data webpage [31]. These confounding outcomes in each country make it difficult to determine why some countries still have an active virus infection and what would be the best fixed-point orientation (policy measure) to reduce virus transmission rates. However, worldwide statistical data can provide a relevant confidence interval analysis if different countries' policies are compared. This would reveal the best approach for reducing virus infections. At the moment, policy is the most effective way to reduce COVID-19 cases since no vaccine or drugs have been consistently effective for treating the disease or stopping virus propagation worldwide.

Research shows that individual behavior and social ties [32-34] are still key for controlling the community transmission of the virus through social distancing measures. These measures must consider the dynamics of groups/communities and the community infrastructure (households, buses, shopping malls, meetings, markets, daily activities, and human behavior). Note that the term "social distancing" is used here to describe the behavior of an uninfected individual outside medical facilities and refers only to the population separation patterns based on ground distances. The term "social physical distancing" refers to one of the measures included in the social distancing policies.

To explain why the virus continues to be transmitted when social physical distancing is practiced, it is important to consider that social contact might still occur as a human physical connection during environmental socialization; that is, physical ground and atmospheric contact may occur. The policy requires individuals to stay 1 or 2 m apart, assuming that this is enough to prevent virus transmission, and has the same effect as sheltering in place (mandatory or not). However, with this measure, there are still many opportunities for social contact within a physical dimension at the ground and atmospheric levels, both indoors or outdoors, as observed in many studies [20,35-39].

We need to theoretically and empirically analyzed two parameters, social distancing policy and social transmission isolation, because environmental transmission may play a role in recurrent community transmission of SARS-CoV-2. The epidemiological methods of prediction and control (which are needed to estimate the supply of financial, economic, and public health resources for the predicted number of infected people) lose their effectiveness due to certain aspects of social transmission isolation and SARS-CoV-2's airborne virulence potential [20,35-39]. This new approach diverges from older approaches, such as the one demonstrated by Hellewell et al [40], since social distancing and social transmission isolation parameters are different stages under atmospheric conditions, which require further empirical investigation.

Many recent viral infectious diseases (severe acute respiratory syndrome [SARS], Middle Eastern respiratory syndrome [MERS], H1N1) are transmitted similarly to SARS-CoV-2 [5], but they have different rates of exponential growth [41]. Therefore, it is important to consider not only the causes of transmission, such as the chemical and biological properties of transmission and the virus-human biological affinity but also the emergent virus and human social behavior in the context of the environment [35-40,42-47]. The nonlinear time series of worldwide policies may present a clue in the form of a high asymptotic stability (dissemination network) [37] about the type of preventive policy measures adopted by each country, as also observed previously by Riou and Althaus [48] with the *k* dispersion parameters and the superspreading prediction possibilities.

Evidence for Airborne Transmission

The presence of these epidemiological factors (forms of transmission, biological-chemical affinities, and emergent social virus transmission behavior) associated with the preventive epidemic framework [49], implemented from January to April 2020, requires considering any given number of infected individuals as an ongoing pandemic threat, since uncertainty prevails. This led to the conclusion that there was no minimum range of infected individuals that would classify the local epidemic as under control. No policy adopted during the period of interest was more effective than those of China and South Korea. At that time, many authorities thought that the epidemic would have a natural upper limit and posterior descendant tail and would end naturally without any human intervention. However, it has not yet been scientifically proven that the pandemic can end naturally or become seasonal. Therefore, this theoretical observation should not have been used as a preventive measure at that time.

Concerning the evolution of the pandemic from January to April 2020, one important issue reported in the media is the difference between maintaining social physical distancing and full social isolation. Social physical distancing means maintaining physical distance in restaurants, parks, drugstore lines, household activities, neighborhoods (especially low-income neighborhoods), household tree proximity, markets, indoor and outdoor social events, windows and balconies, airplanes, ship balconies, hospital rooms, meetings, delivery or mail activities, prisons, residences, commercial establishments, and industrial facilities [50]. Full social transmission isolation, meanwhile, requires ground or atmospheric barriers. News and scientific reports [51,52] show that most of China and South Korea [51] had required residents to wear masks, and full disinfection had been implemented in crowded public spaces [15,53]. There had been some further concerns from public health professionals, as reported by Li et al [54] and Wong et al [55]. These policy actions converged with the physical distancing criteria and possible failures, presenting physical transmission isolation barriers for airborne transmission (aerosol-biosols and atmospheric conditions [20,35-39]). Chinazzi et al [56] discussed community policy actions regarding airplanes. At this point, a counter effect can be seen despite social physical distancing if social activities occur in outdoor spaces without the use of masks or city disinfection. Therefore, risk continues to be present.

Social connection might be one of the unobservable factors of transmission if the virus can spread under atmospheric conditions [35,36,57-60] and is still active in air fluids [20,35-39]. This would mean that a ground preventive framework is insufficient. Most of the recommendations for physical distancing issued during that time addressed the virus's potential to spread on the ground and through the air via human bodily fluid droplets. Complex air-fluid scenarios without droplets involved (eg, pollution) were not considered. Wickramasinghe et al [57] reported several cases of person-to-person transmission patterns in that period, which can be understood as air transmission caused by the lack of virus social transmission isolation policies involving additional barriers, such as masks and city disinfection. Similar observations were made by Cembalest [58], based on a brief analysis, and by Pirouz et al [59], based on mathematical modeling with a deep analysis of how the atmospheric parameters of temperature, humidity, and wind affect the population density output for SARS-CoV-2 infection. These studies came to the proximal conclusion that atmosphere has a strong impact on the patterns of community virus dissemination in countries that adopted social physical distancing without mask policies and city disinfection. Finally, Poirier et al [60] examined the weather conditions capable of generating the full transmission patterns without a social transmission barrier for airborne transmission.

Methods

The main goal of this paper is to identify the differences in outcomes among countries that adopted physical distancing measures in association with mask use and city disinfection during the period of analysis (January to April 2020). In this research, the social distancing framework without additional measures adopted by some countries represents the main model for the constant reproductive dissemination patterns of SARS-CoV-2 community transmission.

This paper takes an experimental approach to identify limitations in social distancing policy. Two groups of countries were selected. The first consisted of countries that adopted social distancing measures without specifying physical distancing, mask use, and city disinfection. The second consisted of

countries that adopted all these measures between January and April 2020 (ie, only China and South Korea).

Results

Empirical Evidence for COVID-19 Transmission Instability

Table 1 presents the selected countries and their fluctuations in daily confirmed cases in random statistical data samples by date [31]. Countries marked with a superscripted "a" presented the best outcomes for daily new cases during the period investigated. The remaining countries in the other group presented inconsistent outcomes of daily new cases. This constitutes empirical evidence of instability in COVID-19 transmission in countries early in the pandemic.

Table 1. Rolling 3-day average of daily new confirmed cases of COVID-19 among selected countries from March 28-30, April 11-13, and May 1-2, 2020. Source: Our World in Data [31].

Country	Rolling 3-day average of new cases		
	March 28-30 (n=56,337)	April 11-13 (n=71,619)	May 1-2 (n=60,807)
United States	19,011	32,606↑	30,399↓
Spain	7536	5054↓	1149↓
Italy	5717	4283↓	1974↓
Germany	5003	4092↓	1354↓
France	3673	3914↑	1116↓
Iran	2968	1814↓	1020↓
United Kingdom	2621	6086↑	5436↓
Turkey	1863	4647↑	2579↓
Belgium	1534	1538↑	566↓
Switzerland	1187	703↓	147↓
Netherlands	1145	1288↑	458↓
Portugal	806	948↑	343↓
Canada	746	1342↑	1682↑
Austria	595	279↓	72↓
Brazil	447	1600↑	6567↑
Norway	315	103↓	51↓
Australia	309	79↓	9↓
Sweden	298	577↑	633↑
Denmark	173	198↑	153↓
China[a]	110	75↓	6↓
South Korea[a]	110	29↓	6↓
Finland	87	139↑	103↓
Singapore	83	225↑	716↑
Argentina	77	114↑	135↑
Chile	255	460↑	881↑
Saudi Arabia	101	367↑	1340↑
United Arab Emirates	45	359↑	552↑
Egypt	31	126↑	284↑
Pakistan	117	238↑	1076↑

[a]Presents the best outcomes of daily new cases during the period investigated.

Maximum Exponential Growth and Epidemic Duration in Days

The statistical data in Figure 1 show the rise in daily new cases around the world, along with all policies adopted by countries, such as social distancing, COVID-19 testing, and physical distancing criteria, in association with (or without) the use of masks and city disinfection, from February to May 2020 [61].

Many European countries are adopting different measures for prevention. However, one specific point beyond social distancing and COVID-19 testing can be highlighted. As of April 2020, these countries had still not introduced mask use and/or constant city disinfection, which had been adopted by China and South Korea early in the pandemic and continued to be implemented later on. In late March and April [4], the infection rates in countries such as Italy, Spain, Iran, the United States, Germany, France, and Brazil were rising, with patterns different from those of China and South Korea (Table 1). This was still the case in May 2020.

In European countries [62], social distancing, COVID-19 testing availability, and physical distancing measures were introduced in late March and at the start of April. Although many citizens disobeyed institutional orders [63-66], reports indicated a reduced number of citizens outside their homes. However, daily infection cases were constantly over the population mean of 30,000 during April for a total of 58 days, from February 28 to April 25, 2020.

In Europe [62], and particularly in Italy (Figure 2), where individuals disobeyed orders to stay at home, these actions could have also generated several random transmission outputs. These specific random aspects contribute to the statistical variance of these countries, including the number of infected people and the mortality rate.

Figure 1. General overview of all reported cases of COVID-19 worldwide from February to May 2020. Source: Worldometer [61].

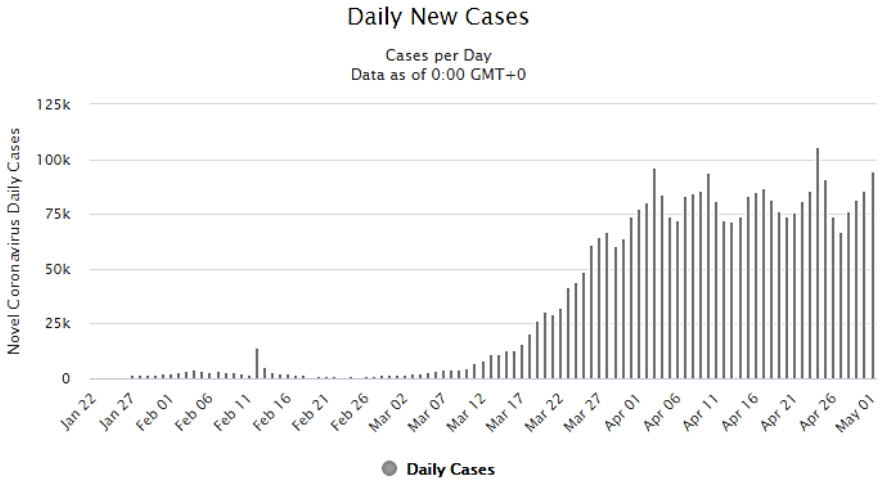
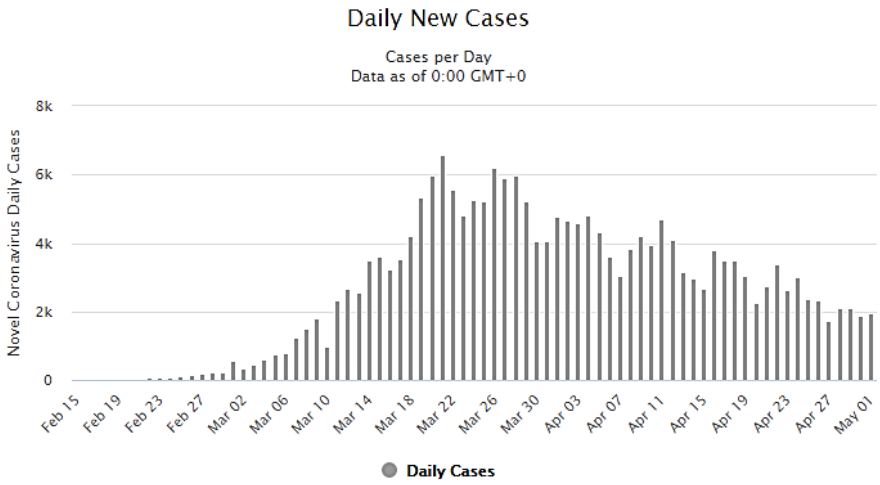


Figure 2. New daily cumulative COVID-19 cases in Italy. Note that Italy's mask use policy for the public was introduced by late March and early April, being this measure carried out until the last date this research was conducted. Source: Worldometer [61].



As shown in Figure 2, in Italy, the number of days of exponential growth represents constant daily infection cases with growing patterns, starting from the epidemic outbreak until a population mean of 4000 (maximum exponential growth rate for a period of 51 days, from February 22 to April 12, 2020).

Many other factors have been discussed to explain why virus spread was still rising in these countries, such as availability of testing and the date a city first implemented social physical distancing measures. Besides, it can also have a strong influence on the virus' undetected phase of exponential growth; the time series of these statistical data also show how much time was

needed for each country to stabilize its virus infection without the measures adopted by China and South Korea. Observing the preventive measures targeting airborne vectors (masks and city disinfection) that were adopted as default by China [67] and South Korea [68], the virus social transmission behavior differs from the other analyzed countries.

According to the data provided by Worldometer [67,68], these countries had adopted social physical distancing with air preventive measures, with a total of 20 days of maximum exponential growth rate over a population mean of 250 (February 19 to March 8, 2020) for South Korea and a total of 28 days of maximum exponential growth rate over a population mean of 1500 (January 23 to February 18, 2020) for China.

It is also important to consider exceptions for a possible microdimension of analysis of population biology that can occur in any country, as a local problem [69-71] does not always contribute to a high exponential growth rate of virus transmission. However, although the microdimensions were able to produce fluctuations in data, the whole scenario can be represented by descriptive statistics.

One other point concerning China is that its high exponential growth was due to the initial conditions of the new disease, and the country needed time to evaluate and adopt policies and scientific measures, as observed by Pan et al [71]. Additionally, China and South Korea adopted these measures early during their local epidemics based on their culture and experience with past epidemics; other countries were still trying to find alternative solutions at that time [63-66].

Compared to other countries, China and South Korea were the only true parameter of analysis of these policies. If we were interested in investigating any of the other numerous policies adopted by countries for any period of time, a country-by-country as well as a policy-by-policy analysis would be needed to check the results of each country's policy. However, even without this kind of analysis, China and South Korea clearly presented the best scores for COVID-19 reduction during the period of interest.

Maximum Exponential Growth Mean and Dissemination Rate Over Time

Table 2 shows the exponential growth patterns over time in China and South Korea. Data from other countries are also included, and the same data are presented in Figure 2 and in reference and news websites [61-68]. The first column of Table 2 presents the maximum growth of infection per population ratio obtained by the maximum exponential growth mean reached in an average day's peak since the outbreak, and therefore does not account for growth above the mean y presented by some countries. This mean represents a critical value per population ratio reached by the infection, and it is counted if there is a positive exponential growth. If a second wave of infection is observed, it will count for this second period with a cumulative time since the outbreak. The second column t presents how many days the infection presented an exponential growth with a maximum mean reached. The third column contains the maximum exponential infection dissemination rate over days, following the theoretical design involving SIR models and missing gaps of this model for COVID-19.

The approach in the third column has similarities to SIR models, but it is based on distinct aspects of analysis of the variables S and R. These variables are removed from the formula, and the focus is mainly on variable I, defined by Weibull parameterizations and exponential distributions. This design of analysis has been very relevant due to the instability aspects of SIR analyses done since the disease outbreak, which occur mainly in the S and R compartments due to infodemics, uncertainty, the apparent lack of overall topological data homology, and other nonlinear aspects of COVID-19. For this reason, the proposed method of analysis considers only the infectious disease aspect of the evolution of cases, rather than assuming full immunity or using deterministic models for population behavior, which in this case is one of the most influential factors of propagating the virus.

For this analysis, it was assumed that the observed infected population samples $Y=(Y_1, \ldots, Y_n)$ experienced the exponential growth $f(Y;\lambda)=\lambda e^{-\lambda Y}$, where the samples were taken from zero cases to the observed maximum exponential growth mean reached per population ratio for each country, with an unknown predictive scale of $exp\ \lambda$ or maximum likelihood estimator of λ due to the nonlinear outputs generated for Y with the heteroscedasticity form. In this simple form, where the mean is defined as $y=1/\lambda$, the numerical representation of the ratio between days and the mean can be obtained by observing the exponential mean scale until it reaches a form like $y=Y$, with y adopted for the calculations with the conditional shape of the Weibull parameterization like $\kappa<1$. At this point, the days counting forward in this condition are rejected to extract the maximum exponential infection dissemination rate according to the formula $R=y/t$, and $t=\kappa$ only in the desired event expression. This approach can be more sensitive in terms of the progress of the disease over time and its potential to infect as time passes. This sensitivity leads to much more accurate predictions due to the exponential behavior of infections in the community phases of infection spread and dissemination patterns.

Table 2. COVID-19 maximum exponential growth patterns per population and time period by country or region from April 7 to May 1, 2020. The *y* and *t* data shown are for May 1, 2020. Data source: Worldometer [61].

Country	*y*	*t*	*R*		
			April 7	April 13	May 1
Worldwide[a]	60,000	99	675.67	886.07↑[b]	606.06↓[b]
Europe[a]	30,000	91	410.95	379.74↓	329.67↓
Italy	4000	51	90.90	78.43↓	78.43=
South Korea	250	20	12.5	12.5=[b]	12.5=
China	1500	28	53.57	53.57=	53.57=
Iran	2000	46	44.44	43.47↓	43.47=
Spain[a]	5000	55	131.57	121.95↓	90.90↓
France	4000	45	138.88	100↓	88.88↓
United States[a]	30,000	53	625	540.54↓	566.03↑
Brazil[a]	5000	51	25	28.57↑	98.03↑
Germany	4000	41	105.26	100↓	97.56↓
Russia[a]	5000	46	15.62	27.02↑	108.69↑
United Kingdom[a]	5000	58	64.51	69.64↑	86.20↑
Singapore[a]	500	57	0.96	1.75↑	8.77↑
Portugal	500	49	15.15	13.15↓	10.20↓
India[a]	1000	58	8.33	9.43↑	17.24↑
Canada[a]	1500	48	27.77	24.39↓	31.25↑
Japan[a]	500	67	3.92	7.14↑	7.46↑
Sweden[a]	500	58	5.71	0.65↓	8.62↑
Argentina[a]	100	57	1.51	2.56↑	1.75↓
Chile[a]	500	52	10	8.33↓	9.61↑
Saudi Arabia[a]	1000	54	3	4.16↑	18.51↑
United Arab Emirates[a]	400	70	4.34	5.76↑	5.71↓
Egypt[a]	200	62	1.31	2.27↑	3.22↑
Pakistan[a]	500	53	3.44	5.71↑	9.43↑

[a]Note that at the time of this writing, some countries were at their maximum exponential infection dissemination (different epidemic phases). For these countries, no final exponential score had been reached yet. However, this does not count for future predictions.

[b]↑, ↓, and = denote increase, decrease, and no change, respectively.

Note that in Table 2, some countries present a lower exponential growth rate than China or South Korea. These data need to be considered in the context of when the country's outbreak started. Many countries were also at their maximum exponential growth at the time the data were collected. For these countries, it is not possible to judge whether their policies had already helped to flatten the curve of daily new cases, and some of them present active exponential growth; therefore, further future analysis is required to compare them to the other countries, as will be explained in the following paragraphs.

China, being the first country to adopt countermeasure policies, experienced some delay, and therefore, the maximum exponential rate was reached before these measures could take effect. In addition, many countries that had adopted measures based on previous experience performed better than the ones that were experiencing an epidemic for the first time. However, since they retained active low exponential growth (eg, Singapore, with a low maximum exponential rate), they did not reach the same results as China and South Korea with the adoption of additional preventive measures of social distancing/city disinfection and a high reduction of exponential virus spreading patterns. The Singapore scenario has occurred in many other countries as well. Singapore also presented a rise in the maximum exponential growth from 50 (April 7) to 500

(May 2). Germany, Italy, Portugal, Iran, and France presented a decline in the mean maximum exponential rate reached at the time the data were retrieved; however, this does not count for future epidemic behavior to be observed based on a deterministic approach.

Figure 2 and data from reference and news sources [61-68] show how long it took for some countries that implemented social physical distancing measures plus airborne transmission preventive methods to flatten the exponential growth of community infections. Countries that only applied social distancing of any sort without mask use or city disinfection at the early stages required many more days than other countries that applied airborne transmission prevention measures [63-66]. Many other scenarios were also observed since policies about mask use and city disinfection were still in the implementation phase in many countries.

It is also important to note that in Table 2 the data refer to different epidemic phases of data collection for each country. These distinct phases are important to consider together because a methodology is needed that can extract the behavior of the disease in the nonoptimal (deterministic) evolution of the virus infection and policies adopted by countries. This reveals a complex scenario involving the disease dynamics, a confounding environment, and possible convergence behavior of the policies adopted to mitigate the disease.

Maximum Exponential Growth Mean × Time × Cases per 1 Million Population

Table 3 compares case counts in the selected countries on May 1, 2020 [61]. China and South Korea both have low case counts per 1 million population, low epidemic duration, and stable exponential growth. Notably, some countries present lower case counts per 1 million population, but they all have growing patterns of infection propagation, longer epidemic duration, and high exponential growth rate patterns. At the time of the analysis, China and South Korea had the best scores for the correlation between total cases per 1 million population over the period of infection and COVID-19 growth pattern stability. This is further evidence of the effectiveness of their policies. Note that any range of analysis to be performed will have its values of time and maximum exponential mean modified according to the selection taken. The higher the range, the better the *R* precision.

Even with good scores, some countries did not have optimal values for all the columns in Table 3 and presented an exponential growth rate, as of May 1, 2020. Although many of these countries are located close to China and South Korea, they do not match these countries' later results; several factors influenced the oscillations and differences in the numbers. Notably, Argentina had the best score in South America and was ahead of many other regions worldwide. Voluntarily and later obligatory mask use and city disinfection took Argentina to the same epidemic scenario as China and South Korea, leading to successful results. The United Arab Emirates and Portugal, with their decreasing exponential growth rate, could reach better results by introducing air transmission preventive measures.

Table 3 clearly displays much of the unpredictability based on nonlinear factors such as the health policies adopted by each country, public health infrastructure, population genetics, COVID-19 testing availability, and citizens' adherence to social distancing of any type. These data indicate that further studies are still necessary to obtain more accurate numerical results, since each country undergoes a period of disease dissemination with different rates. Although these variances produce large differences in outcomes, most countries adopted social distancing as a method of virus spread prevention, with no obligation of social physical distancing, which became a default pattern for prevention in late February and early March. This also contributed to the virus incubation period and caused the dissemination rates to increase much more than in China and South Korea. These results point to the conclusion that while many factors influence outcomes, some specific patterns occur only in these two countries and in none of the others. By April 30, 2020, China and South Korea had shorter epidemic durations than other countries, stable low disease exponential growth patterns, and low confirmed case counts per 1 million population [14].

Table 4 extends this analysis to the period from May 1 to June 2, 2020.

Between May 1 and June 2, out of the 25 countries analyzed, 11 presented differing infection dissemination patterns, while 14 had a constant evolution of infection that also indicates a positive analysis for the predictive statistics, despite the long period of time considered (sensitivity and prediction for 33 days).

The analysis shows that prediction for a shorter or longer time frame is highly associated with the type of policies adopted by the selected countries as compared to China and South Korea. China and South Korea still had the best results for local epidemic reduction. Notably, Spain and Italy reached a stable point in transmission during the period of analysis through lockdown measures rather than mask use or city disinfection. However, while lockdowns helped them reach the same status as China and South Korea, these policy measures worked differently. The first difference is the time it took to reach stability. For China and South Korea, it was approximately 28 and 20 days, respectively. On the other hand, Spain and Italy took 55 and 51, respectively. While the lockdown was active and no mass mask use was mandatory, the time it took to reach the peak and flatten the curve was higher in these countries. Resurgences of infection also occurred, and it was difficult to reach a very low mean of daily new cases after the curve was flattened [61]. This suggests that lockdown measures alone were not enough to flatten the curve to the level of China and South Korea. Gradually, these countries, as well as many others, started to use masks and carry out city disinfection in May, June, and July 2020.

Table 3. Countries with COVID-19 dissemination and total infected cases per 1 million population, as of May 1, 2020. Data source: Worldometer [61].

Country	Total cases, N	Total cases per 1 million population	*t*	*R* on May 1
United States	1,159,430	3503	53	566.03↑[a]
Italy	209,328	3462	51	78.43=[a]
China[b]	82,875	58	28	53.57=
Spain	245,567	5252	55	90.90↓[a]
Germany	164,967	1969	41	97.56↓
Iran	96,448	1148	46	43.47=[c]
France	168,396	2580	45	88.88↓
United Kingdom	182,260	2685	58	86.20↑
Sweden	22,082[c]	2186	58	8.62↑[c]
India	39,699[c]	29[c]	58	17.24↑[c]
Japan	14,305[c]	113[c]	67	7.46↑[c]
South Korea[b]	10,780	210	20	12.50=
Russia	124,054	850	46	108.69↑
Singapore	17,548[c]	2999	57	8.77↑[c]
Portugal	25,190[c]	2470	49	10.20↓[c]
Canada	56,714[c]	1503	48	31.25↑[c]
Brazil	96,559	454	51	98.03↑
Argentina	4532[c]	100[c]	57	1.75↓[c]
Chile	18,435[c]	964	52	9.61↑[c]
Saudi Arabia	25,459[c]	731	54	18.51↑[c]
United Arab Emirates	13,599[c]	1375	70	5.71↓[c]
Egypt	6193[c]	61[c]	62	3.22↑[c]
Pakistan	19,022[c]	86[c]	53	9.43↑[c]

[a]↑, ↓, and = denote increase, decrease, and no change, respectively.

[b]Indicate the best scores reached by China and South Korea.

[c]Indicates countries that reached the best score compared to China and South Korea.

Table 4. COVID-19 maximum exponential growth patterns per population and time period by country or region from May 1 to June 2, 2020. Data source: Worldometer [61].

Country	*R*	
	May 1	June 2
Worldwide	606.06↓[a]	572.51↓
Europe	329.67↓	162.60↓
Italy	78.43=[a]	78.43=
South Korea[b]	12.50=	0.09↓[a]
China	53.57=	53.57=
Iran[b]	43.47=	25.64↓
Spain	90.90↓	90.90=
France	88.88↓	3.89↓
United States[b]	566.03↑	235.29↓
Brazil	98.03↑	180.72↑
Germany	97.56↓	2.73↓
Russia[b]	108.69↑	96.15↓
United Kingdom[b]	86.20↑	22.22↓
Singapore[b]	8.77↑	5.61↓
Portugal	10.20↓	1.85↓
India	17.24↑	64.44↑
Canada[b]	31.25↑	9.37↓
Japan[b]	7.46↑	0.30↓
Sweden[b]	8.62↑	6.66↓
Argentina[b]	1.75↓	6.17↑
Chile	9.61↑	41.66↑
Saudi Arabia[b]	18.51↑	17.44↓
United Arab Emirates	5.71↓	5.39↓
Egypt	3.22↑	7,.44↑
Pakistan	9.43↑	23.52↑

[a]↑, ↓, and = denote increase, decrease, and no change, respectively.

[b]Countries that presented a different behavior of infection dissemination compared to that observed on May 1, 2020, the start date of the analysis.

Discussion

Principal Findings

The nonlinear aspects and variables of COVID-19 transmission and prevention require multiple factors to be considered, such as health infrastructure facilities, new design of workflows/structures to prevent infection in health facilities, type and availability of personal protective equipment, public health policies adopted by each country, population genetics, COVID-19 testing availability and rapid response, social distancing, economic activities in some essential and nonessential sectors, government policies for supporting the population and survivability, citizens' collaboration with policies, and other public health and social policies. We did not aim to produce statistical numerical results involving all these variables, due to the likely lack of significance of data correlation (heteroscedasticity) for demonstrating that the results presented in this paper are due only to the selected type of policy interventions. All the nonlinear aspects mentioned affect epidemics in different ways. However, we focused on three aspects: the amount of time that has passed since the infection has occurred; what the maximum infected population range was; and how many people per million have been infected. These questions address specific preventive measures, and in this context, the type of policy analyzed can be considered the main countermeasure. Therefore, statistical analysis with numerical results is unlikely to provide any important information about community transmission in terms of

seasonality due to the limited time period for which the data were available and to the nonlinear properties of the variables necessary for predicting daily new virus cases in each country. For this reason, the influence of policies on daily new cases was roughly described by filtering out other factors that were unlikely to accommodate the nonlinear scenario of the disease. The results show that policies directly affected the population; they can also influence many of the nonlinear sets of variables described earlier (a convergence aspect of higher-order nonautonomous functions).

However, an overview of the nonparametric data was provided to assess the types of policies investigated in this research for a seasonal forcing behavior with a strong influence on the overall scenario. While this research did not focus on statistical numerical results for all relevant variables, these inferences were done in terms of the conceptualization of *z* and *P* value tests, SD, variance analysis, and linear regression analysis of the policies in selected countries, as shown schematically in Figure 3.

Figure 3. Representative scheme of SARS-CoV-2 reproductive patterns among countries whose policies might or might not converge toward a very low maximum exponential rate of infection per population/days. Note that countries with a low maximum exponential rate (Table 2) also present active infection patterns, with this feature being a nonconvergence of the type of policies adopted and, hence, expressing an exponential probability of infection constant growth (false null hypothesis).

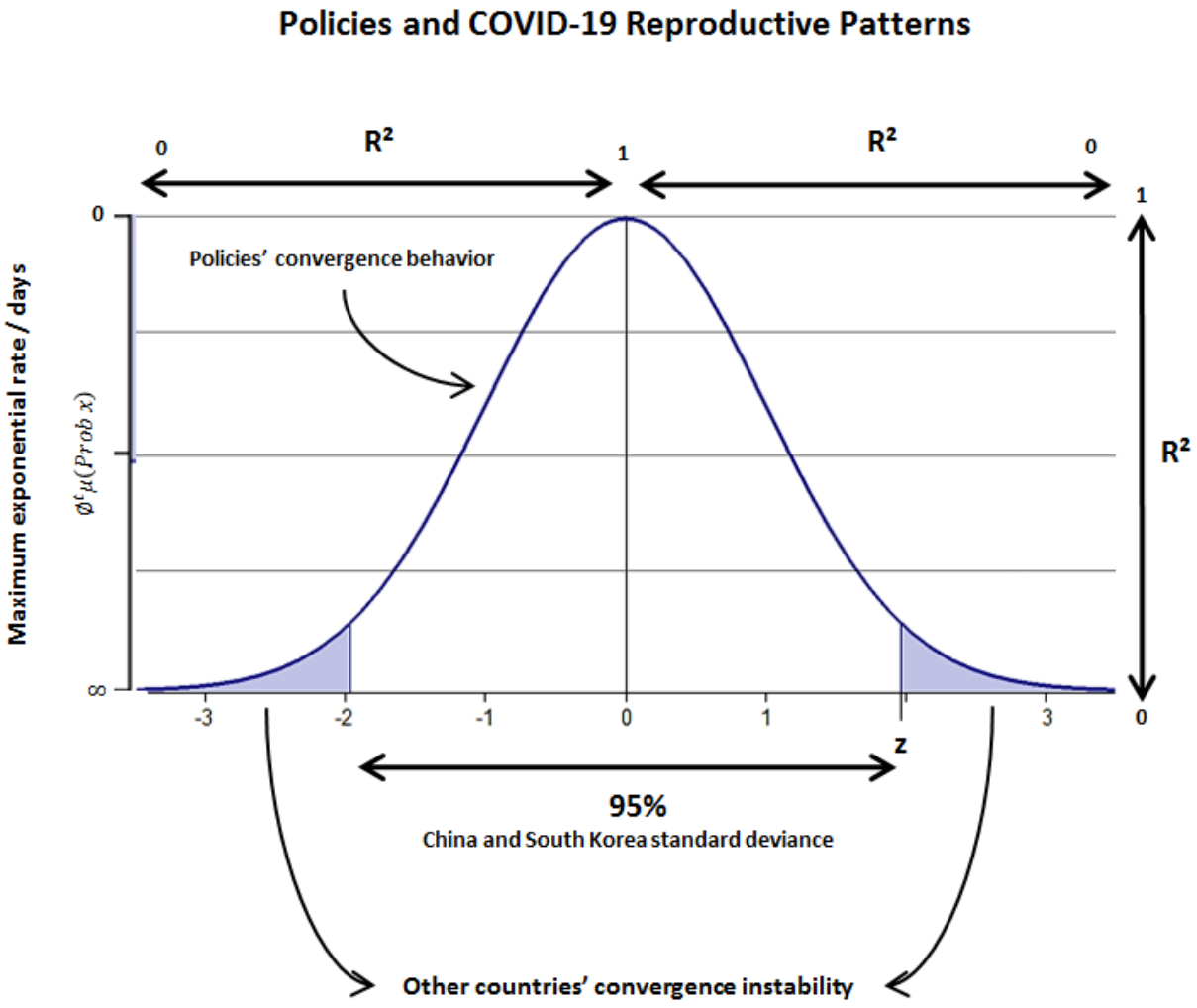


Figure 3 shows that the nonlinear behavior of COVID-19, with preventive policies as mandatory measures to be adopted. Although many policies do not stop virus dissemination entirely at the minimum rate, the results demonstrate that China's and South Korea's policies might be more successful at keeping the virus exponential growth at a low rate.

The COVID-19 event was analyzed from a theoretical point of view using the qualitative theory of differential equations framework to understand how the input of many variables and output in terms of convergence and stability of the policies adopted by each country could yield visible differences in daily new cases and maximum time for exponential infection growth. The results show true differences between the policies adopted and the parameters mentioned earlier; however, future studies from this point of view are needed.

Furthermore, while the variance observed in daily new cases among countries over the period of interest was produced by different factors in each country, points of convergence (the policy type fixed-point theoretical approach) are considered stable from a policy analysis point of view and have high stability (COVID-19 reduction) in many solutions obtained from the confounding environment. Even with high variance

produced by other variables that influence COVID-19 transmission, these fixed-point stable parameters can create a confidence region of statistical analysis by reducing the maximum exponential growth of the virus over time; therefore, it could be more conclusive than many mathematical infectious disease models (SIR stochastic or deterministic approaches) developed since the beginning of the epidemic and later pandemic dissemination. Official, preassumed forms of social physical distancing measures were adopted to avoid COVID-19 transmission during that time, and the possible new patterns of atmospheric disease transmission may constitute a previously unobserved, continuous (not discretized) form of transmission (partially unpredictable) due to airborne instability properties. These time-varying, unresolved empirical data have been presented roughly, since this paper evaluated the entire epidemic scenario with aggregated data.

These results, from January to April 2020 [72], demonstrates that even 20 infected individual hosts can constitute a risk of propagating the disease [48]. This was observed by the end of March in China and Japan when the policies adopted by successful countries were eased. Nevertheless, the statistical data presented in this research strongly suggest that social distancing fails in some countries, but succeeds in others because of the additional use of masks and city disinfection.

The asymptotic instability aspect of the statistical data in Figure 2, as well as data from internet sources [61-68], yields lower infection rates for some countries (China and South Korea) and exponential infection rates for others. This can be explained as the virus asymptote transmission behavior of the emergent phenomenon [35-39,73,74] caused by community behavior [75] based on social distancing failures in most of the countries, while the use of masks and city disinfection in China and South Korea yielded the best results in reducing disease spread and dissemination patterns.

While this research was being conducted, the daily new cases in European countries started declining (March 31, 2020). This can be attributed to the effect of the social physical distancing policy. However, China and South Korea used different measures based on previous experience. The maximum range of infection reduction with only social physical distancing is limited, since many workforce sectors are still active. Therefore, this research suggests that active citizens should use masks [75], and countries should start to disinfect public spaces, including public transport vehicles and routes. These measures will require the introduction of policies to relax the lockdown in cities by strategically and gradually allowing the population outside their homes with additional new social distancing preventive methods.

Digital behavior (infodemics) [76,77] was not considered here, despite its potentially high influence on virus transmission due to misinformation and misuse of scientific information. This is a limitation of this research, since even if a country has adopted all the necessary measures, its citizens can undermine it. This factor should be considered case by case, and it does not significantly contradict the results.

Conclusions

This study theoretically and empirically investigated preventive measures in different countries; the results show that virus transmission patterns are closely linked with human social behavior and the environmental airborne transmission of SARS-CoV-2. Therefore, countries should adopt preventive policy measures and control individual behavior.

Countries that adopted policy measures based on evidence of the atmospheric transmission of COVID-19 reported shorter local epidemic duration, fewer cases per 1 million population, a lower maximum exponential growth mean rate per population, and a lower rate of the COVID-19 daily new cases over time.

Looking at policy measures holistically, social physical distancing and COVID-19 testing availability are mandatory for any country's policy since they are the most reliable and convergent ways to reduce community virus transmission and flatten the curve. Concerning the transmission isolation observed in China and South Korea and the superspreading patterns observed in other countries from January to April 2020, the results show full convergence of nonlinear variables for higher virus infection reduction affecting the input-output of SARS-CoV-2 propagation over time with the adoption of COVID-19 testing availability and social physical distancing by 1- 2 m, along with the additional use of masks and sanitization (city disinfection). Remarkably, China and South Korea adopted these policy measures early in the pandemic, in contrast to other countries. Due to these measures, China and South Korea obtained better results in controlling the local epidemic.

The results observed in South Korea are consistent with those of China. Other countries that did not follow use masks or perform city disinfection presented high nonlinear outputs of SARS-CoV-2 transmission; a common feature for these countries was the constant growth in new infection cases day by day even with the use of social physical distancing measures. This observation suggests that the virus can be transmitted beyond the recommended distance of 1 or 2 m. This was confirmed by Liu et al [15] in April 2020 and by Morawska et al [3] in July 2020. The use of masks and city disinfection appears to be the best strategy for reducing SARS-CoV-2 spread patterns (forms of transmission) and dissemination patterns early in the worldwide pandemic.

Another important point is that if COVID-19 testing is not fully available, social physical distancing measures along with the use of masks and city disinfection can help prevent spread, since they help to isolate undetected infected individuals (including asymptomatic cases), prevent airborne transmission, and protect uninfected people from environmental transmission.

While this research was being conducted in April and early May, some European countries analyzed in this study implemented city disinfection, mask use, and lockdowns, which likely helped to reduce the airborne transmission of SARS-CoV-2. In addition, in Brazil, the most basic physical distancing policy was ignored by many citizens and publicly ignored by the country's president. This may be why Brazil had the third highest number of confirmed COVID-19 cases in the

world on September 9, 2020, and has, as of March 2021, a mean rate of more than 2500 COVID-19 deaths daily.

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Conflicts of Interest

None declared.

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Abbreviations

MERS: Middle Eastern respiratory syndrome
SARS: severe acute respiratory syndrome
SIR: susceptible, infected, removed
TCID: tissue culture infective dose

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Original Paper

Consumer-Based Activity Trackers as a Tool for Physical Activity Monitoring in Epidemiological Studies During the COVID-19 Pandemic: Development and Usability Study

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Abstract

Background: Consumer-based physical activity trackers have increased in popularity. The widespread use of these devices and the long-term nature of the recorded data provides a valuable source of physical activity data for epidemiological research. The challenges include the large heterogeneity between activity tracker models in terms of available data types, the accuracy of recorded data, and how this data can be shared between different providers and third-party systems.

Objective: The aim of this study is to develop a system to record data on physical activity from different providers of consumer-based activity trackers and to examine its usability as a tool for physical activity monitoring in epidemiological research. The longitudinal nature of the data and the concurrent pandemic outbreak allowed us to show how the system can be used for surveillance of physical activity levels before, during, and after a COVID-19 lockdown.

Methods: We developed a system (mSpider) for automatic recording of data on physical activity from participants wearing activity trackers from Apple, Fitbit, Garmin, Oura, Polar, Samsung, and Withings, as well as trackers storing data in Google Fit and Apple Health. To test the system throughout development, we recruited 35 volunteers to wear a provided activity tracker from early 2019 and onward. In addition, we recruited 113 participants with privately owned activity trackers worn before, during, and after the COVID-19 lockdown in Norway. We examined monthly changes in the number of steps, minutes of moderate-to-vigorous physical activity, and activity energy expenditure between 2019 and 2020 using bar plots and two-sided paired sample *t* tests and Wilcoxon signed-rank tests.

Results: Compared to March 2019, there was a significant reduction in mean step count and mean activity energy expenditure during the March 2020 lockdown period. The reduction in steps and activity energy expenditure was temporary, and the following monthly comparisons showed no significant change between 2019 and 2020. A small significant increase in moderate-to-vigorous physical activity was observed for several monthly comparisons after the lockdown period and when comparing March-December 2019 with March-December 2020.

Conclusions: mSpider is a working prototype currently able to record physical activity data from providers of consumer-based activity trackers. The system was successfully used to examine changes in physical activity levels during the COVID-19 period.

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KEYWORDS

COVID-19; energy expenditure; steps; smart watch; fitness tracker; actigraphy; public health; lockdown; SARS-CoV-2; pandemic; wearables

Introduction

Physical activity is an important lifestyle factor [1] associated with a range of health outcomes [2]. Physical activity questionnaires and accelerometers are widely used to measure physical activity in epidemiological studies. The widespread use of advanced consumer-based activity trackers with a growing list of sensors and capabilities [3] has increased the use of activity trackers for research purposes [4]. New activity trackers are continuously released, and although the validity of most currently used activity trackers is unknown, a recent systematic review showed that interdevice reliability is often very strong [5].

This unique source of longitudinal physical activity recordings can be used to measure change in physical activity over time. It is therefore of interest to develop a system for automatic and continuous recording of physical activity data from available providers. This system can be used in a range of different research projects, including as a tool for physical activity surveillance.

The disease outbreak of COVID-19 (SARS-CoV-2) started in China December 2019, spread rapidly, and became a global pandemic. The first case of COVID-19 in Norway was confirmed February 26, 2020. On March 12, the Norwegian government implemented a lockdown of all schools, kindergartens, universities, high schools, gyms, etc, with additional restrictions in the following days. Although a national curfew was not instigated, people were encouraged to stay at home if possible. The most restrictive measures were gradually lifted from the end of April throughout May 2020. Less intrusive social distancing restrictions were gradually reintroduced throughout the Autumn, but no second lockdown was instigated in 2020.

In addition to the societal cost of the COVID-19 pandemic [6], physical inactivity during the lockdown and failing to revert to normal physical activity routines after the lockdown may cause health harm [7].

The aim of this study was to develop a system for automatic continuous recording of physical activity data from a range of consumer-based activity tracker providers and to examine its usability as a tool for physical activity monitoring in epidemiological research. The longitudinal nature of the data, and concurrent pandemic allowed us to examine how this system could be used to monitor change in physical activity before, during, and after the COVID-19 lockdown.

Methods

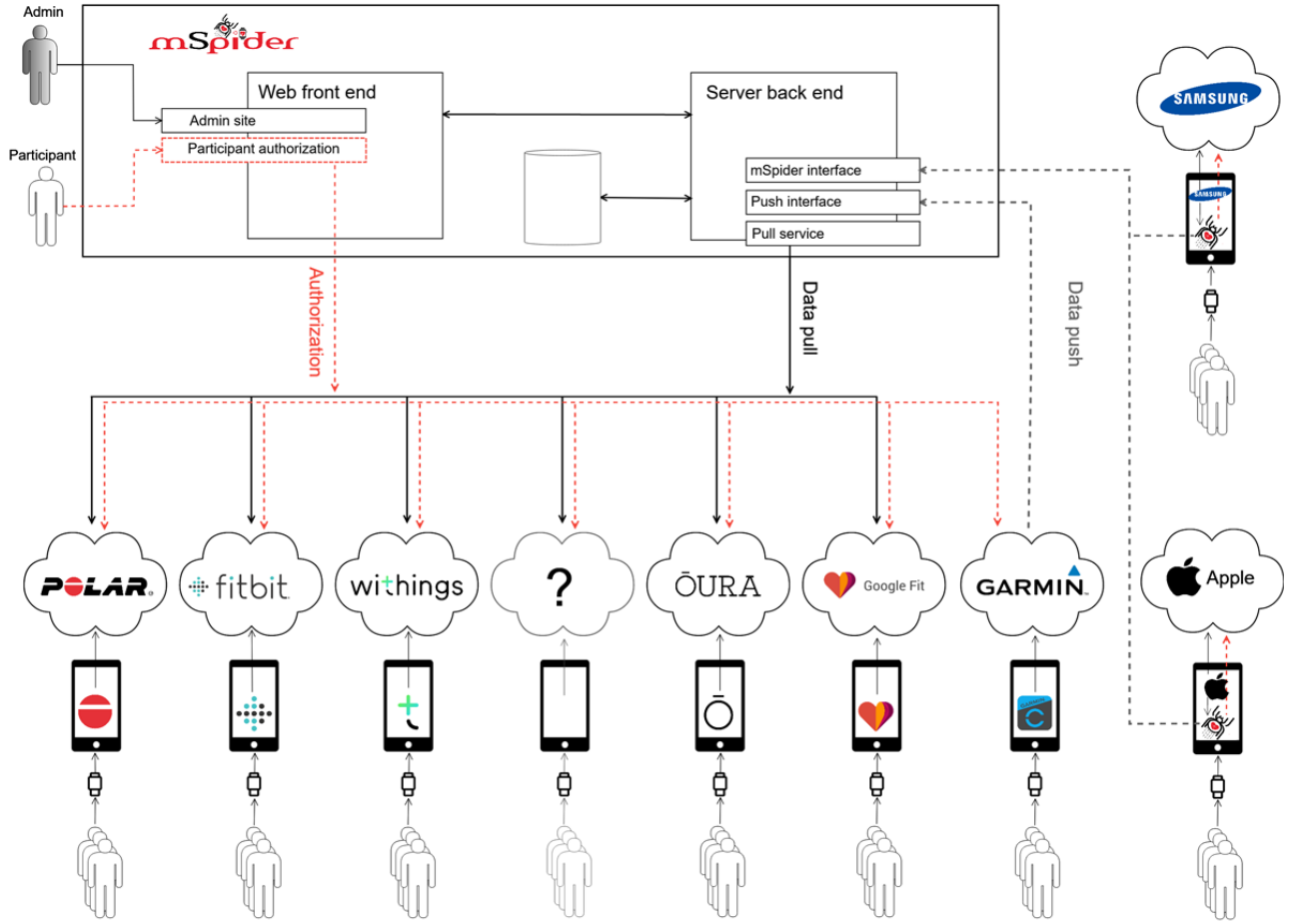
System Architecture

We designed and developed an experimental system, mSpider, intended for automatic and continuous recording of physical activity data using consumer-based activity trackers. The system collects data on physical activity, energy expenditure, pulse, sleep, and related variables over an extended period and from a range of providers and activity tracker models.

The system consists of three modules (see Figure 1): (1) the *web front end*, (2) *the server back end*, and (3) the *mobile app*. The *web front end* is used for managing surveys and to facilitate participant authorization when granting access to their activity tracker data. The *server back end* stores participant authorization access information, handles data transfer between mSpider and the cloud storages of supported providers, and stores downloaded activity tracker data. The *mobile app* further facilitates authorization and data transfer for providers where communication cannot be performed directly between the server back end and the provider cloud storage (eg, Samsung and Apple activity trackers). For these providers, communication is performed through the provider mobile app and uploaded to the mSpider server back end via the mSpider mobile app.

Figure 1 gives an architectural overview of the mSpider system, which providers are supported, and communications paths between systems. Red dashed lines indicate communication paths for participant authorization. To share data, users of Samsung and Apple activity trackers must install the mSpider mobile app and initiate authorization through this app via the provider mobile app. All other supported providers initiate authorization via the web front end, using open authorization, and participants are not required to install the mSpider app. Black solid lines between the *server back end* and external systems show providers where the server back end initiates a pull request to fetch data directly from the provider cloud storage, after access is granted by the participant. Gray dashed lines show providers where data transfer is initiated at the provider side (eg, Garmin) using a push request to provider-specific interfaces on the server back end. Data collected by the mSpider mobile app are also pushed to the mSpider server back end.

Figure 1. mSpider system architectural overview.



Authorization

Participants authorize the mSpider system and grant access to their activity tracker data using OAuth. OAuth is an open protocol for allowing users to securely authorize data sharing between systems, without sharing user log-on credentials [8].

Pull requests from the mSpider system to external application programming interfaces (APIs; eg, Fitbit Web API) contain a *client identifier* and *client secret*, identifying mSpider as an authorized app for data retrieval. These credentials are given by the external system (ie, providers) upon successful registration of the mSpider app with each provider.

In addition, a *token identifier* and *token secret* are provided by the external system when an activity tracker user registers to participate in a study. Tokens are used to identify participants in future pull requests to the provider cloud storage (or push request from the provider). No directly identifiable information is transferred between the provider systems and the mSpider system. All communication is encrypted through the secure socket layer protocol (ie, HTTPS).

Provider Support and Available Data Types

We developed support for activity trackers from Fitbit, Polar, Garmin, Withings, Samsung, Oura, and Apple, as well as providers that store data in Google Fit or Apple Health open health clouds (eg, Huawei). Except Samsung and Apple, supported providers offers a representational state transfer (REST) API web service. The REST software architectural style provides a set of constraints for distributed systems [9] and is a style commonly used when developing web services. A RESTful API (ie, an API using http requests; eg, GET, POST) uses a stateless architecture where the necessary information, including participant identification (ie, tokens), is transferred with the request. To access data from providers not supporting a REST API, the mSpider mobile app was developed using provider-specific software development kits (SDKs), which give access to activity tracker data via the provider-specific mobile app. Table 1 gives an overview of providers and which API or SDK we used to access data.

Each provider offers a different set of data types through their API or SDK. Steps is the only variable supported by all providers. Table 2 gives a list of available variables relevant for this study for each provider and how we used these variables to define valid days (ie, days where activity tracker wear time was sufficient enough to be included in daily physical activity analysis). A complete list of available variables can be found in the provider documentations (Table 1).

Table 1. Provider data access details.

Provider documentation	API[a]/SDK[b]	Version
Apple [10]	HealthKit	6.4
Fitbit [11]	Web API	1/1.2
Garmin (must register to gain access)	Health API	2.9.7
Google [12]	Fit API	1
Oura [13]	Cloud API	1
Polar [14]	AccessLink API	3.36.0
Samsung [15]	Health SDK	1.4.0
Withings [16]	Data API	2.0

[a]API: application programming interface.

[b]SDK: software development kit.

Table 2. Available variables by provider.

Provider	Variables	Valid day calculation
Apple	Steps, AEE[a], REE[b], sleep	Step>150
Fitbit	Steps, TEE[c], AEE, LPA[d], MPA[e], VPA[f], sleep	Step>150
Garmin	Steps, TEE, AEE, MPA, VPA	(Sleep + sedentary time + LPA + MPA + VPA) >10 hours
Google Fit	Steps, TEE	Step>150
Oura	Steps, TEE, AEE, sedentary time, LPA, MPA, VPA, nonwear time	Step>150
Polar	Steps, TEE, AEE, sedentary time, LPA, MPA, VPA, sleep	Nonwear time<14 hours
Samsung	Steps, AEE, sleep	(Sleep + sedentary time + LPA + MPA + VPA) >10 hours
Withings	Steps, TEE, AEE, LPA, MPA, VPA, sleep	Step>150

[a]AEE: activity energy expenditure.

[b]REE: resting energy expenditure.

[c]TEE: total energy expenditure.

[d]LPA: light physical activity.

[e]MPA: moderate physical activity.

[f]VPA: vigorous physical activity.

Recruitment of Volunteer and Study Participants

Volunteers (Development Phase)

To test the system during development and increase the likelihood of long-term recording, we used convenience sampling to recruit 35 volunteers with the following inclusion criteria: 18 years or older, willing to wear a provided activity tracker for an extended period, and willing to share collected physical activity data. Data from these volunteers were used for system development and debugging purposes only and were not included in the longitudinal analysis of physical activity.

Volunteers were recruited during the development phase (from February 2019 to August 2020) and equipped with an activity tracker from Apple, Fitbit, Garmin, Huawei, Oura, Polar, Samsung, or Withings. Two volunteers also shared mobile phone–collected physical activity data stored in Google Fit. One volunteer withdrew after a few days, and two volunteers withdrew after a few months. We gave no instructions on activity tracker use, except giving instructions on how to initiate automatic data sharing with the mSpider system. Volunteers were given written and oral information about the mSpider system and informed that all collected data would be stored at the activity tracker provider's cloud storage. All volunteers signed informed consent.

Study Participants (Physical Activity Study)

Through online news media advertisement, we recruited 130 people with privately owned activity trackers, worn before, during, and after the Norwegian COVID-19 lockdown. Inclusion criteria were owned an activity tracker from Garmin, Fitbit, Withings, or Oura and willing to share physical activity data. Recruitment was conducted in October 2020. Participants received an email invitation with a letter of information and instructions on how to grant access to the mSpider system. Participants gave informed consent by actively granting access to their data.

Privacy

The 35 volunteers who received an activity tracker were required to register a user account at the activity tracker provider. Although the mSpider system only accessed nonidentifiable

information, volunteers were informed that, by registration of a provider account, all data collected by the activity tracker would be uploaded to the provider cloud storage, including potential identifiable information (eg, GPS data).

The 130 study participants for analysis of activity tracker data already owned an activity tracker and thus already had a provider user account. After downloading the relevant data, we removed user tokens from the mSpider database and thus stored data anonymously.

Data Collection

Daily estimates for steps, activity energy expenditure, moderate physical activity, and vigorous physical activity were downloaded from study participants. A variable for moderate-to-vigorous physical activity (MVPA) was created by combining moderate physical activity and vigorous physical activity for participants where these variables were available. We further downloaded light physical activity, sedentary time, sleep duration, and nonwear time, to be used for activity tracker wear time estimates. Data download was limited to days between January 1, 2019, and December 31, 2020. Only data from study participants (ie, not from volunteers) were included in the physical activity analyses.

Only days where the activity tracker was worn for at least 10 hours were labeled as *valid days* [17]. As this was not possible for all providers (Table 2), days with less than 150 recorded steps were excluded. After data download was completed, we removed the connection between the user's provider and the mSpider tool by deleting user tokens. All data on physical activity was thus stored anonymously. An anonymous online questionnaire was sent to participants to collect self-reported data on sex, age, height, and weight.

Statistical Analysis

Participant characteristics from the online questionnaire are presented as means, SDs, and ranges. For each participant, we used valid days to create monthly and yearly averages for steps per day (steps/day), activity energy expenditure in kilocalories per day (kcal/day), and MVPA in minutes per day (minutes/day) for 2019 and 2020. March 2020 was divided into two periods (up to and after March 12; ie, the lockdown date). For each variable we compared the following: 2019 (March-December) with 2020 (March-December); March 2019 with March 1-12, 2020; March 2019 with March 13-31, 2020; April 2019 with April 2020, May 2019 with May 2020, etc; March 2020, 1-12 with 13-31.

We created bar plots to visualize differences between time periods. Normality was checked using histograms. We used two-sided paired sample *t* test or two-sided paired Wilcoxon signed-rank test, depending on normality, to test differences in physical activity between time periods. Differences between periods were analyzed by only including participants with data from both periods. Two-sided *P* values <.05 were considered statistically significant. Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing).

Ethical Approval

The Regional Committees for Medical and Health Research Ethics North (reference 164780) and the Norwegian Center for Research Data (reference 628485) reviewed the study.

Results

Participant Characteristics

Of the 130 recruited study participants, 14 did not respond to the following invitation email and three owned an unsupported activity tracker. A final sample of 113 participants were thus included in the analysis. Of the included participants, 106 completed the online questionnaire and provided their characteristics (Table 3).

Due to the anonymous nature of the data collection, we did not have access to information about participant's activity tracker model, only their provider. Altogether, 39 participants used Fitbit activity trackers, and 74 participants used Garmin activity trackers. No participants owned a Withings or Oura activity tracker.

Both Fitbit and Garmin provide data on steps, MVPA, and activity energy expenditure. All 113 participants were thus included when generating monthly means for all three variables. Monthly means were calculated from 66.274 measurements (ie, valid person-days).

Table 3. Participant characteristics (n=106).

Variable	Value	Range
Height (cm), mean (SD)	173.5 (8.0)	158-194
Weight (kg), mean (SD)	76.0 (14.3)	53.5-147.0
BMI (kg/m^2), mean (SD)	25.2 (4.0)	18.3-50.3
Age (years), mean (SD)	40.6 (10.6)	21-69
Females, n (%)	59 (56.2)	N/A[a]

[a]N/A: not applicable.

Change in Physical Activity

On average, participants walked 797 fewer steps per day in March 13-31, 2020, compared to March 2019 (*P*=.02). Similarly, participants walked on average 913 fewer steps per day in March 13-31, 2020 (postlockdown), compared to March 1-12, 2020, (prelockdown; *P*<.001). The remaining step comparisons showed no differences.

Mean activity energy expenditure was 74 kcal/day lower in March 13-31, 2020, compared to March 2019 (*P*=.02). In addition, mean activity energy expenditure was 85 kcal/day lower in March 13-31, 2020 (postlockdown), compared to March 1-12, 2020, (prelockdown; *P*=.001). However, activity energy expenditure was on average 54 kcal/day higher in September 2020 compared to September 2019 (*P*=.02). The remaining activity energy expenditure comparisons showed no difference.

For MPVA, monthly comparisons showed a significant increase from 2019 to 2020 for May (*P*=.01; with a median difference of 8 minutes), September (*P*=.008; with a median difference of 3 minutes), October (*P*=.02; with a median difference of 5 minutes), and December (*P*=.04; with a median difference of 4 minutes), as well as the yearly comparison (*P*=.03; with a median difference of 4 minutes). The remaining MVPA comparisons showed no difference.

A summary of mean difference per day between periods for steps and activity energy expenditure, with 95% CIs and *P* values from each *t* test, is given in Table 4. The table also gives the median of the difference per day between periods for MVPA, with IQRs and *P* values from each Wilcoxon test. Because we used paired tests, analysis only include participants with data in both the preperiod and the postperiod, thus is based on data from 76 to 107 participants. Figure 2 and Figure 3 gives monthly mean step count and activity energy expenditure from March 2019 through December 2020. Figure 4 gives the median MVPA for the same periods.

Table 4. Difference per day between preperiods and postperiods.

Monthly comparison 2019-2020	Steps (steps/day), mean difference (95% CI)	*P* value[a]	AEE[b] (kcal/day), mean difference (95% CI)	*P* value	MVPA[c] (min/day), median (IQR)	*P* value
March-December	349 (–4 to 702)	.05	29 (–2 to 60)	.07	4 (–6 to 4)	.03
March 1-12[d]	28 (–608 to 664)	.93	21 (–40 to 82)	.49	–2 (–14 to –2)	.57
March 13-31[e]	–797 (–1468 to –126)	.02	–74 (–136 to –11)	.02	2 (–11 to 2)	.83
April	–123 (–850 to 605)	.74	–35 (–105 to 34)	.32	–1 (–15 to –1)	.81
May	53 (–586 to 692)	.87	2 (–59 to 64)	.94	8 (–6 to 8)	.01
June	301 (–276 to 878)	.30	45 (–7 to 97)	.09	4 (–10 to 4)	.07
July	442 (–232 to 1117)	.20	44 (–15 to 104)	.14	1 (–14 to 1)	.53
August	326 (–271 to 922)	.28	24 (–24 to 72)	.33	2 (–14 to 2)	.53
September	324 (–148 to 797)	.17	54 (8 to 100)	.02	3 (–7 to 3)	.008
October	361 (–290 to 1011)	.27	41 (–7 to 89)	.10	5 (–6 to 5)	.02
November	242 (–442 to 927)	.48	42 (–22 to 106)	.20	4 (–11 to 4)	.34
December	491 (–6 to 988)	.05	32 (–21 to 84)	.24	4 (–8 to 4)	.04

[a]*P* values from paired sample *t* test or paired Wilcoxon signed-rank test.

[b]AEE: activity energy expenditure.

[c]MVPA: moderate-to-vigorous physical activity.

[d]Comparing March 2019 with March 1-12, 2020.

[e]Comparing March 2019 with March 13-31, 2020.

Figure 2. Bar plot of mean step count per day, by month, with SD (error bars).

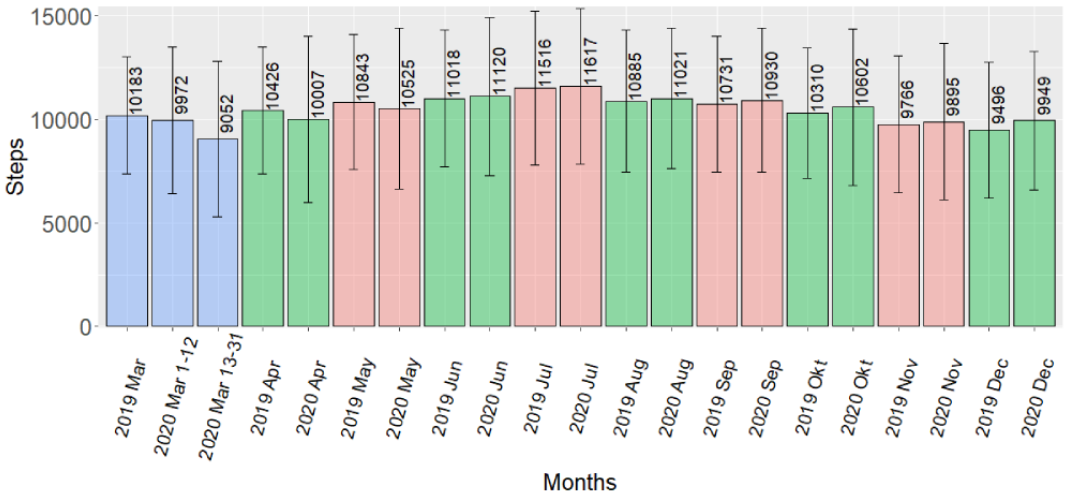


Figure 3. Bar plot of mean AEE per day, by month, with SD (error bars). AEE: activity energy expenditure.

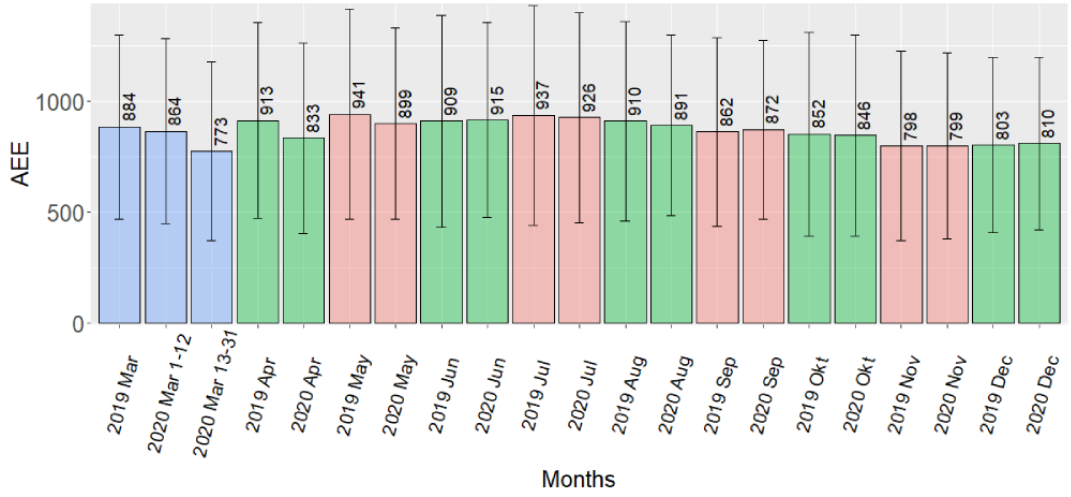
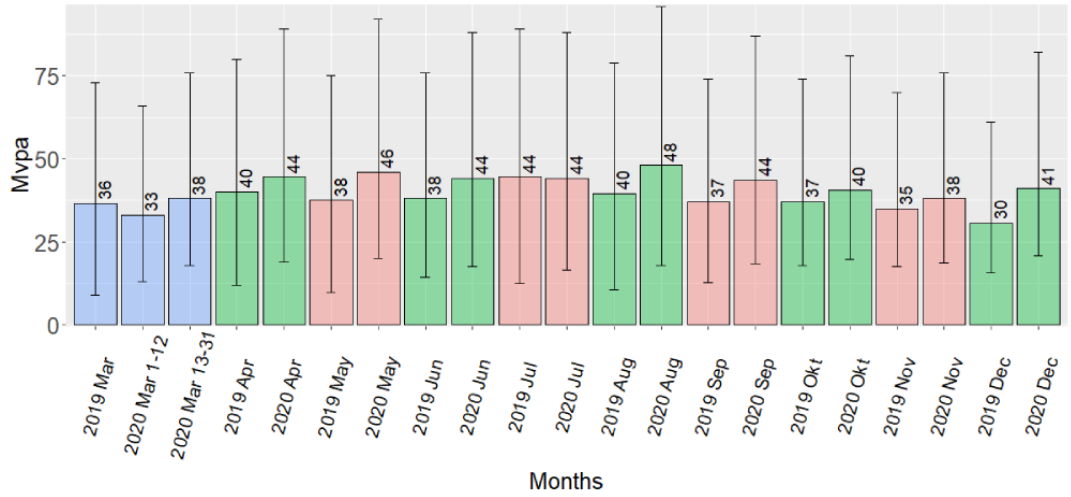


Figure 4. Bar plot of median minutes of MVPA per day, by month, with IQR (error bar). Mvpa: moderate-to-vigorous physical activity.



Discussion

Principal Findings

In this study, the mSpider system was successfully used to download historic data on steps, activity energy expenditure, and MVPA from Garmin and Fitbit activity tracker users. The longitudinal data showed changes in physical activity during the COVID-19 pandemic.

Findings indicate a short-term reduction in steps and activity energy expenditure due to the COVID-19 lockdown but no reduction in MVPA. However, participants increased their level of MVPA the month after the lockdown period (ie, May 2020) and some months in the autumn of 2020 (ie, September, October, and December) compared to 2019.

Comparison With Previous Work

Results in this study are supported by reports from providers of consumer-based activity trackers. Garmin have released a statement showing that users globally had a distinct decline in step count during the last 2 weeks of March 2020 and that the reduction in step counts was compensated by increase in other activities [18]. Withings have reported a temporary decline in step counts among users during national lockdowns [19]. Similarly, a study of UK adults using physical activity data recorded by a smartphone app showed a significant decrease in physical activity during the March 2020 UK national lockdown [20].

Google Trend analysis of community interest in physical activity during the COVID-19 outbreak and lockdown showed an increase in Google search rates on physical activity topics in Australia, the United Kingdom, and the United States [21]. A study among German athletes using activity tracker data showed that shorter and more vigorous exercise sessions replaced longer sessions [22].

These studies support our finding that, although restrictions confined people to their home, they found alternative ways to keep their habitual physical activity level. Conversely, based on online physical activity questionnaires, a study from Thailand did not show any increase in physical activity after the lockdown was lifted [23], and a study from Bangladesh showed a high prevalence of inactivity during lockdown [24].

In summary, activity tracker data from several vendors and groups of users including athletes and patients with a chronic disease have shown changes in physical activity levels and

patterns during the COVID-19 pandemic, but findings vary between countries.

mSpider as a Method for Data Collection on Physical Activity

The analysis of physical activity changes related to the COVID-19 pandemic period showed that the mSpider system can be a valuable tool for collection of long-term data on physical activity, including historical data and detecting changes in physical activity over time.

In this study, we used the proposed system to access data retrospectively from participants with privately owned activity trackers. Previously, we have successfully used the same technology for long-term prospective physical activity monitoring among participants in a lifestyle intervention study wearing a provided activity tracker for up to 1 year ([25,26] and Hopstock et al, unpublished data, 2020).

A system similar to mSpider, Remote Assessment of Disease and Relapses (RADAR)–base, was used by Sun et al [27], who observed change in daily steps during national lockdowns among participants with chronic disease equipped with a Fitbit tracker. RADAR-base is an open-source platform for collecting physical activity data from smartphones, Fitbit and Garmin activity trackers, and some research grade accelerometers [28]. RADAR-base uses similar technology as mSpider, but data collection is limited to only two providers of consumer-based activity trackers.

A study by Radin et al [29] successfully mapped historic Fitbit data (provided manually by Fitbit) to known influenza outbreaks. This also shows the potential for the proposed system as a tool for disease outbreak surveillance, where clusters of participants with a combination of physical activity reduction and elevated resting heart rate can be used to indicate disease outbreaks in an area.

The quality of accelerometer-based physical activity data is dependent on participant wear compliance. Future epidemiological research may benefit from the proposed system by facilitating long-term data recording, especially from younger adults who may be less compliant when wearing traditional accelerometers compared to older adults [30] but more likely to own and wear an activity tracker [31]. Long-term activity tracker data can thus add to and enrich accelerometer-based data collections, especially from younger participants.

In summary, we found the mSpider system to be an interesting supplement to current tools for physical activity monitoring in epidemiological studies. However, major challenges must be kept in mind. First, self-selected users of activity trackers are often more physically active compared to nonusers [31,32]. Second, the accuracy of different activity trackers can be highly variable and the choice of activity tracker will therefore affect reported performance [5,33,34]. At the population level, the system may perform better to detect change in physical activity over time than to estimate the absolute levels of physical activity.

Strengths and Limitations

The major strength of this study is the long-term recording with up to 2 years of daily physical activity data per participant. This allowed for month-to-month comparisons between 2019 and 2020, thus taking potential seasonal differences in physical activity levels into account.

The study has limitations that can affect the study results. The participants were self-selected owners of physical activity trackers who were likely to be more physically active than the general population. A recent study by Anyan et al [35] investigating physical activity change during the Norwegian lockdown (using questionnaire data) found that 14% of participants reported a reduction, 22% reported an increase, and 64% reported no change in physical activity level. Therefore, there is a risk of selection bias in this study (ie, the sample may not be representative of the general population). Nevertheless, the observed changes in physical activity levels in this sample during the study period demonstrate the usefulness of the mSpider system. Further, due to anonymous data collection, we could not link participant characteristics to physical activity data to examine physical activity in strata of sex, age, or other characteristics (eg, activity tracker model).

Conclusion

mSpider is a working prototype currently able to record physical activity data from several providers of consumer-based activity trackers. The system was successfully used to detect longitudinal changes in physical activity levels before, during, and after the Norwegian COVID-19 lockdown period in 2020. To our knowledge, this is the first study reporting change in physical activity caused by the COVID-19 lockdown in Norway using 2 years of objective consumer-based activity tracker data.

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Conflicts of Interest

None declared.

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Abbreviations

API: application programming interface
MVPA: moderate-to-vigorous physical activity
RADAR: Remote Assessment of Disease and Relapses
REST: representational state transfer
SDK: software development kit

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Original Paper

Texas Public Agencies' Tweets and Public Engagement During the COVID-19 Pandemic: Natural Language Processing Approach

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Abstract

Background: The ongoing COVID-19 pandemic is characterized by different morbidity and mortality rates across different states, cities, rural areas, and diverse neighborhoods. The absence of a national strategy for battling the pandemic also leaves state and local governments responsible for creating their own response strategies and policies.

Objective: This study examines the content of COVID-19–related tweets posted by public health agencies in Texas and how content characteristics can predict the level of public engagement.

Methods: All COVID-19–related tweets (N=7269) posted by Texas public agencies during the first 6 months of 2020 were classified in terms of each tweet's functions (whether the tweet provides information, promotes action, or builds community), the preventative measures mentioned, and the health beliefs discussed, by using natural language processing. Hierarchical linear regressions were conducted to explore how tweet content predicted public engagement.

Results: The information function was the most prominent function, followed by the action or community functions. Beliefs regarding susceptibility, severity, and benefits were the most frequently covered health beliefs. Tweets that served the information or action functions were more likely to be retweeted, while tweets that served the action and community functions were more likely to be liked. Tweets that provided susceptibility information resulted in the most public engagement in terms of the number of retweets and likes.

Conclusions: Public health agencies should continue to use Twitter to disseminate information, promote action, and build communities. They need to improve their strategies for designing social media messages about the benefits of disease prevention behaviors and audiences' self-efficacy.

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KEYWORDS

COVID-19; public health agencies; natural language processing; Twitter; health belief model; public engagement; social media; belief; public health; engagement; communication; strategy; content analysis; dissemination

Introduction

COVID-19 is a new infectious disease that is caused by SARS-CoV-2, a new and potentially deadly coronavirus. The ongoing COVID-19 pandemic is characterized by different morbidity and mortality rates across different states, cities, rural areas, and diverse neighborhoods. The absence of a national strategy for battling the pandemic also leaves state and local

governments responsible for creating their own response strategies and policies [1]. However, misinformation and disinformation continue to circulate on social media platforms with unprecedented volume and velocity, which affects the public's trust in and response to governmental restrictions and corrective actions [2,3]. Thus, it is crucial to examine how state and local health departments communicate with their stakeholders on social media platforms.

Public health agencies have been actively using platforms such as Twitter and Facebook to communicate with their stakeholders during public health crises. The accumulating literature on organizational social media use has identified the following three primary functions: information, action, and community [4]. The information function refers to the organizational use of social media to provide the public with emergency and risk information [5]. It includes a wide range of activities such as making emergency updates, advisories, and warnings; providing scientific explanations and public education; and clarifying misinformation about an unfolding epidemic [6]. The action function refers to how organizations can use social media to encourage their followers to adopt or avoid certain behaviors [4], such as attending events, making monetary donations, volunteering, and adopting other recommended behaviors. In the context of health and risk communication, action-oriented messages may specify how individuals can protect themselves when an imminent threat arises, and this function is directly related to the overarching goal of public health agencies, which is to mitigate risk behaviors during an epidemic [7]. The community function revolves around building relationships with community members, providing social and emotional support, and communicating about collective identities. Providing emotional support and boosting community morale can enhance public trust and cooperative behaviors [8], of which both are essential for effective risk mitigation. Although health agencies are generally advised to use multiple social media functions, such as those outlined above, a large body of earlier studies has suggested that most public agencies' social media messages are disseminated via one-way communication [9]. Thus, we propose the first research question (RQ) about the functions of public agencies' tweets during the COVID-19 pandemic, as follows: to what extent do public health agencies' Twitter messages fulfill the functions of information, action, and community during the COVID-19 pandemic (RQ1)?

According to the Health Belief Model (HBM), a person's decision to adopt a recommended health behavior is influenced by their desire to avoid an illness and their belief that the recommended behavior can help prevent an illness [10]. The following two factors affect one's desire to avoid an illness: perceived severity and perceived susceptibility. When a person thinks that an illness is serious (perceived severity) and that they have a high chance of contracting it (perceived susceptibility), they will be more alarmed and want to avoid the illness. Further, an individual's preventative behavior is also influenced by their beliefs about (1) whether the recommended behavior can indeed provide health benefits, such as preventing the illness (perceived benefits); (2) the obstacles associated with adopting the recommended behavior, such as cost and time (perceived barriers); and (3) their ability to engage in the behavior (self-efficacy). A meta-analysis study on the decades of research that involved the use of the HBM has indicated that perceived benefits and perceived barriers are the strongest predictors of behavioral change [11].

The original HBM was a psychological model that was created to predict an individual's health behaviors. It has recently been used to guide the design of health messages for effectively promoting health behaviors and evaluate the presence or absence of elements in media content that might contribute to people's health beliefs [12]. Understanding the extent to which public health agencies' tweets address different health beliefs could offer insights into how these tweets might inform the public about the threats of COVID-19 and encourage proper preventative measures. Hence, we propose the next set of RQs, as follows: (1) what are the recommended preventative behaviors (RQ2a) and (2) to what extent do public health agencies communicate severity, susceptibility, benefits, barriers, and self-efficacy information in their Twitter messages about COVID-19 (RQ2b)?

In addition to behavioral outcomes, public engagement is another indicator of the effectiveness of public agencies' crisis communication efforts. Public engagement refers to the various forms of communicative interaction between the public and government agencies, such as the public sharing or replying to governmental agencies' messages [13]. Public engagement has several benefits. First, greater public engagement with public health agencies' social media content typically indicates higher levels of exposure to, attention toward, and information absorption of the content in messages (eg, advisories, warnings, or other educational materials), which are essential in helping the public form accurate risk perceptions and encouraging risk-reduction behaviors [14]. Second, public engagement can be an indicator or precursor of trust in health institutions, which leads to better health adherence and other positive behavioral changes [15]. Finally, public engagement can help public health agencies identify, clarify, and correct misinformation, resulting in more effective health promotion [16]. Although public engagement is generally associated with positive outcomes, it should be noted that scholars distinguish between positive and negative engagement, suggesting that the latter may lead to the "denial, rejection, avoidance and negative word-of-mouth" of an organization [17]. For example, in the context of a crisis, it has been found that certain types of engagement may generate misinformation and undermine the authority of crisis management agencies [18].

We adopted Johnson and Taylor's [19] conceptualization of public engagement at the individual level, which they defined as the public's psychological and behavioral involvement and participation with public health agencies' messages. In social media–mediated crisis communication, such individual-level engagement manifests in two forms: the public's resharing behavior on social media [19,20] and the behavior of "liking" or endorsing public agencies' social media messages. The first form of engagement (ie, sharing public agencies' social media content with one's own social networks) is viewed as an important outcome of effective health risk communication. Individuals' sharing behavior on social media is a key mechanism that enables the amplification of public health

agencies' messages [21]. By sharing these messages via functions such as retweets, the public not only relays relevant health content to their immediate communities but also promotes collective sharing behaviors that can generate normative influences, which results in intended behavioral changes [22]. Additionally, it has been determined that endorsing public health agencies' messages through Twitter's "favorite" function or Facebook's "like" function is a form of public engagement that is distinct from resharing [23,24]. Specifically, this endorsement behavior has been conceptualized as a type of affective engagement that indicates the audience's feelings of support for or symbolic alignment with an organization with regard to a specific issue [25]. Although endorsement does not fully equate to the psychological acceptance of a message, research suggests that positive assessments are significantly associated with health message acceptance, especially when such endorsements are made by celebrities [26]. We thus propose the following question: how do the features of tweets predict public engagement in terms of the number of favorites and retweets during the COVID-19 pandemic (RQ3)?

Methods

Sampling and Data Collection

This study focused on public agencies in the state of Texas. Texas was chosen because this state became one of the disease epicenters following the enforcement of Governor Abbott's state reopening measures in April 2020. At the time of data collection (mid-July 2020), Texas was facing the second peak of COVID-19 cases and had the highest 7-day average number of daily new cases (n=15,038) [27]. In addition, with Texas being the second largest and second most populous state in the United States, its public agencies may face the particularly challenging task of reaching out to the diverse population and coordinating with peer agencies. Since this study examined the public tweets of governmental agencies, it was exempt from human subjects ethics review.

We conducted the following steps to select the sample tweets for analysis. First, we identified all of the active Twitter accounts of public health departments and Office of Emergency Management (OEM) organizations at the city, county, and state levels in Texas. To identify public health departments, we obtained a list of health department directories from the Centers for Disease Control and Prevention and the US Department of Health and Human Services. Additionally, a list of local-level health agencies was obtained from the National Association of County and City Health Officials. In this step, we identified a total of 26 Texas public health departments that actively tweeted during the studied period. We also used a list of Texas city and county names to conduct searches on Twitter and identified an additional 56 official OEM organization Twitter accounts, which yielded a total of 82 organizations. Second, we created a list of 25 COVID-19–related keywords ("covid," "corona," "koronavirus," "ncov," "sars," "pandemic," "epidemic," "quarantine," "outbreak," "handwash," "wuhan," "panic," "chinese virus," "lock down," "sheltering in place," "shelter in place," "flatten the curve," "safer at home," "stay home," "face covering," "wear mask," "get tested," "quarantine," "ppe," and "n95"). All tweets from the 82 organizations that contained at least one of these keywords and were published between January 1 and June 30, 2020, were downloaded using Twitter's developer application programming interface (n=15,382).

Measurements

A codebook was developed to guide the coding of the training data set. It included the following variables: functions, types of recommended actions, and HBM variables. Each tweet was coded in terms of the presence or absence of COVID-19–related content. Tweets that contained COVID-19–related content were further coded.

First, each tweet was coded in terms of the functions it served. Tweets served the information function if they shared information about COVID-19, such as COVID-19 symptoms, risks of the disease, prevention information, current infection rates or case numbers, and testing information, or if they described actions that agencies were taking to contain COVID-19 spread. Tweets served the action function if they urged readers to adopt a certain health behavior. Tweets served the community function if they built community by asking readers to interact with each other and with the sender, providing emotional support, and boosting morale. These descriptions of functions were adapted from Kang [25]. Each tweet was evaluated in terms of whether it contained any of these three types of information.

Second, each tweet was coded in terms of whether it included one or more of the following actions: (1) handwashing, (2) social distancing, (3) mask wearing or face covering, (4) staying at home or sheltering in place, (5) getting tested, (6) learning more information, and (7) other behaviors.

Finally, HBM variables, including severity (any reference to the magnitude and seriousness of COVID-19), susceptibility (the likelihood that a person, a group, or the public in general will contract COVID-19), benefits (the benefits of recommended behaviors and their effectiveness in preventing or treating COVID-19 or containing the pandemic on the societal level), barriers (the difficulties associated with adopting or implementing the recommended behaviors), and self-efficacy (one's ability to engage in recommended behaviors) were coded. TThe coding of these health beliefs was adapted from Tang and Park [12], respectively).

Development of the Training Data Set

Several rounds of training sessions were conducted to assist two coders with understanding each item in the codebook. Afterward, around 20% (3000/15,000) of the tweets were used for the development of a training data set. Two coders coded 150 tweets that were randomly selected from the remaining 80% (12,000/15,000) of the tweets. These tweets achieved satisfactory intercoder reliability (Cohen κ: mean 0.83; range 0.56-0.96). Two items (barriers and self-efficacy) were dropped from the codebook because they were nearly completely absent from the collected tweets. Afterward, each coder independently coded half of the training data set.

Computer-Assisted Classification Based on Natural Language Processing

Data cleaning was conducted by following the steps laid out by Du et al [28]. The bidirectional encoder representations from transformers (BERT), a natural language processing program developed by Google, was trained to automatically classify tweets [29]. The pretrained BERT-large model from Huggingface was used [30]. We divided the initial, manually coded data sets (3000 tweets) into a training data set (number of tweets: 2400/3000, 80%) and a testing data set (number of tweets: 600/3000, 20%). In our training set, some labels had a relatively low frequency (<250 occurrences), which resulted in these labels being mostly ignored in the model's training process. To train such low-frequency categories, we doubled all instances of tweets with minority labels to give them a stronger signal in the model. The model was trained for 3 epochs by using the AdamW optimizer with a learning rate of 2e − 5.

Precision, recall, and overall F1 score (the harmonic mean of precision and recall) were calculated for each variable. We also calculated the microaveraging F1 score and macroaveraging F1 score to evaluate variables' performance in each classification task. We summed up all of the individual true positives, false positives, and false negatives for the microaveraged score. For the macroaveraged score, we used the average of the F1 scores of different categories. Overall, our model achieved good results (Table 1). Afterward, we used the program to automatically classify all of the tweets in the sample.

Table 1. Bidirectional encoder representations from transformers classification of the performance of tweets about the COVID-19 pandemic that were published by Texas public health agencies between January 1 and June 30, 2020.

Variables	Precision[a]	Recall[b]	F1 score[c]
About COVID-19 or not	.93	.93	.93
Information function	.85	.92	.88
Action function	.68	.83	.75
Community function	.58	.58	.58
Handwashing	.75	1.00	.53
Social distancing	.80	.80	.80
Mask wearing or face covering	.85	.96	.90
Staying at home or sheltering in place	.74	.78	.76
Getting tested	.69	.90	.78
Learning more information	.77	.92	.84
Other behaviors	.27	.54	.36
Severity	.69	.92	.79
Susceptibility	.84	.86	.85
Benefit	.42	.70	.52

[a]The microaverage, macroaverage, weighted average, and sample average precision scores were .78, .70, .80, and .46, respectively.

[b]The microaverage, macroaverage, weighted average, and sample average recall scores were .88, .83, .88, and .50, respectively.

[c]The microaverage, macroaverage, weighted average, and sample average F1 scores were .83, .76, .84, and .47, respectively.

Data Analysis

Hierarchical linear regressions or stepwise linear regressions were used to answer RQ3 (ie, how various tweet features predicted the numbers of favorites and retweets). This method enabled the assessment of separate effects from different blocks of variables. Since both variables for measuring engagement were highly skewed, we adopted the standard practice of log-transforming these metrics before they were entered into regression models. In the two regression models, the independent variables consisted of the following three blocks: (1) the information, action, and community message types; (2) the dichotomous thematic categories, which included social distancing, face covering, sheltering in place, getting tested, information seeking, and other behaviors; and (3) the health belief variables, which included severity, susceptibility, and benefits. To control for the effect of account popularity (popular accounts were more likely to promote greater public engagement), we entered the log-transformed number of followers as a control variable in each model.

Results

A total of 7269 tweets were related to COVID-19. Of the 82 public health and OEM agencies, only 61 tweeted about COVID-19. These organizations tweeted about COVID-19 for an average of 119 times (SD 203.09).

RQ1 asked about the functions of tweets. Sharing information was the most prominent function of the tweets posted by public health agencies (6835/7269, 94.03%), followed by the action function (2491/7269, 34.27%). Community building was the least salient function, as only 10.19% (741/7269) of the tweets promoted the engagement of community members and provided emotional support.

RQ2 asked about the types of actions that tweets promoted and the health beliefs that tweets mentioned. Of the behaviors recommended by agencies, learning more information was the most recommended action among the tweets (3402/7269, 46.80%), followed by getting tested (1076/7269, 14.80%), staying at home or sheltering in place (911//7269, 12.53%), social distancing (700/7269, 9.63%), face covering (651/7269, 8.96%), and handwashing (616/7269, 8.47%). Figure 1 shows the number of tweets from public health agencies that mentioned different health behaviors over time. Handwashing was initially the most frequently recommended behavior, and its importance was continuously emphasized. Tweets that promoted staying at home or sheltering in place exhibited the sharpest increase in incidence, which dropped precipitously after April. Tweets that mentioned the action of getting tested increased in incidence between February and May but decreased in incidence during May and June. The number of tweets that mentioned social distancing started to plateau in March. The number of tweets that discussed the wearing of face coverings was minimal in the first 3 months, but this number started to consistently increase in March. In terms of HBM variables, severity (1389/7269, 19.11%), susceptibility (2057/7269, 28.30%), and benefits (1238/7269, 17.03%) were the three concepts that were frequently mentioned in public health agencies' tweets.

RQ3 was proposed to examine the relationship between the content of tweets and public engagement. Overall, the public's engagement with the tweets posted by public health agencies was relatively low, as each tweet had an average of 13.05 retweets (SD 43.16) and 19 favorites/likes (SD 59.97). Tables 2 and 3 present the two hierarchical regression models for predicting the two public engagement variables.

Figure 1. Longitudinal changes in the number of tweets promoting different health behaviors by public health agencies in Texas (January 1 to June 30, 2020).

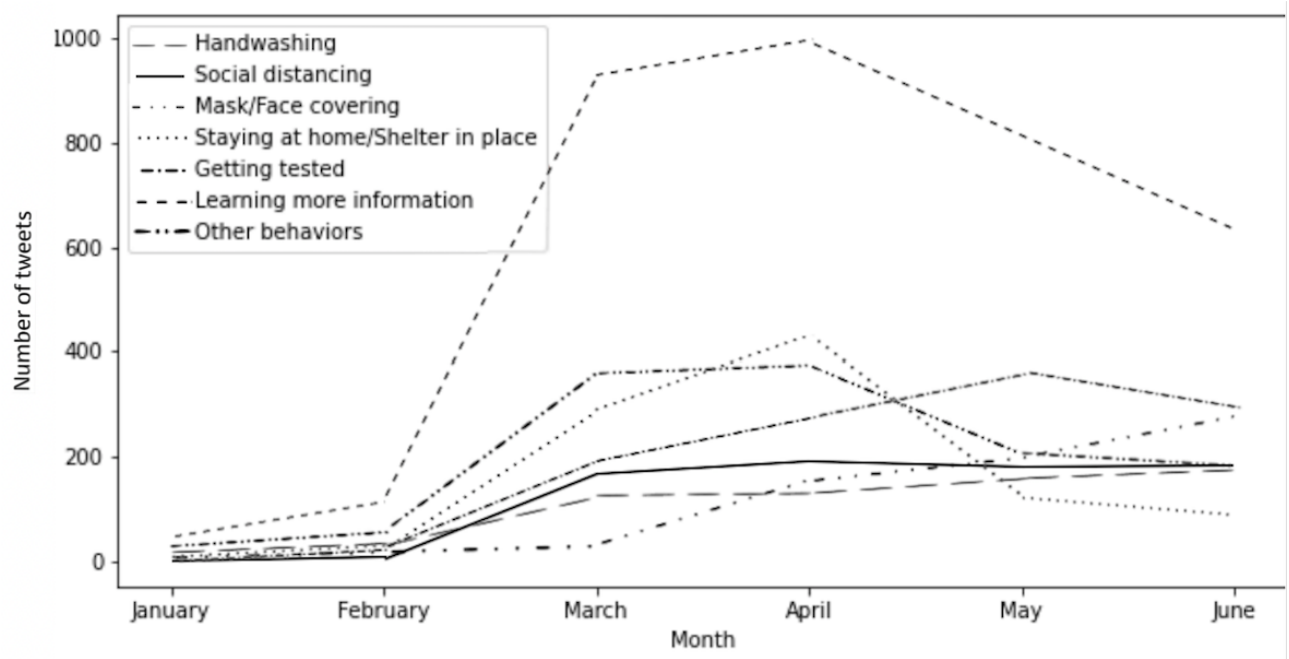

Table 2. Hierarchical ordinary least squares regression of predictors for the number of retweets (based on Texas public health agencies' COVID-19–related tweets that were posted between January 1 and June 30, 2020; N=7269).

Variables	Number of retweets					
	Model 1[a]		Model 2[b]		Model 3[c]	
	β[d] (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Control						
Followers	.43 (.01)	<.001	.43 (.01)	<.001	.50 (.01)	<.001
Functions						
Information	.10 (.03)	<.001	.09 (.02)	<.001	.04 (.03)	<.001
Action	.10 (.01)	<.001	.09 (.01)	<.001	.12 (.02)	<.001
Community	.01 (.02)	.35	.02 (.01)	.07	.04 (.02)	.001
Types of actions proposed						
Handwashing	N/A[e]	N/A	−.01 (.03)	.36	−.05 (.03)	<.001
Social distancing	N/A	N/A	.02 (.03)	.13	.02 (.03)	.16
Mask wearing or face covering	N/A	N/A	.01 (.03)	.64	.03 (.03)	.01
Staying at home	N/A	N/A	.05 (.02)	<.001	.04 (.02)	.001
Getting tested	N/A	N/A	.03 (.02)	.004	.11 (.02)	<.001
Learning more information	N/A	N/A	.05 (.01)	<.001	.06 (.01)	<.001
Other behaviors	N/A	N/A	−.04 (.02)	.01	.03 (.02)	.08
Health Belief Model variables						
Severity	N/A	N/A	N/A	N/A	.10 (.01)	<.001
Susceptibility	N/A	N/A	N/A	N/A	.20 (.01)	<.001
Benefits	N/A	N/A	N/A	N/A	−.002 (.01)	.91
Model of *f* values	494.52	<.001	186.74	<.001	207.11	<.001

[a]Model 1 had a change in R^2 of 0.21 and a total R^2 of 0.21.

[b]Model 2 had a change in R^2 of 0.01 and a total R^2 of 0.22.

[c]Model 3 had a change in R^2 of 0.07 and a total R^2 of 0.21.

[d]β is a standardized coefficient.

[e]N/A: not applicable.

Table 3. Hierarchical ordinary least squares regression of predictors for the number of favorites (based on Texas public health agencies' COVID-19–related tweets that were posted between January 1 and June 30, 2020; N=7269).

Variables	Number of favorites					
	Model 1[a]		Model 2[b]		Model 3[c]	
	β[d] (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
Control						
Followers	.50 (.01)	<.001	.50 (.01)	<.001	.55 (.01)	<.001
Functions						
Information	.05 (.03)	<.001	.05 (.03)	<.001	.01 (.03)	.31
Action	.09 (.01)	<.001	.09 (.02)	<.001	.11 (.02)	<.001
Community	.08 (.02)	<.001	.08 (.02)	<.001	.09 (.02)	<.001
Types of actions proposed						
Handwashing	N/A[e]	N/A	−.03 (.03)	.049	−.06 (.03)	<.001
Social distancing	N/A	N/A	.03 (.03)	.03	.03 (.03)	.04
Mask wearing or face covering	N/A	N/A	−.001 (.03)	.91	.03 (.03)	.12
Staying at home	N/A	N/A	.04 (.02)	<.001	.04 (.02)	.004
Getting tested	N/A	N/A	−.01 (.02)	.58	.05 (.02)	<.001
Learning more information	N/A	N/A	−.01 (.01)	.64	.01 (.01)	.56
Other behaviors	N/A	N/A	−.03 (.02)	.07	.02 (.02)	.14
Health Belief Model variables						
Severity	N/A	N/A	N/A	N/A	.04 (.01)	.008
Susceptibility	N/A	N/A	N/A	N/A	.19 (.01)	<.001
Benefits	N/A	N/A	N/A	N/A	−.01 (.01)	.62
Model of *f* values	707.52	<.001	260.29	<.001	243.51	<.001

[a]Model 1 had a change in R^2 of 0.28 and a total R^2 of 0.28.

[b]Model 2 had a change in R^2 of 0.003 and a total R^2 of 0.28.

[c]Model 3 had a change in R^2 of 0.04 and a total R^2 of 0.32.

[d]β is a standardized coefficient.

[e]N/A: not applicable.

In terms of promoting public sharing or retweeting behaviors, tweets that fulfilled the information and action functions were more likely to be retweeted. Tweets that contained mentions of covering one's face, sheltering in place, getting tested, and seeking COVID-19–related information were also more likely to be retweeted, whereas those containing handwashing information were significantly less likely to be retweeted (*P*<.001). Additionally, severity and susceptibility significantly promoted retweeting tendencies (severity: *P*<.001; susceptibility: *P*<.001).

In terms of predicting the number of favorites that tweets received, the results showed slightly different patterns. Tweets that were primarily about promoting action and building community were more likely to receive favorites from the public compared to those about providing information. Furthermore, content that included information about social distancing, sheltering in place, and getting tested were more likely to be favorited, whereas tweets that mentioned handwashing behaviors had a consistently low chance of being favorited by the public. Consistent with the other engagement indicator, the severity and susceptibility health beliefs also significantly predicted the chance of being favorited by the public (severity: *P*=.008; susceptibility: *P*<.001).

Discussion

Principal Findings

Governmental agencies are among the most trusted sources of COVID-19–related information [31]. Public health agencies shoulder the responsibility of promptly providing locally relevant pandemic updates, prevention guidelines, and relevant policies to the public during the COVID-19 pandemic. This study uses the HBM and examines social media functions to understand how public health agencies in Texas communicate COVID-19 pandemic–related information to the public via Twitter and assesses the empirical relationships between various message features and social media engagement outcomes. We found that public health agencies mostly used Twitter to share information and they used Twitter to promote action and community with less frequency. Tweets that served the action

function were the most likely to be retweeted and liked. Beliefs about susceptibility, severity, and benefits were the most frequently covered health beliefs. Tweets that provided susceptibility and severity information resulted in more public engagement in terms of the number of retweets and endorsements.

The information function was the most prominent function among the studied tweets, followed by the action and community functions. This is consistent with the findings of an earlier study that examined the tweets of Canadian public health agencies [32]. Information is of paramount importance to the public, especially during the early stages of an infectious disease outbreak, which are characterized by a lack of information and a high level of uncertainty. In terms of public engagement, tweets that served the information function were more likely to be retweeted. An existing study with a smaller sample size than that of our study has also shown that science-based tweets about COVID-19 are more likely to be retweeted than tweets that contain false information [33]. This means that useful information can be further disseminated through retweeting. Furthermore, tweets that promoted different preventive measures were the most likely to be retweeted and liked, which shows that the Twitter users are spreading such recommendations through retweeting. Finally, retweets that served the action and community functions were more likely to be liked. This means that readers tend to respond favorably to such tweets to show their support.

Although the HBM has been traditionally used to study psychological predictors of individuals' adoption of preventative behaviors, it was used in this study to examine the public's collective responses to health messages in terms of public engagement. Beliefs about susceptibility, severity, and benefits were the most frequently covered health beliefs, whereas information about barriers and self-efficacy was absent from most tweets. This means that communicating the risks of COVID-19 to the public was the priority of Texas public health agencies. Emphasizing health benefits is conducive to the adoption of preventative behaviors [11]. In addition, we found that tweets containing beliefs about susceptibility often resulted in more public engagement in terms of the number of favorites and retweets, whereas the benefits of prevention methods did not increase public engagement. It appears that the public is more interested in learning about the risks of COVID-19 than in learning about preventive behaviors during the early stage of a public health crisis, as the Crisis and Emergency Risk Communication Model has indicated previously [34]. Although this study focused on how message characteristics affect public engagement, other research has shown that public health agencies' positions in a network (eg, whether the organization occupies a "star" position, which represents their network centrality) also affected the two-way communication between agencies and the public [35].

Public Health Implications

Our findings identified several strategies that public agencies could adopt to more effectively communicate risk information during an unfolding pandemic. First, the fact that informative tweets were more likely to be retweeted suggests that public agencies should continue to use Twitter as an information dissemination tool to increase their community outreach efforts. The sharing and retweeting function of social media can allow public health agencies to disseminate timely, credible, and easy-to-share information at a large scale, which directly and indirectly helps combat health misinformation [21]. Furthermore, as action-oriented messages were more likely to be favored, public agencies should consider incorporating specific action items into their tweets. In other words, the public needs not only factual information about the pandemic but also specific guidance and concrete action items, which can further boost the public support of public agencies.

Second, although emphasizing the susceptibility and severity of the disease increased public engagement, directly communicating the benefits of preventive behaviors was less effective in promoting public engagement. Given the importance of educating the public about prevention behaviors for infectious diseases, public agencies need to be more creative when designing, framing, and implementing social media messages about preventive behaviors. Furthermore, self-efficacy information was almost completely absent from the tweets of public health agencies. Telling the public that they are capable of performing a recommended behavior is essential in increasing the adoption of such behaviors.

Methodological Implications

In terms of methodology, this study demonstrates the feasibility of using natural language processing to identify theoretical constructs such as social media functions and health beliefs. We showed that a relatively small training data set could be used to create algorithms for the classification of a much larger corpus of Twitter data. The method established in this study can be easily used to classify COVID-19–related tweets according to different types of organizations (eg, hospitals, community organizations, and media) and individuals (eg, politicians and physicians) in and beyond the state of Texas.

Limitations and Directions for Future Research

This study only examined public health agencies' tweets from a single state in the United States, and our data only covered the first wave of the COVID-19 outbreak in the United States. According to the Crisis and Emergency Risk Communication Model, the public has different informational and emotional needs during different stages of an outbreak [34]. It is important to examine agencies' Twitter content during the later stages of the outbreak. Fortunately, our research method can be easily and longitudinally scaled to study more Twitter content from different parts of the United States. Future studies may examine how message features may vary across different stages of the pandemic and how their resulting public engagement outcomes shift over time. We only examined the text of tweets but did not examine pictures and videos. Future studies should examine how pictures or videos affect public engagement. Additionally, in terms of the communication functions of governmental organizations, an earlier study has suggested that their communication efforts are often fragmented; there is a lack of Twitter mentions, coordination, and mutual retweets among different governmental organizations [36]. Future research could examine the coordination and inconsistency among public health

agencies at the local, state, national, and international levels. This approach was piloted in a recent study [37].

Conclusions

This study examines the content of COVID-19–related tweets that were published by the public health agencies in Texas during the first 6 months of 2020. We found that although public health agencies mostly used Twitter to disseminate pandemic-related information, they could use the Twitter platform to further promote preventative actions, since in this study, the public positively responded to tweets that promoted actions. Furthermore, the public was most likely to engage with tweets that described people's susceptibility to contracting COVID-19, as such information helped them to understand the risk of the disease. However, there was a lack of information that convinced the public of the high feasibility of proposed preventative behaviors and increased the public's confidence. Public health agencies can vastly expand their reach during public health crises by steadily building up their follower bases.

Conflicts of Interest

None declared.

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Abbreviations

BERT: bidirectional encoder representations from transformers
HBM: Health Belief Model
OEM: Office of Emergency Management
RQ: research question

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Original Paper

Latin America and the Caribbean SARS-CoV-2 Surveillance: Longitudinal Trend Analysis

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Abstract

Background: The COVID-19 pandemic has placed unprecedented stress on economies, food systems, and health care resources in Latin America and the Caribbean (LAC). Existing surveillance provides a proxy of the COVID-19 caseload and mortalities; however, these measures make it difficult to identify the dynamics of the pandemic and places where outbreaks are likely to occur. Moreover, existing surveillance techniques have failed to measure the dynamics of the pandemic.

Objective: This study aimed to provide additional surveillance metrics for COVID-19 transmission to track changes in the speed, acceleration, jerk, and persistence in the transmission of the pandemic more accurately than existing metrics.

Methods: Through a longitudinal trend analysis, we extracted COVID-19 data over 45 days from public health registries. We used an empirical difference equation to monitor the daily number of cases in the LAC as a function of the prior number of cases, the level of testing, and weekly shift variables based on a dynamic panel model that was estimated using the generalized method of moments approach by implementing the Arellano–Bond estimator in R. COVID-19 transmission rates were tracked for the LAC between September 30 and October 6, 2020, and between October 7 and 13, 2020.

Results: The LAC saw a reduction in the speed, acceleration, and jerk for the week of October 13, 2020, compared to the week of October 6, 2020, accompanied by reductions in new cases and the 7-day moving average. For the week of October 6, 2020, Belize reported the highest acceleration and jerk, at 1.7 and 1.8, respectively, which is particularly concerning, given its high mortality rate. The Bahamas also had a high acceleration at 1.5. In total, 11 countries had a positive acceleration during the week of October 6, 2020, whereas only 6 countries had a positive acceleration for the week of October 13, 2020. The TAC displayed an overall positive trend, with a speed of 10.40, acceleration of 0.27, and jerk of –0.31, all of which decreased in the subsequent week to 9.04, –0.81, and –0.03, respectively.

Conclusions: Metrics such as new cases, cumulative cases, deaths, and 7-day moving averages provide a static view of the pandemic but fail to identify where and the speed at which SARS-CoV-2 infects new individuals, the rate of acceleration or deceleration of the pandemic, and weekly comparison of the rate of acceleration of the pandemic indicate impending explosive growth or control of the pandemic. Enhanced surveillance will inform policymakers and leaders in the LAC about COVID-19 outbreaks.

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KEYWORDS

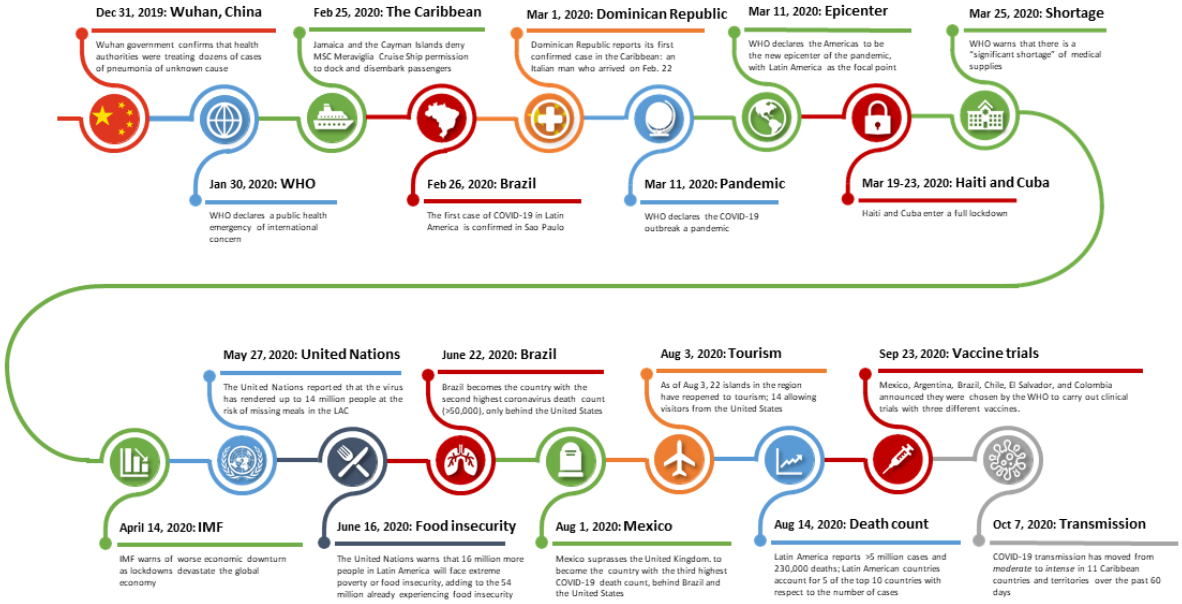
7-day persistence; acceleration; Arellano–Bond estimator; COVID-19 surveillance system; COVID-19; dynamic panel data; econometrics; economic; generalized method of moments; global COVID-19 surveillance; Latin America and the Caribbean; longitudinal; metric; persistence; policy; public health surveillance; SARS-CoV-2; second wave; surveillance metrics; transmission deceleration; transmission jerk; transmission speed; trend analysis

Introduction

Background

The first confirmed case of COVID-19 in Latin America and the Caribbean (LAC) was an Italian national who entered the Dominican Republic on February 22, 2020, and tested positive for COVID-19 on March 1, 2020. By late May 2020, the World Health Organization declared the Americas as the new epicenter of the pandemic, with Latin America presenting particular concern [1] because by October 19, 2020, the World Health Organization confirmed 39,944,882 COVID-19 infections and 1,111,998 COVID-19–related deaths globally, of which 10,463,251 cases and 379,942 deaths were reported in the LAC [2]. Figure 1 shows the timeline of COVID-19 in the LAC.

Figure 1. Timeline of the COVID-19 pandemic in Latin America and the Caribbean. IMF: International Monetary Fund, LAC: Latin America and the Caribbean, MSC: Mediterranean Shipping Company, WHO: World Health Organization.



Based on similar economies, geographies, and developments in the region, the World Bank defines the LAC to consist of Argentina, Belize, Bolivia, Brazil, Colombia, Chile, Costa Rica, Ecuador, El Salvador, Guatemala, Guyana, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Uruguay, and Venezuela, Antigua and Barbuda, Aruba, the Bahamas, Barbados, Bermuda, the British Virgin Islands, Cayman Islands, Cuba, Curaçao, Dominica, Dominican Republic, Grenada, Haiti, Jamaica, Puerto Rico (the United States), Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, Sint Maarten (the Netherlands), Trinidad and Tobago, Turks and Caicos Islands, and the US Virgin Islands [3]. As of this writing, the LAC represents many populations including the descendants of indigenous groups, European colonialists, enslaved Africans, and immigrants from East Asia and the Middle East, resulting in a shared history that still impacts social relations, economic structure, and political stability in the LAC [4]. Vulnerabilities within this shared history have become apparent during the COVID-19 pandemic, as manifested by climate change, poverty, food insecurity, political unrest, poor health care infrastructure, and economic instability, thus providing an important context in which transmission and surveillance of the SARS-CoV-2 must be understood [5].

Economics

SARS-CoV-2 transmission has significantly affected the economies of several LAC countries. Approximately 700,000 jobs in Caribbean countries were lost between February and April, 2020, resulting in a projected 7.9% reduction in the gross domestic product (GDP), the largest decline recorded since 1930 [6]. Much of this loss stems from heavy dependence on tourism, which contributes to >25% of the average GDP and is the source of employment for >55% of the population in some Caribbean islands [7]. Containment measures, such as lockdowns, have devastated tourism-related businesses and depressed tax revenues. Latin America was already experiencing its lowest economic growth since the 1950s as the region is poised to face a 5.3% reduction in GDP [8]. The economic impact of the pandemic is amplified as nationwide lockdowns led to reductions in economic activity, global demand for regional exports, and commodity prices [9]. Nationwide lockdowns, quarantine, and curfew policies pose a particular issue for the

140 million informal workers in Latin America who are currently presented with limited employment opportunities [10]. Migrant remittances, another source of income for the most impoverished regions, are projected to decline by 20% [11]. Some aid comes from the United States or Europe, further compromising Latin America's ability to combat the pandemic and its economic consequences [12]. Corruption and weak public health compliance has burdened health care systems with higher rates of disease transmission [13].

Public Health Policies

Every Caribbean country with reported data adopted measures to limit the transmission of SARS-CoV-2. During the early stages of the pandemic, all countries implemented containment policies targeting the spread of COVID-19 through travel, tourism, and gatherings [14-16].

In June and July, many Caribbean countries reopened their borders to air travel subject to the following restrictions: (1) visitors are required to submit negative results on COVID-19 tests prior to arrival or within 7 days and (2) visitors from countries with high or increasing infection rates, including the United States, are prohibited entry [17]. However, these policies have not been able to prevent local transmission of SARS-CoV-2. Reports indicate that current transmission patterns are primarily driven by community spread with disease transmission due to tourism having less of an impact relative to the initial stages of the pandemic [18]. As of October 2020, these policies remain in flux and are likely to be revised as infection rates increase and decrease in the United States, Canada, European countries, and other countries that have historically accounted for large numbers of tourists to the Caribbean.

Latin America represents a mosaic of failures and success stories regarding public health policies, displaying the varying effects of governmental unity and disunity. As an example of political disunity, as of December 11, 2020, Brazil has reported 6,728,452 cases and Mexico has reported 1,205,229 cases [2], both countries are affected by inadequate responses to the pandemic owing to delayed onset of public health guidelines, presidential apathy, premature reopening, and population density [19-21]. Mexican President Andrés Manuel López Obrador downplayed the severity of the virus and advocated for citizens to combat the disease at home, which led to death due to COVID-19 at home among many people in Mexico without confirmatory testing. This has underscored the true death toll even as Mexico is currently faced with an increasingly intense COVID-19 outbreak with 86,059 deaths. In a similar move, despite testing positive for COVID-19, Brazilian President Jair Bolsonaro consistently undermined quarantine, social distancing, and other public health measures by encouraging mass gatherings, dismissing the danger of the virus, promoting unproven remedies, and calling on citizens to go back to work in defiance of advice from the Brazilian Health ministry [22-24]. Owing to this intragovernmental conflict, the disease spread within these 2 countries, disproportionately affecting rural and indigenous populations [25,26]. For example, much of Brazil relies on the Amazon river to transport food, medicine, and emergency aid to 30 million people [27]. The indigenous people of Brazil have a 6-fold higher risk of COVID-19 compared to European, African, Asian, and other ethnic Brazilians not only owing to their vulnerability to infection given their paucity of exposure to outsiders [26], but also because government health workers are transmitting the virus because they do not have proper protective equipment or adequate access to tests, nor do they follow preventive measures recommended by public health authorities [28].

In contrast with Brazil and Mexico, Uruguay is a true success story in the region, as it was able to reopen public schools in June 2020, and is the only Latin American country whose locals are allowed to enter the European Union [29]. Uruguay implemented lockdowns in March as the government and public health experts presented a united front with consistent advice for the population [30]. With this political unity in combination with its robust national health system, Uruguay has been able to avoid the pitfalls that other Latin American countries have faced.

Methods

The Foundation for Innovative New Diagnostics, Our World in Data, and The COVID Tracking Project [31-33] compile data from multiple sources across individual websites, statistical reports, and press releases; data for the most recent 7 weeks were accessed from the GitHub repository [34-36] using application programming interface. This yielded a panel of 32 countries in the LAC with 45 days in each panel (n=1440). An empirical difference equation was used, in which the number of positive cases in each country on each day is a function of the prior number of cases, the level of testing, and weekly shift variables that determine whether the contagion accelerated, decelerated, or remained unchanged compared to previous weeks. This resulted in a dynamic panel model that was estimated using the generalized method of moments approach by implementing the Arellano–Bond estimator in R [37-39]. Arellano–Bond estimation of difference equations has several statistical advantages: (1) it allows for statistical examination of the model's predictive ability and the validity of the model specification, (2) it corrects for autocorrelation and heteroscedasticity, (3) it has favorable properties for data with a small number of time periods and large number of states, and (4) it corrects for omitted variables and provides a statistical test of correction validity [40,41]. With these advantages, the method is applicable to ascertaining and statistically validating changes in the evolution of the pandemic within a period of ≤1 week, such as changes in the reproduction rate.

Results

Country-Wise Regression Analysis

In accordance with the World Bank regional division, we grouped 32 countries into the broader LAC region. The results of the associative regression are reflected in Table 1 and are the basis of the weekly surveillance metrics.

As seen in Table 1, the Wald statistic for regression is significant (χ^2_{11}=932; P<.001) and the Sargan statistic for validity is

nonsignificant (χ^2_{481}=32; *P*=.99), failing to reject the validity of overidentifying restrictions.

As shown in Table 1, the 1-day lag coefficient and the weekend effect are both nonsignificant. The 7-day lag coefficient is positive and significant (0.94; *P*<.001), suggesting a marked impact of infections from 1 week prior on infections at the time of data collection. The shift parameter for the week of October 6 is negative and significant (–1.36; *P*=.02), suggesting a rate change in disease transmission. The cumulative tests coefficient is slightly positive and significant (<0.001; *P*=.04).

Table 1. Arellano–Bond dynamic panel data modeling of the number of daily infections reported by Latin American and Caribbean countries from September 30 to October 13, 2020.

Variable	Coefficient (*P* value)
1-day lag coefficient	–0.16 (.08)
7-day lag coefficient	–0.94 (<.001)
Cumulative tests	<0.001 (.04)
Shift parameter for the week of October 6, 2020	–1.36 (.02)
Shift parameter for the week of October 13, 2020	–2.68 (.10)
Weekend effect	–0.08 (.56)
Wald statistic for regression (χ^2 [df=11])	932 (<.001)
Sargan statistic for validity (χ^2 [df=481])	32 (.99)

Interpretation: Regression Analysis for the LAC

The lagging indicators and shift parameters suggest a recent change in disease transmission. As anticipated, the cumulative test effect is predictive of daily infections. No weekend effect was observed.

Surveillance Results

Tables 2-7 include static and dynamic surveillance metrics for the weeks of October 6, 2020, and October 13, 2020. Static metrics include the number of new COVID-19 cases, cumulative COVID-19 cases, the 7-day moving average of new cases, the rate of infection, number of new deaths, cumulative deaths, the 7-day moving average of the number of deaths, and death rates (Tables 2 and 3). Novel dynamic metrics provide an overview of the impact of past cases on current cases and the potential trajectory of cases in the future. Novel dynamic metrics include (1) speed or the weekly average of new daily cases per 100,000 individuals, (2) acceleration or the day-to day-change in speed, (3) jerk or the week-over-week change in acceleration, and (4) the 7-day persistence effect or the number of new cases per 100,000 individuals reported thus far that are associated with new cases reported 7 days ago (Tables 4 and 5). The persistence effect is the only surveillance metric that controls for incomplete case ascertainment and data contamination. It also is consistent with superspreader events or an underlying condition that persists from the last week to the current week.

Static surveillance metrics are presented in Table 2 for the week of September 30 to October 6, 2020, and in Table 3 for the week of October 7 to 13, 2020. New cases in the region totaled to 79,053 on October 6, 2020, and to 42,837 on October 13, 2020. The 7-day moving average of new cases for the week of October 6, 2020, was 56,106 and that for the week of October 13, 2020, was 47,276. The total infection rate decreased from 12.42 per 100,000 population to 6.73 per 100,000 population, accompanied by a reduction in the mortality rate from 0.33 per 100,000 population to 0.24 per 100,000 population.

Within the region, on September 30, 2020, Brazil reported the largest number of new cases at 41,906, followed by Argentina at 14,740, Colombia at 7650, and Mexico at 4828 (Table 2). On October 7, 2020, Argentina reported the largest number of new cases at 13,305, followed by Brazil at 10,220, Colombia at 5014, and Mexico at 4295 (Table 3). For both weeks, Brazil had the highest 7-day moving average, followed by Argentina.

As shown in Table 2, the countries with the highest infection rates for the week of October 6, 2020, include Argentina at 32.8, the Bahamas at 27.5, Costa Rica at 20.1 and Brazil at 19.9. Infection rates, a measure of cases per 100,000 individuals in the population, generally decreased during the following week. For the week of October 6, 2020, death rates were the highest in the Bahamas at 1.03, Belize at 1.02, and Argentina at 0.8. Brazil and Costa Rica, while having some of the highest infection rates in the region, had markedly lower death rates of 0.39 and 0.34, respectively (all measured as cases per 100,000 population). With the exception of Argentina, where a slight increase was observed, death rates generally decreased during the following week.

During the week of October 6, 2020, (Table 4), the countries with the highest speed or average of new daily cases per 100,000 individuals in the population included Argentina at 27.9, the Bahamas at 24.1, and Costa Rica at 21.3, largely consistent with the infection rates during that week. All 3 countries had positive acceleration or change in speed during the week of October 6, 2020. These 3 countries also had the top speeds in the region in the following week, although the Bahamas had a reduction in speed to 22.2, while Costa Rica and Argentina had an increase in speed to 22.9 and 29.4, respectively. Mexico, while having a high number of cases in the region in accordance with its population, had a reduction in speed from 6.3 during the week of October 6, 2020, to 3.4 during the following week.

The utility of the speed metric is further enhanced by considering acceleration and jerk, which provide insight into potential infection trajectory. For the week of October 6, 2020,

Belize had the highest acceleration and jerk in the region, at 1.7 and 1.8, respectively, which is particularly concerning considering its high mortality rate. The Bahamas also had a high acceleration of 1.5. In total, 11 countries had a positive acceleration during the week of October 6, 2020, whereas only 6 countries had a positive acceleration for the week of October 13, 2020 (Table 5). The LAC displayed an overall positive trend, with a speed of 10.40, acceleration of 0.27, and jerk of –0.31, all decreasing the subsequent week to 9.04, –0.81, and –0.03, respectively.

The 7-day persistence metric identifies the impact of the 7-day lag of speed on the current value of speed. New cases from 7 days prior have an echo effect, which impacts the current number of cases. Table 6 shows the countries with the highest 7-day persistence, which refers to the number of new cases reported per 100,000 population as of this writing, which is a result of new cases reported 7 days prior. Argentina maintained the highest 7-day persistence during both weeks, followed by Costa Rica, the Bahamas, and Panama.

Complete surveillance data for the LAC are provided in Multimedia Appendices 1-4.

Table 2. Static surveillance metrics for the week of September 30 to October 6, 2020.

Country	New weekly COVID-19 cases	Cumulative COVID-19 cases	7-Day moving average of new cases	Infection rate per 100,000 individuals	New weekly deaths	Cumulative deaths	7-Day moving average of deaths	Death rate per 100,000 individuals
Antigua and Barbuda	N/A[a]	107	0.86	N/A	N/A	3	N/A	N/A
Argentina	14,740	824,468	12,551.29	32.8	359	21,827	758.3	0.80
The Bahamas	107	4559	93.71	27.5	4	100	1.3	1.03
Barbados	N/A	200	1.43	N/A	N/A	7	N/A	N/A
Belize	47	2243	50.29	12.0	4	34	1.4	1.02
Bolivia	361	137,468	403.86	3.1	27	8156	32.1	0.23
Brazil	41,906	4,969,141	27,374.14	19.9	819	147,494	653.3	0.39
Chile	1,560	473,306	1715.14	8.2	33	13,070	49.3	0.17
Colombia	7650	869,808	6538.00	15.2	173	27,017	169.9	0.34
Costa Rica	1013	82,142	1076.86	20.1	17	1004	17.7	0.34
Cuba	38	5883	50.29	0.3	N/A	123	0.1	N/A
Dominica	N/A	31	0.14	N/A	N/A	N/A	N/A	N/A
Dominican Republic	317	115,371	495.86	3.0	5	2149	6.9	0.05
Ecuador	717	142,056	901.00	4.1	21	11,702	55.7	0.12
El Salvador	95	29,634	93.29	1.5	4	869	4.3	0.06
Grenada	N/A	24	N/A	N/A	N/A	N/A	N/A	N/A
Guatemala	688	94,870	557.43	4.1	8	3310	10.3	0.05
Guyana	N/A	3188	48.86	N/A	2	92	2.0	0.26
Haiti	11	8838	14.00	0.1	N/A	229	0.3	N/A
Honduras	642	80,662	652.00	6.6	14	2447	17.7	0.14
Jamaica	97	7109	100.14	3.3	3	123	3.1	0.10
Mexico	4828	794,608	8063.57	3.8	471	82,348	740.7	0.37
Panama	683	116,602	678.43	16.1	10	2440	10.9	0.24
Paraguay	932	45,647	792.29	13.2	19	966	17.9	0.27
Peru	1830	829,999	3040.71	5.6	92	32,834	72.9	0.28
St Kitts and Nevis	N/A	19	N/A	N/A	N/A	N/A	N/A	N/A
St Lucia	N/A	27	N/A	N/A	N/A	N/A	N/A	N/A
St Vincent and the Grenadines	N/A	64	N/A	N/A	N/A	N/A	N/A	N/A
Suriname	11	4965	14.57	1.9	N/A	106	0.3	N/A
Trinidad and Tobago	79	4846	54.71	5.7	1	83	1.3	0.07
Uruguay	22	2177	20.57	0.6	1	49	0.1	0.03
Venezuela	679	79,796	776.14	2.4	7	665	6.3	0.02

[a]N/A: not applicable.

Table 3. Static surveillance metrics for the week of October 7 to 13, 2020.

Country	New weekly COVID-19 cases	Cumulative COVID-19 cases	7-Day moving average of new cases	Infection rate per 100,000 individuals	New weekly deaths	Cumulative deaths	7-Day moving average of deaths	Death rate per 100,000 individuals
Antigua and Barbuda	N/A[a]	111	0.57	N/A	N/A	3	N/A	N/A
Argentina	13,305	917,035	13,223.86	29.6	386	24,572	392.1	0.86
The Bahamas	N/A	5163	86.29	N/A	N/A	108	1.1	N/A
Barbados	2	210	1.43	0.7	N/A	7	N/A	N/A
Belize	16	2585	48.86	4.1	2	39	0.7	0.51
Bolivia	227	138,922	207.71	2.0	25	8351	27.9	0.22
Brazil	10,220	5,113,628	20,641.00	4.8	309	150,998	500.6	0.15
Chile	1448	484,280	1567.71	7.6	20	13,396	46.6	0.11
Colombia	5014	924,098	7755.71	10.0	156	28,141	160.6	0.31
Costa Rica	1015	90,238	1156.57	20.1	16	1124	17.1	0.32
Cuba	17	6017	19.14	0.1	N/A	123	N/A	N/A
Dominica	N/A	32	0.14	N/A	N/A	N/A	N/A	N/A
Dominican Republic	165	119,008	519.57	1.5	4	2183	4.9	0.04
Ecuador	856	148,171	873.57	4.9	17	12,235	76.1	0.10
El Salvador	284	30,480	120.86	4.4	5	899	4.3	0.08
Grenada	N/A	25	0.14	N/A	N/A	N/A	N/A	N/A
Guatemala	554	98,380	501.43	3.3	23	3410	14.3	0.14
Guyana	44	3565	53.86	5.6	2	106	2.0	0.26
Haiti	5	8887	7.00	0.0	N/A	230	0.1	N/A
Honduras	439	84,852	598.57	4.5	7	2528	11.6	0.07
Jamaica	97	7910	114.43	3.3	N/A	146	3.3	N/A
Mexico	4295	825,340	4390.29	3.4	475	84,420	296.0	0.37
Panama	494	121,296	670.57	11.6	9	2511	10.1	0.21
Paraguay	853	51,197	792.86	12.1	12	1108	20.3	0.17
Peru	2803	853,974	3425.00	8.6	62	33,419	83.6	0.19
St Kitts and Nevis	N/A	19	N/A	N/A	N/A	N/A	N/A	N/A
St Lucia	N/A	29	0.29	N/A	N/A	N/A	N/A	N/A
St Vincent and the Grenadines	N/A	64	N/A	N/A	N/A	N/A	N/A	N/A
Suriname	14	5072	15.29	2.4	N/A	107	0.1	N/A
Trinidad and Tobago	11	5127	40.14	0.8	1	93	1.4	0.07
Uruguay	24	2337	22.86	0.7	N/A	51	0.3	N/A
Venezuela	635	84,391	656.43	2.2	6	710	6.4	0.02

[a]N/A: not applicable.

Table 4. Novel surveillance metrics for the week of September 30 to October 6, 2020.

Country	Speed: daily number of positive cases per 100,000 individuals (weekly average of new daily cases per 100,000 individuals)	Acceleration: day-to-day change in the number of positive cases per day (weekly average per 100,000 individuals)	Jerk: week-over-week change in acceleration (per 100,000 individuals)	7-Day persistence effect on speed (number of new cases per day per 100,000 individuals)
Antigua and Barbuda	0.9	0.0	0.0	0.1
Argentina	27.9	0.4	0.6	23.5
The Bahamas	24.1	1.5	0.0	13.7
Barbados	0.5	0.0	0.0	–0.5
Belize	12.9	1.7	1.8	7.8
Bolivia	3.5	–0.1	0.0	3.0
Brazil	13.0	0.7	0.7	10.7
Chile	9.0	–0.1	0.1	8.0
Colombia	13.0	0.5	0.0	11.2
Costa Rica	21.3	0.3	–0.5	19.5
Cuba	0.4	0.0	0.0	–0.2
Dominica	0.2	0.0	0.0	0.5
Dominican Republic	4.6	0.1	–0.3	2.5
Ecuador	5.2	–0.1	–0.1	5.4
El Salvador	1.4	–0.2	0.0	1.4
Grenada	0.0	0.0	0.0	–0.6
Guatemala	3.4	0.0	–0.1	2.8
Guyana	6.2	–1.1	–2.5	6.1
Haiti	0.1	0.0	0.0	–0.5
Honduras	6.7	0.1	1.0	4.4
Jamaica	3.4	-0.7	–0.5	4.4
Mexico	6.3	0.0	–2.7	2.7
Panama	16.0	0.4	0.7	13.2
Paraguay	11.2	0.5	1.0	9.0
Peru	9.4	–0.7	–1.3	15.1
St Kitts and Nevis	0.0	0.0	0.0	–0.6
St Lucia	0.0	0.0	0.0	–0.6
St Vincent and the Grenadines	0.0	0.0	0.0	–0.6
Suriname	2.5	–0.4	–0.7	1.7
Trinidad and Tobago	3.9	0.0	0.2	3.4
Uruguay	0.6	0.0	0.0	–0.2
Venezuela	2.7	–0.1	0.0	2.1

Table 5. Novel surveillance metrics for the week of October 7 to 13, 2020.

Country	Speed: daily number of positive cases per 100,000 individuals (weekly average of new daily cases per 100,000 individuals)	Acceleration: day-to-day change in the number of positive cases per day (weekly average per 100,000 individuals)	Jerk: week-over-week change in acceleration (per 100,000 individuals)	7-Day persistence effect on speed (number of new cases per day per 100,000 individuals)
Antigua and Barbuda	0.6	0.0	0.0	0.2
Argentina	29.4	–0.5	0.1	24.5
The Bahamas	22.2	–3.9	–5.5	21.0
Barbados	0.5	0.1	0.1	–0.1
Belize	12.5	–1.1	–0.1	11.0
Bolivia	1.8	–0.2	0.0	2.6
Brazil	9.8	–2.1	–1.9	11.0
Chile	8.3	–0.1	0.0	7.5
Colombia	15.4	–0.7	–0.9	11.1
Costa Rica	22.9	0.0	0.5	18.5
Cuba	0.2	0.0	0.0	–0.2
Dominica	0.2	0.0	0.0	–0.4
Dominican Republic	4.8	–0.2	0.1	3.5
Ecuador	5.0	0.1	0.1	4.1
El Salvador	1.9	0.4	0.6	0.7
Grenada	0.1	0.0	–0.1	–0.6
Guatemala	3.0	–0.1	0.0	2.4
Guyana	6.9	0.8	1.6	5.0
Haiti	0.1	0.0	0.0	–0.5
Honduras	6.1	–0.3	–0.2	5.4
Jamaica	3.9	0.0	0.1	2.5
Mexico	3.4	–0.1	2.7	5.1
Panama	15.8	–0.6	–0.2	13.7
Paraguay	11.3	–0.2	–0.4	9.5
Peru	10.5	0.4	2.5	7.8
St Kitts and Nevis	0.0	0.0	0.0	–0.6
St Lucia	0.2	0.0	0.0	–0.6
St Vincent and the Grenadines	0.0	0.0	0.0	–0.6
Suriname	2.	0.1	0.2	1.7
Trinidad and Tobago	2.9	–0.7	–1.4	2.9
Uruguay	0.7	0.0	0.0	–0.1
Venezuela	2.3	0.0	0.0	1.8

Table 6. Comparison of 7-day persistence.

7-Day persistence in the week of September 30, 2020		7-Day persistence in the week of October 6, 2020	
Argentina	23.5	Argentina	24.5
Costa Rica	19.5	Bahamas	21.0
Peru	15.1	Costa Rica	18.5
Bahamas	13.7	Panama	13.7
Panama	13.2	Colombia	11.1

Table 7. The most populous Latin American and Caribbean countries in 2020.

Country	Population as of 2020
Brazil	212,559,417
Mexico	128,932,753
Colombia	50,882,891
Argentina	45,195,774
Peru	32,971,854
Venezuela	28,435,940

Discussion

Principal Findings

The LAC comprises 32 countries and has an extremely varied response to the COVID-19 pandemic. Part of the variation is explained by the population density, being land-locked, or being on an island, while other variations are explained by national and subnational policies on COVID-19 control with various degrees of implementation and enforcement of lockdowns, quarantines, crowd control, hygiene, and social distancing. Caribbean countries are more likely to experience economic pressure to restart economies and lift travel restrictions to support tourism. Differences among LAC countries are further impacted by varying high rates of obesity and other chronic diseases, combined with a largely young population, thus affecting the severity of disease progression and the death rate.

Metrics such as new cases, cumulative cases, deaths, and 7-day moving averages provide a static view of the pandemic but fail to identify where and the speed at which SARS-CoV-2 infects new individuals, the rate of increase or reduction in speed between the current and subsequent weeks, and how the rate of acceleration increases or decreases, which would indicate impending explosive growth or control of the pandemic. It is important to monitor large caseloads; however, sole reliance on the number of new infections would limit the analysis of the pandemic to countries with large populations. While this information is necessary, it is not sufficient. Measures including the 7-day persistence provide retrospective context for current figures and help identify superspreader events for targeted intervention.

The entire LAC saw a reduction in speed, acceleration, and jerk for the week of October 13, 2020, compared to the week of October 6, 2020, accompanied by a reduction in new cases and the 7-day moving average. This is largely due to reductions in the number of infections in Brazil and Mexico, the 2 countries containing over 50% of the population in the region. However, Brazil continues to have the highest 7-day moving average in the region, >2-fold that of Argentina, the next highest in the region, for the week of October 6, 2020.

Colombia and Peru are among the top 5 most populous countries in the region and they showed minor increases in speed, as did Argentina. Argentina displayed the highest infection rate and speed in the region, which can be attributed to insufficient testing and extremely loose restrictions, allowing the pandemic to progress uninhibited. In contrast, Venezuela is progressing at one-tenth the speed of Argentina, with negative acceleration probably owing to an extremely intense military and government responses to the pandemic, led by Venezuelan security forces, which is not observed elsewhere in the LAC.

Brazil and Costa Rica have relatively high infection rates and speeds in the region, both ranking within the top 5 countries in the week of October 6, 2020. However, both countries have a death rate that is approximately one-third that of Argentina and the Bahamas, the 2 of which have the highest infection rates. In addition, Belize has a lower infection rate than the average infection rate of the LAC but has the second highest death rate in the region. These discrepancies between infection rates and death rates are driven by factors beyond age because Belize has a younger age structure.

In addition to Argentina, the Bahamas and Costa Rica had the top 3 infection rates in the region in the week of October 6, 2020. The static and novel surveillance metrics for these countries also had the top 3 speeds in the region and positive acceleration in the week of October 6, 2020, indicating future growth in COVID-19 caseloads. These 3 countries featured in the top 5 for 7-day persistence over both weeks, with the Bahamas and Argentina seeing an increase in the 7-day persistence week over week, suggesting that these countries are still experiencing echoes from previously high numbers of new cases. The Bahamas and Costa Rica have both loosened travel

restrictions to protect their tourist-driven economy, which has resulted in higher COVID-19 caseloads.

Overall, there is reason to be cautiously optimistic as speed, acceleration, and jerk are displaying an overall downward trend. Countries with positive acceleration for the week of October 6, 2020, displayed reductions in acceleration to zero or negative values for the week of October 13, 2020. The number of countries with positive acceleration decreased from 11 for the week of October 6, 2020, to 6 for the week of October 13, 2020. While these reductions are notable, outbreaks and a reversion of trends are possible if the status quo changes.

Comparison to Prior Studies

This study is part of the global SARS-CoV-2 surveillance project on policy, persistence, and transmission carried out at Northwestern Feinberg School of Medicine. This research program has developed novel surveillance metrics including speed, acceleration, jerk, and 7-day persistence and applied them to all global regions.

Limitations

Our data are limited by variations in reporting practices across countries, both in terms of granularity and frequency. In addition, variation in testing practices and the health care infrastructure may impact the discrepancy in the number of reported cases and their true value. The data are reported at the national level, which prevents the analysis of subnational-level data.

Conclusion

The LAC surveillance metrics suggest that the region as a whole is displaying a downward trend, largely owing to increased control over COVID-19 outbreaks in the most populous countries. However, certain countries, such as Brazil and Argentina, continue to struggle in controlling the pandemic. The overall progress is precarious, and without consistent measures to control the pandemic, is likely to give way to continued outbreaks.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
LAC weekly statistics.
[PNG File , 243 KB - publichealth_v7i4e25728_app1.png]

Multimedia Appendix 2
Weekly Latin America and Caribbean statistics by country.
[PNG File , 283 KB - publichealth_v7i4e25728_app2.png]

Multimedia Appendix 3
Weekly LA 7 Day Persistence Map.
[PNG File , 281 KB - publichealth_v7i4e25728_app3.png]

Multimedia Appendix 4
Weekly LA Acceleration Jerk Map.
[PNG File , 346 KB - publichealth_v7i4e25728_app4.png]

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Abbreviations

GDP: gross domestic product
LAC: Latin America and the Caribbean

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Original Paper

Association Between Smoking and SARS-CoV-2 Infection: Cross-sectional Study of the EPICOVID19 Internet-Based Survey

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Abstract

Background: Several studies have reported a low prevalence of current smoking among hospitalized COVID-19 cases; however, no definitive conclusions can be drawn.

Objective: We investigated the association of tobacco smoke exposure with nasopharyngeal swab (NPS) test results for SARS-CoV-2 infection and disease severity accounting for possible confounders.

Methods: The nationwide, self-administered, cross-sectional web-based Italian National Epidemiological Survey on COVID-19 (EPICOVID19) was administered to an Italian population of 198,822 adult volunteers who filled in an online questionnaire between April 13 and June 2, 2020. For this study, we analyzed 6857 individuals with known NPS test results. The associations of smoking status and the dose-response relationship with a positive NPS test result and infection severity were calculated as odds ratios (ORs) with 95% CIs by means of logistic and multinomial regression models adjusting for sociodemographic, clinical, and behavioral characteristics.

Results: Out of the 6857 individuals (mean age 47.9 years, SD 14.1; 4516/6857, 65.9% female), 63.2% (4334/6857) had never smoked, 21.3% (1463/6857) were former smokers, and 15.5% (1060/6857) were current smokers. Compared to nonsmokers, current smokers were younger, were more educated, were less affected by chronic diseases, reported COVID-19–like symptoms less frequently, were less frequently hospitalized, and less frequently tested positive for COVID-19. In multivariate analysis, current smokers had almost half the odds of a positive NPS test result (OR 0.54, 95% CI 0.45-0.65) compared to nonsmokers. We also found a dose-dependent relationship with tobacco smoke: mild smokers (adjusted OR [aOR] 0.76, 95% CI 0.55-1.05), moderate smokers (aOR 0.56, 95% CI 0.42-0.73), and heavy smokers (aOR 0.38, 95% CI 0.27-0.53). This inverse association also persisted when considering the severity of the infection. Current smokers had a statistically significantly lower probability of having asymptomatic (aOR 0.50, 95% CI 0.27-0.92), mild (aOR 0.65, 95% CI 0.53-0.81), and severe infections (aOR 0.27, 95% CI 0.17-0.42) compared to those who never smoked.

Conclusions: Current smoking was negatively associated with SARS-CoV-2 infection with a dose-dependent relationship. Ad hoc experimental studies are needed to elucidate the mechanisms underlying this association.

Trial Registration: ClinicalTrials.gov NCT04471701; https://clinicaltrials.gov/ct2/show/NCT04471701

(JMIR Public Health Surveill 2021;7(4):e27091) doi:10.2196/27091

KEYWORDS

SARS-CoV-2; COVID-19; smoking habit; dose-response relationship; nasopharyngeal swab testing; infection severity; web-based survey; self-reported; cross-sectional design

Introduction

In June 2020 the World Health Organization released a report warning that smoking habits could be associated with adverse COVID-19 prognosis [1]. Based on extensive evidence, the report highlighted the negative impact of tobacco use on lung health and its causal association with both viral and bacterial respiratory infections [1]. In humans, the binding pathway of the spike protein with angiotensin-converting enzyme 2 (ACE2) constitutes a cell-binding site for the SARS-CoV-2 spike protein [2]. ACE2 was found to be upregulated in the small airway epithelia of smokers [3], which partially explains the increased risk of severe COVID-19 in this subpopulation [4].

However, studies from several European and non-European countries, including China [5], the United States [6], Mexico [7], Israel [8], France [9], the United Kingdom [10], and Italy [11-13], have shown an unusually low proportion of active smokers among hospitalized patients with respect to the general population. Moreover, a negative association between current smoking prevalence and COVID-19 occurrence at the population level was found in an ecological study performed in 38 European countries [14] and in a few nonhospitalized populations [15-17]. Possible biological mechanisms have been proposed to explain the counterintuitive underrepresentation of smokers among COVID-19 patients [18,19], strengthening the concept of the "smoker's paradox" [20,21].

Nevertheless, possible explanations for these findings could be due to biases in the available data. Considering the emergency of the epidemic, it has been suggested that the smoking status and smoking history of patients, including the duration, the quantity, or the time from possible smoking cessation, may not have been accurately recorded or some patients may not have been able to report their smoking habits, leading to a misclassification of smoking status. Moreover, the ascertainment of smoking exposure has not been supported by the use of objective biomarkers [19,20], or smokers may be taking medications or exhibiting behaviors that induce some protection against COVID-19 [22]. Finally, the majority of the studies conducted to date were performed in clinical settings without a detailed evaluation of possible confounders (ie, area of residence and socioeconomic factors), and in meta-analyses, heterogeneous studies were pooled together [23].

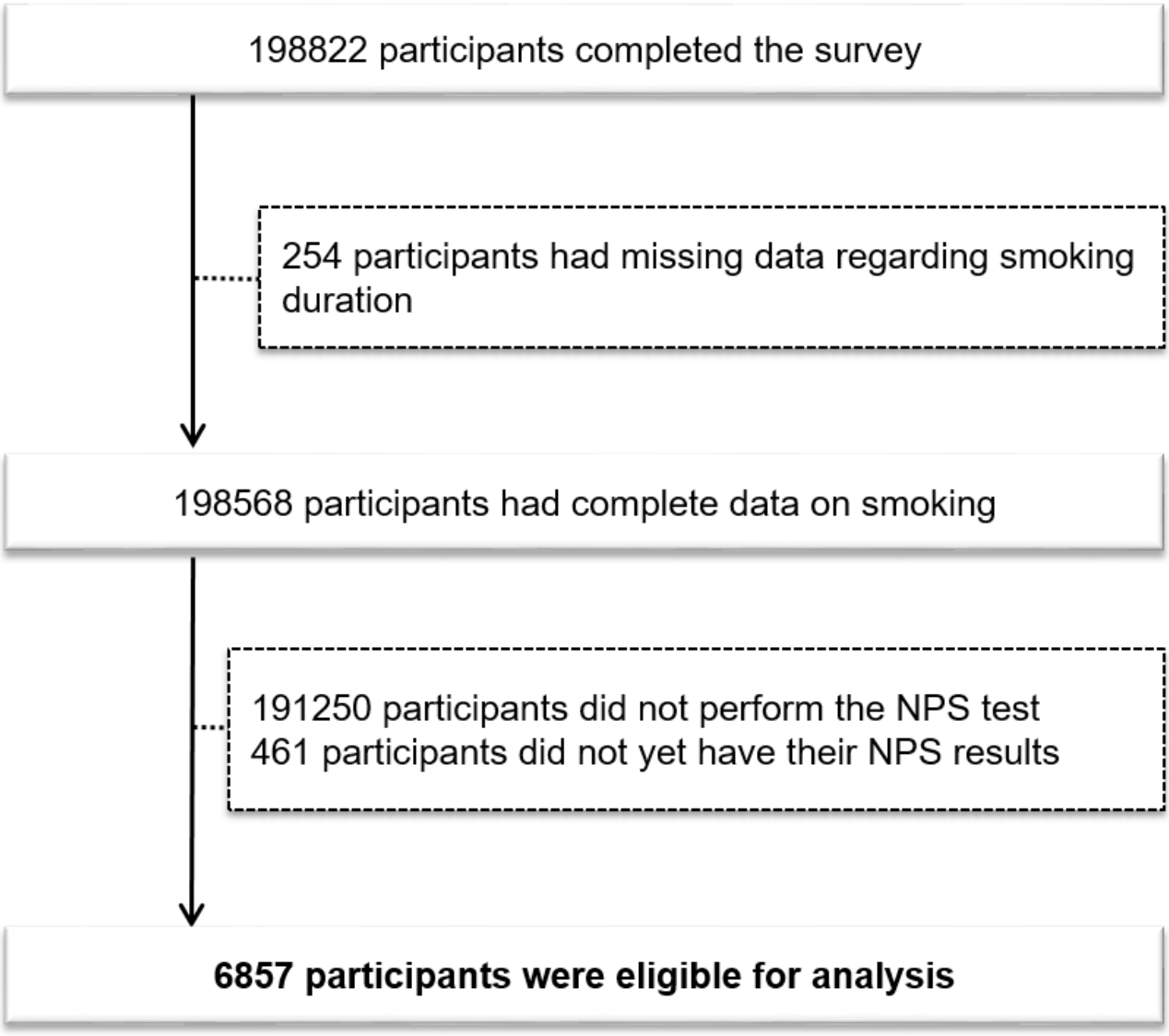
Bearing these considerations in mind, in this study we postulated that smoking habits were associated with both SARS-CoV-2 infection and disease severity in the general population, with a dose-response relationship independent of confounding factors not considered in previous studies. To verify this hypothesis, we used data from the self-administered web-based EPICOVID19 (Italian National Epidemiological Survey on COVID-19) with the following aims: (1) to evaluate the frequency distribution of sociodemographic, clinical, and behavioral characteristics among participants according to smoking status and (2) to investigate the cross-sectional association of smoking patterns (ie, intensity and duration) with SARS-CoV-2 nasopharyngeal swab (NPS) test results and infection severity, taking into account a wide number of potential confounding factors.

Methods

Study Design, Setting, and Population

The study population was derived from the EPICOVID19 national internet-based survey [24] that was conducted using a cross-sectional research design in a self-selected sample of adult volunteers living in Italy during the lockdown from March to May 2020; during this same period, the total confirmed COVID-19 infected cases in Italy were 233,515 [25]. The study procedures were described elsewhere [24]. Briefly, the link to the web-based survey was implemented using the EUSurvey management tool. The survey was uploaded and shared from April 13 to June 2, 2020, via several channels: emails, social media platforms (ie, Facebook, Twitter, Instagram, and WhatsApp), press releases, internet pages, local radio and TV stations, institutional websites, mailing lists, and the study website. The inclusion criteria to take part in the survey were being aged 18 years or older; having access to a mobile phone, computer, or tablet with internet connectivity; and providing online consent to participate in the study. Out of the 198,822 participants who provided consent to participate and completed the online survey, 254 had missing data about smoking duration; 191,250 did not perform the NPS test; and 461 did not yet know their NPS test result, leading to a final sample of 6857 (3.4%) participants for this study's analysis (Figure 1).

Figure 1. Flowchart of participant recruitment and eligibility for the EPICOVID19 (Italian National Epidemiological Survey on COVID-19) study. NPS: nasopharyngeal swab.



Compared to the people who were excluded (n=191,250) for not having performed the NPS test, those who were included (N=6857) in the analysis were more likely to be female, less educated, employed, employed in white collar jobs, health care professionals, residents in northern regions, affected by chronic diseases, and frequently vaccinated for flu and pneumococcal disease. They were also more likely to report symptoms, be frequently hospitalized, never have smoked, be living in big suburbs or cities and crowded houses, have frequently reported contacts with COVID-19 cases and called the emergency numbers, and have had a lower self-perceived health status (Table S1 in Multimedia Appendix 1).

Ethical Approval

The Ethics Committee of the Istituto Nazionale per le Malattie Infettive IRCCS Lazzaro Spallanzani (protocol No. 70, 12/4/2020) approved the EPICOVID19 study protocol. When participants first accessed the web-based platform, they were informed about the study and its purpose, the data to be collected, and the methods of storage; they then filled in the informed consent form. Participation was voluntary and no compensation was expected for respondents. The planning, conduct, and reporting of the study were in line with the Declaration of Helsinki, as revised in 2013. Data were handled and stored following the European Union General Data Protection Regulation (EU GDPR) 2016/679, and data transfer was safeguarded by encrypting and decrypting data and password protection. The study was registered at ClinicalTrials.gov (NCT04471701).

Data Collection and Variables Definition

The EPICOVID19 study was established as a collaborative project of a working group including epidemiologists, physicians who were experts in infectious diseases, biostatisticians, and public health professionals to improve SARS-CoV-2–related knowledge. To guarantee maximal comparability with other studies, several questions were defined based on standardized and validated questionnaires, as described elsewhere in detail [24,26,27]. The participants were asked to complete an anonymous 38-item questionnaire (Multimedia Appendix 2) that mainly contained mandatory and closed questions divided into six sections: sociodemographics, clinical features, personal

characteristics, behaviors before the lockdown, lifestyles, and behaviors following the lockdown (Multimedia Appendix 1).

Smoke Exposure

Several questions on present and past smoking habits were asked in the questionnaire. These included smoking status defined as *never smoked* (ie, persons who had never smoked regularly or had smoked less than 100 cigarettes), *former smokers* (ie, regular smokers who have smoked at least 100 cigarettes during their lifetime and did not smoke at the time of the survey), and *current smokers* [28]. To explore the dose-response effect, we created a variable by collapsing data on smoking status and smoking duration in years as follows: *former smokers* (ie, categorized for the smoking duration of ≤10 years or >10 years), *current smokers grouped in with mild smokers* (ie, ≤10 cigarettes/day for <15 years), *moderate smokers* (ie, ≤10 cigarettes/day for ≥15 years or >10 cigarettes/day for <15 years), and *heavy smoker*s (ie, >10 cigarettes/day for ≥15 years).

Main Outcomes

We investigated two different outcomes: (1) positive result for the NPS molecular test and (2) SARS-CoV-2 infection severity by combining information from the NPS test, symptoms, and hospitalization for COVID-19 defined as follows:

- No infection — negative NPS test
- Asymptomatic infection — positive NPS test without COVID-19–like symptoms excluding pneumonia
- Mild infection — positive NPS test with at least one COVID-19–like symptom excluding pneumonia
- Severe infection — positive NPS test with pneumonia and/or hospitalization for COVID-19.

Statistical Analysis

The continuous variables were represented as means and SDs and the categorical variables as counts and percentages. Continuous and categorical data according to smoking status were compared using one-way analyses of variance and chi-square tests, respectively. To explore the association between smoking habits, positive versus negative NPS test results, and the 4-level infection-severity dependent variable (ie, no infection, asymptomatic infection, mild infection, and severe infection), logistic regression and multinomial regression models were used to estimate the odds ratios (ORs) and 95% CIs. The first model was adjusted for age and sex. In the fully adjusted model, we further controlled for variables that were considered potential confounders, such as education, occupation, area of residence, heart diseases, lung diseases, hypertension, metabolic diseases, contact with suspected or confirmed COVID-19 cases, living area, crowding index, and living with at-risk cohabitants. Models were applied considering the smoking status and the dose-response relationship as exposures separately. We explored our data for potential effect modification by sex, age, and education by adding cross-product terms of these variables to the regression models. When heterogeneity was present, stratum-specific estimates were evaluated. Three sensitivity analyses were performed to evaluate whether the effect of smoking on SARS-CoV-2 infection was primarily due to the current amount of cigarettes smoked and/or to the smoking history during the lifespan. In the first sensitivity analysis, we categorized current smokers based on years of smoking into the following groups: <15 years, 15-30 years, and >30 years. The second sensitivity analysis explored the association between the number of cigarettes smoked, categorized as ≤10 cigarettes/day or >10 cigarettes/day, and the NPS test result. The third sensitivity analysis repeated the analysis by calculating the pack-years of smoking. We assigned a median number of cigarettes per day to each current smoking category (5 for <10 cigarettes/day; 15 for 10-20 cigarettes/day; 25 for >20 cigarettes/day), then we multiplied the number of packs per day (1 pack = 20 cigarettes) by the number of years the person had smoked; finally, we categorized the variable into tertiles. All statistical analyses were performed using Stata 15.0 (StataCorp LLC), and a two-sided *P* value <.05 was considered statistically significant.

Results

Characteristics of the Participants

The participants' characteristics regarding their smoking status are summarized below. The mean age of the whole sample was 47.9 (SD 14.1) years, 65.9% (4516/6857) were females, and 70.5% (4834/6857) had a university degree or higher. Out of 6857 individuals, 63.2% (n=4334) had never smoked, 21.3% (n=1463) were former smokers, and 15.5% (n=1060) were current smokers. A total of 24.7% (1691/6857) of the participants had a positive NPS test; among them, 9.2% (156/1691) were asymptomatic, 62.0% (1049/1691) had a mild infection, and 28.7% (486/1691) reported conditions compatible with a severe infection. Compared with those who never smoked, current smokers were younger, had higher educational levels, more frequently worked as employers, were health care professionals, and were frequently residents in central and southern regions (Table 1).

Table 1. Sociodemographic characteristics of study participants with known molecular test results by smoking status in Italy, from April 13 to June 2, 2020 (N=6857).

Sociodemographic characteristics	Never smoked (n=4334)	Former smoker (n=1463)	Current smoker (n=1060)	*P* value (current vs never)	*P* value (overall)	All participants (N=6857)
All participants, n (%)	4334 (63.2)	1463 (21.3)	1060 (15.5)	N/A[a]	N/A	6857 (100)
Sex (female), n (%)	2991 (69.0)	807 (55.2)	420 (70.1)	.42	<.001	4516 (65.9)
Age (years), mean (SD)	47.7 (14.7)	50.5 (13.1)	45.0 (12.4)	<.001	<.001	47.9 (14.1)
European ethnicity, n (%)	4281 (98.8)	1458 (99.7)	1052 (99.3)	.20	.01	6791 (99.0)
Education, n (%)				.01	.01	
Illiterate or primary school	359 (8.3)	96 (6.6)	30 (5.0)			525 (7.7)
Middle or high school	893 (20.6)	347 (23.7)	126 (21.0)			1498 (21.9)
University or postgraduate degree	3082 (71.1)	1020 (69.7)	443 (74.0)			4834 (70.5)
Employment status, n (%)				<.001	<.001	
Employed	3626 (83.7)	1223 (83.6)	548 (91.5)			5811 (84.8)
Student	125 (2.9)	18 (1.2)	19 (3.2)			172 (2.5)
Unemployed	63 (1.5)	28 (1.9)	8 (1.3)			106 (1.6)
Retired	291 (6.7)	144 (9.8)	8 (1.3)			459 (6.7)
Other	229 (5.3)	50 (3.4)	16 (2.7)			309 (4.5)
Occupational cluster[b], n (%)				.07	<.001	
White collar	3428 (79.1)	1173 (80.2)	804 (75.9)			5405 (78.8)
Blue collar	58 (1.3)	37 (2.5)	17 (1.6)			112 (1.6)
Other	848 (19.6)	253 (17.3)	239 (22.6)			1340 (19.5)
Health professional	2164 (49.9)	680 (46.5)	628 (59.3)	<.001	<.001	3472 (50.6)
Italian area of residence, n (%)				.01	.01	
Northern	3318 (76.6)	1084 (74.1)	755 (71.2)			5157 (75.2)
Central	686 (15.8)	231 (15.8)	204 (19.3)			1121 (16.4)
Southern	320 (7.8)	144 (9.8)	98 (9.3)			562 (8.2)
Other	10 (0.2)	4 (0.3)	3 (0.3)			17 (0.3)

[a]N/A: not applicable; *P* value was not calculated.

[b]White collar occupations include legislators, senior officials and managers, professionals, technicians, associate professionals, clerks and service workers, and shop and market sales workers; blue collar occupations include skilled agricultural and fishery workers, craft and related trades workers, plant and machine operators and assemblers, elementary occupations, others including armed forces, and unspecified occupations.

Current smokers were less affected by heart diseases (ie, cardiovascular disease [CVD]), hypertension, oncological diseases, and allergies compared to those who never smoked. They were less dependent in their daily activities, were less frequently vaccinated for flu and pneumococcal infections, less frequently took thyroid drugs and supplements, and more frequently took anti-inflammatory drugs. Smokers reported COVID-19–like symptoms less frequently, such as fever, olfactory and taste disorders, shortness of breath, cough, and pneumonia; they were less frequently hospitalized for COVID-19, had fewer NPS positive tests, and were less likely to be infected by SARS-CoV-2 in comparison with those who never smoked (Table 2).

Table 2. Clinical features of study participants with known molecular test results by smoking status in Italy, from April 13 to June 2, 2020 (N=6857).

Clinical features	Never smoked (n=4334)	Former smoker (n=1463)	Current smoker (n=1060)	*P* value (current vs never)	*P* value (overall)	All participants (N=6857)
All participants, n (%)	4334 (63.2)	1463 (21.3)	1060 (15.5)	N/A[a]	N/A	6857 (100)
Self-reported diseases, n (%)						
Lung diseases	340 (7.8)	130 (8.9)	77 (7.3)	.53	.29	547 (8.0)
Heart diseases	196 (4.5)	76 (5.2)	26 (2.5)	.01	.01	298 (4.4)
Hypertension and/or medications	723 (16.7)	326 (22.3)	143 (13.5)	.01	<.001	1192 (17.4)
Oncological diseases	138 (3.2)	67 (4.6)	16 (1.5)	.01	.001	221 (3.2)
Liver diseases	39 (0.9)	14 (1.0)	6 (0.6)	.28	.52	59 (0.9)
Renal diseases	52 (1.2)	14 (1.0)	10 (0.9)	.48	.64	76 (1.1)
Metabolic diseases and/or medications	238 (5.5)	86 (5.9)	47 (4.4)	.17	.27	371 (5.4)
Depression or anxiety and/or medications	505 (11.7)	167 (11.4)	122 (11.5)	.90	.97	794 (11.6)
Immune system diseases	431 (9.9)	146 (10.0)	88 (8.3)	.10	.25	665 (9.7)
Surgical procedures last year	168 (3.9)	82 (5.6)	38 (3.6)	.66	.01	288 (4.2)
Transplants	12 (0.3)	6 (0.4)	0 (0)	.09	.13	18 (0.3)
Allergies	786 (18.1)	223 (15.2)	163 (15.4)	.04	.01	1172 (17.1)
Dependency in daily activities	209 (4.8)	15 (1.0)	9 (0.9)	<.001	<.001	233 (3.4)
Flu shot during last autumn	1542 (35.6)	489 (33.4)	273 (25.8)	<.001	<.001	2304 (33.6)
Antipneumococcal vaccine in the last 12 months	219 (5.1)	73 (5.0)	37 (3.5)	.03	.10	329 (4.8)
Self-reported medications, n (%)						
Aspirin	192 (4.4)	131 (9.0)	46 (4.3)	.10	<.001	369 (5.4)
Cholesterol treatment drugs	252 (5.8)	161 (11.0)	69 (6.5)	.39	<.001	482 (7.0)
Oncological drugs	42 (1.0)	23 (1.6)	6 (0.6)	.21	.04	71 (1.0)
Corticosteroids	95 (2.2)	39 (2.7)	24 (2.3)	.89	.58	158 (2.3)
Thyroid drugs	369 (8.5)	131 (9.0)	64 (6.0)	.01	.02	564 (8.2)
Anti-inflammatory drugs	222 (5.1)	108 (7.4)	101 (9.5)	<.001	<.001	431 (6.3)
Supplements or vitamins	928 (21.4)	304 (20.8)	190 (17.9)	.01	.04	1422 (20.7)
Self-reported symptoms, n (%)						
Fever	1221 (28.2)	491 (33.6)	184 (17.4)	<.001	<.001	1896 (27.7)
Headache	1594 (36.8)	570 (39.0)	397 (37.5)	.68	.33	2561 (37.4)
Muscle or bone pain	1476 (34.1)	563 (38.5)	340 (32.1)	.22	<.001	2379 (34.7)
Olfactory and taste disorders	903 (20.8)	365 (25.0)	180 (17.0)	.01	<.001	1448 (21.1)
Shortness of breath	643 (14.8)	264 (18.1)	127 (12.0)	.02	<.001	1034 (15.1)
Chest pain	596 (13.8)	224 (15.3)	144 (13.6)	.89	.30	964 (14.1)
Heart palpitations	572 (13.2)	185 (12.7)	118 (11.1)	.07	.19	875 (12.8)
Gastrointestinal disturbances	1210 (27.9)	441 (30.1)	275 (25.9)	.20	.06	1926 (28.1)
Conjunctivitis	527 (12.2)	174 (11.9)	117 (11.0)	.31	.60	818 (11.9)
Sore throat or rhinorrhea	1579 (36.4)	558 (38.1)	392 (37.0)	.74	.50	2529 (36.9)
Cough	1537 (35.5)	536 (36.6)	294 (27.7)	<.001	<.001	2367 (34.5)
Pneumonia	354 (8.2)	170 (11.6)	32 (3.0)	<.001	<.001	556 (8.1)
No symptoms	1154 (26.6)	321 (21.9)	308 (29.1)	.11	<.001	1783 (26.0)

Clinical features	Never smoked (n=4334)	Former smoker (n=1463)	Current smoker (n=1060)	*P* value (current vs never)	*P* value (overall)	All participants (N=6857)
Hospitalized for COVID-19	319 (7.4)	175 (12.0)	33 (3.1)	<.001	<.001	527 (7.7)
Positive NPS[b] test result	1124 (25.9)	407 (27.8)	160 (15.1)	<.001	<.001	1691 (24.7)
Infection severity[c], n (%)				N/A	<.001	
No infection	3210 (74.1)	1056 (72.2)	900 (84.9)			5166 (75.3)
Asymptomatic	117 (2.7)	27 (1.9)	12 (1.1)			156 (2.3)
Mild	697 (16.1)	225 (15.4)	127 (12.0)			1049 (15.3)
Severe	310 (7.2)	155 (10.6)	21 (2.0)			486 (7.1)

[a]N/A: not applicable; *P* value was not calculated.

[b]NPS: nasopharyngeal swab.

[c]No infection: negative NPS test result; asymptomatic infection: positive NPS test result without COVID-19–like symptoms excluding pneumonia; mild infection: positive NPS test result with at least one COVID-19–like symptom excluding pneumonia; and severe infection: positive NPS test with pneumonia and/or hospitalization for COVID-19

Current smokers lived less frequently with cohabitants who were at risk of COVID-19 infection; after the lockdown, they more frequently went out and used public transport, they contacted the emergency number less frequently, and they were more afraid of themselves or family members becoming infected than were nonsmokers (Table 3).

In comparison with people who never smoked and current smokers, former smokers were significantly older; retired; more affected by chronic conditions, such as heart diseases and hypertension; and more frequently took aspirin, drugs for lowering cholesterol, and oncological and thyroid drugs. They reported COVID-19–like symptoms less frequently and were more likely to be hospitalized for COVID-19.

Table 3. Behavioral characteristics of study participants with known molecular test results by smoking status in Italy, from April 13 to June 2, 2020 (N=6857).

Behavioral characteristics	Never smoked (n=4334)	Former smoker (n=1463)	Current smoker (n=1060)	*P* value (current vs never)	*P* value (overall)	All participants (N=6857)
All participants, n (%)	4334 (63.2)	1463 (21.3)	1060 (15.5)	N/A[a]	N/A	6857 (100)
Housing conditions, n (%)						
Traffic near house				.25	.17	
Low	1880 (43.4)	655 (44.8)	461 (43.5)			2996 (43.7)
Moderate	1499 (34.6)	525 (35.9)	388 (36.6)			2412 (35.2)
High	955 (22.0)	283 (19.3)	211 (19.9)			1449 (21.1)
Cohabitants at risk[b]	934 (21.6)	250 (17.1)	182 (17.2)	.01	<.001	1366 (19.9)
Residence area				.32	.25	
Countryside	492 (11.4)	164 (11.2)	136 (12.8)			792 (11.6)
Small town	1797 (41.5)	609 (41.6)	411 (38.8)			2817 (41.1)
Suburbs: >100,000 inhabitants	772 (17.8)	233 (15.9)	198 (18.7)			1203 (17.5)
City or town: >100,000 inhabitants	1273 (29.4)	457 (31.2)	315 (29.7)			2045 (29.8)
Household crowding index[c]				.33	.10	
Low	3941 (90.9)	1354 (92.6)	974 (91.9)			6269 (91.4)
Middle	387 (8.9)	105 (7.2)	86 (8.1)			578 (8.4)
High	6 (0.1)	4 (0.3)	0 (0)			10 (0.2)
Behaviors before the lockdown, n (%)						
Number of daily contacts				.17	.01	
<10	738 (17.0)	293 (20.0)	162 (15.3)			1193 (17.4)
≥10	3596 (83.0)	1170 (80.0)	898 (84.7)			5664 (82.6)
Physical activity				.88	<.001	
>2.5 h/week	1099 (25.4)	449 (30.7)	275 (25.9)			1826 (26.6)
10 min/week to 2.5 h/week	1870 (43.1)	631 (43.1)	449 (42.4)			2950 (43.0)
<10 min/week	1363 (31.5)	383 (26.2)	336 (31.7)			2082 (30.4)
Behaviors after the lockdown, n (%)						
Contact with COVID-19 cases[d]	3118 (71.9)	989 (67.6)	754 (71.1)	.60	.01	4861 (70.9)
Weekly outings				<.001	<.001	
Never	1043 (24.1)	364 (24.9)	140 (13.2)			1547 (22.6)
1-3	1083 (25.0)	417 (28.5)	290 (27.4)			1790 (26.1)
≥4	2208 (51.0)	682 (46.6)	630 (59.4)			3520 (51.3)
Use of public transport				.05	.05	
Never	4186 (96.6)	1423 (97.3)	1008 (95.1)			6617 (96.5)
1-3 times/week	62 (1.4)	18 (1.2)	25 (2.4)			105 (1.5)
≥4 times/week	86 (2.0)	22 (1.5)	27 (2.6)			135 (2.0)
Personal characteristics, n (%)						
Contacted emergency number				<.001	<.001	
No	2323 (53.6)	722 (49.4)	676 (63.8)			3721 (54.3)
No, but I went to a hospital on my own initiative	103 (2.4)	47 (3.2)	18 (1.7)			168 (2.5)

Behavioral characteristics	Never smoked (n=4334)	Former smoker (n=1463)	Current smoker (n=1060)	*P* value (current vs never)	*P* value (overall)	All participants (N=6857)
Yes, and they did not suggest that I self-isolate	235 (5.4)	88 (6.0)	72 (6.8)			395 (5.8)
Yes, and they suggested that I self-isolate	1361 (31.4)	448 (30.6)	239 (22.6)			2048 (29.9)
Yes, I was sent to a hospital	312 (7.2)	158 (10.8)	55 (5.2)			525 (7.7)
Self-perceived health status				.81	.59	
Good	3493 (80.6)	1155 (79.0)	863 (81.4)			5511 (80.4)
Adequate	769 (17.7)	282 (19.3)	179 (16.9)			1230 (17.9)
Bad	72 (1.7)	26 (1.8)	18 (1.7)			116 (1.7)
Afraid to be infected				.02	.01	
No	1556 (35.9)	521 (35.6)	401 (37.8)			2478 (36.1)
Neutral	918 (21.2)	253 (17.3)	184 (17.4)			1355 (19.8)
Yes	1860 (42.9)	689 (47.1)	475 (44.8)			3024 (44.1)
Afraid for family members				<.001	<.001	
No	669 (15.4)	251 (17.2)	179 (16.9)			1099 (16.0)
Neutral	514 (11.9)	118 (8.1)	64 (6.0)			696 (10.2)
Yes	3151 (72.7)	1094 (74.8)	817 (77.1)			5062 (73.8)

[a]N/A: not applicable; *P* value was not calculated.

[b]This includes elderly persons or anyone who is immunocompromised or has chronic disease conditions.

[c]Number of cohabitants per number of rooms.

[d]Suspected or confirmed COVID-19 cases.

Association Analyses

Table S2 in Multimedia Appendix 1 and Figure 2 show the logistic regression results for positive NPS tests. In the age- and sex-adjusted model, current smoking was significantly inversely associated with a positive NPS test (OR 0.54, 95% CI 0.45-0.65), with *never smoked* as the reference category. Results did not change when potential confounders were accounted for in the fully adjusted model (adjusted OR [aOR] 0.54, 95% CI 0.44-0.65). Being a former smoker was not associated with a positive NPS test (aOR 1.03, 95% CI 0.90-1.19), even when we considered the dose-response relationship and the lifetime smoking duration (≤10 years and >10 years). The aOR for testing positive was 0.76 in mild smokers (95% CI 0.55-1.05), although not statistically significant; 0.56 in moderate smokers (95% CI 0.42-0.73); and 0.38 in heavy smokers (95% CI 0.27-0.53), suggesting a dose-response relationship between smoking habit and NPS test result.

Figure 2. Adjusted odds ratios and relative 95% CIs for smoking status, intensity, and duration (N=6857). Odds ratios were adjusted for age, sex, education, occupation, area of residence, heart diseases, lung diseases, hypertension, metabolic and oncological diseases, contact with confirmed or suspected COVID-19 cases, living area, crowding index, and living with at-risk cohabitants. Dots and vertical lines indicate adjusted odds ratios and 95% CIs, respectively. Mild smokers: ≤10 cigarettes/day for <15 years; moderate smokers: ≤10 cigarettes/day for ≥15 years or >10 cigarettes/day for <15 years; heavy smokers: >10 cigarettes/day for ≥15 years. cig: cigarettes.

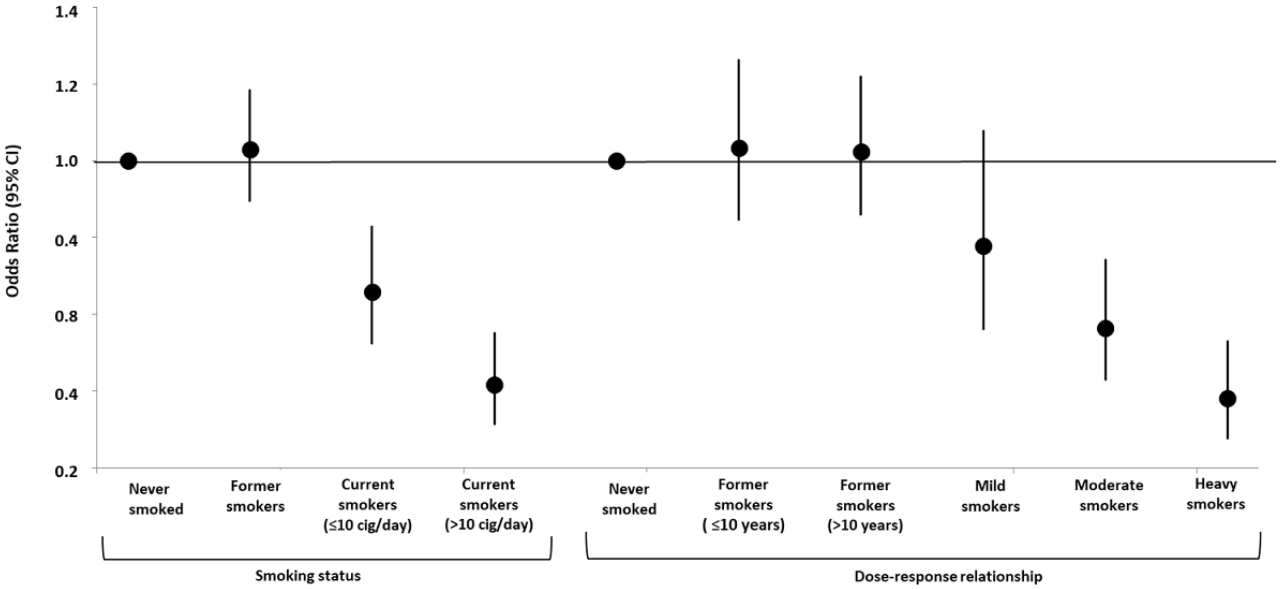


Table 4 reports the association between smoking status and infection severity. Current smokers had a statistically significant lower probability of having an asymptomatic infection (aOR 0.50, 95% CI 0.27-0.92), mild infection (aOR 0.65, 95% CI 0.53-0.81), and severe infection (aOR 0.27, 95% CI 0.17-0.42) compared to people who never smoked. The inverse dose-dependent relationship also persisted when considering the gravity of the infection, showing a gradient of association across smoking patterns. Since we found a significant interaction between smoking status and age (*P*=.001), we created a 6-level variable by combining age—dichotomized into ≤48 years and >48 years (median) groups—and smoking status. Compared to people who never smoked and were 48 years of age or younger, people who never smoked or former smokers who were over 48 years of age had a 1.5-fold and 1.7-fold higher probability of a positive NPS test, respectively.

The odds were reduced by 33% and 42% in current smokers aged 48 years or younger and those more than 48 years of age, respectively (Table S3 in Multimedia Appendix 1). In sensitivity analyses, considering *never smoked* as the reference category, we found that the inverse relationship between smoking and a positive NPS test was stronger in heavy smokers (>10 cigarettes/day; aOR 0.42, 95% CI 0.31-0.56), in long-term smokers (smoked for >30 years; aOR 0.40, 95% CI 0.26-0.61), and in those in the highest pack-years category (pack-years 11.3-65; aOR 0.43, 95% CI 0.32-0.58). In moderate smokers (≤10 cigarettes/day; aOR 0.64, 95%CI 0.51-0.81), more recent current smokers (smoked for <15 years; aOR 0.70, 95% CI 0.53-0.92), and those in the lowest category of pack-years of smoking (pack-years 0.5-4.9; aOR 0.73, 95% CI 0.54-1.00), the odds reduction was lower (Figure 3 and Table S4 in Multimedia Appendix 1).

Table 4. Odds ratios (ORs)[a] of SARS-CoV-2 severity[b] by smoking habit (N=6857).

Smoking habit	No infection (n=5166), n (%)	Asymptomatic infection (n=156)		Mild infection (n=1049)		Severe infection (n=486)	
		OR (95% CI)	n (%)	OR (95% CI)	n (%)	OR (95% CI)	n (%)
Total participants (N=6857)	5166 (75.3)	N/A[c]	156 (2.3)	N/A	1049 (15.3)	N/A	486 (7.1)
Smoking status							
Never smoked	3210 (62.1)	1 (reference)	117 (75.0)	1 (reference)	697 (66.4)	1 (reference)	310 (63.8)
Former smokers	1056 (20.4)	0.78 (0.50-1.21)	27 (17.3)	0.99 (0.84-1.18)	225 (21.5)	1.20 (0.97-1.50)	155 (31.9)
Current smokers	900 (17.4)	0.50 (0.27-0.92)	12 (7.7)	0.65 (0.53-0.81)	127 (12.1)	0.27 (0.17-0.42)	21 (4.3)
Dose-response relationship							
Never smoked	3210 (62.1)	1 (reference)	117 (75.0)	1 (reference)	697 (66.4)	1 (reference)	310 (63.8)
Former smokers (≤10 years)	487 (9.4)	0.84 (0.42-1.71)	9 (5.8)	1.00 (0.79-1.27)	99 (9.4)	1.22 (0.88-1.69)	50 (10.3)
Former smokers (>10 years)	569 (11.0)	0.74 (0.44-1.27)	18 (11.5)	0.98 (0.79-1.22)	126 (12.0)	1.20 (0.92-1.55)	105 (21.6)
Mild smokers[d]	249 (4.8)	1.16 (0.41-3.29)	4 (2.6)	0.84 (0.59-1.18)	42 (4.0)	0.23 (0.07-0.73)	3 (0.6)
Moderate smokers[e]	365 (7.1)	0.42 (0.15-1.15)	4 (2.6)	0.67 (0.49-0.91)	52 (5.0)	0.35 (0.19-0.66)	11 (2.3)
Heavy smokers[f]	286 (5.5)	0.36 (0.13-0.99)	4 (2.6)	0.50 (0.34-0.72)	33 (3.2)	0.20 (0.09-0.43)	7 (1.4)

[a]ORs were adjusted for age, sex, education, occupation, area of residence, heart diseases, lung diseases, hypertension, metabolic and oncological diseases, contact with COVID-19 cases, living area, crowding index, and living with at-risk cohabitants.

[b]No infection: negative nasopharyngeal swab (NPS) test (reference category); asymptomatic infection: positive NPS test without symptoms; mild infection: positive NPS test with at least one symptom; and severe infection: positive NPS test with pneumonia and/or hospitalization for COVID-19.

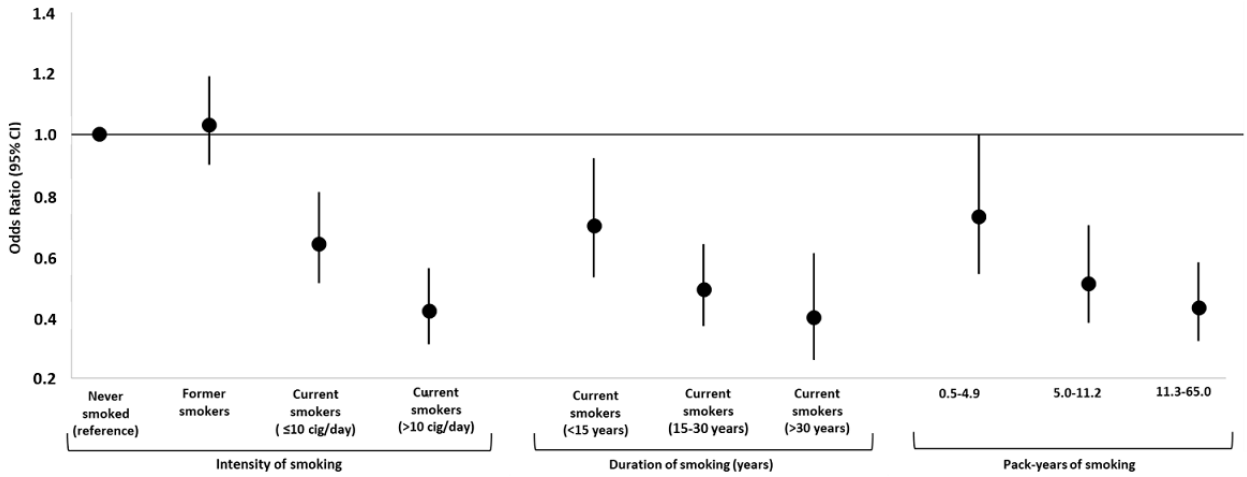
[c]N/A: not applicable.

[d]Mild smokers: ≤10 cigarettes/day for <15 years.

[e]Moderate smokers: ≤10 cigarettes/day for ≥15 years or >10 cigarettes/day for <15 years.

[f]Heavy smokers: >10 cigarettes/day for ≥15 years.

Figure 3. Adjusted odds ratios for positive SARS-CoV-2 tests by smoke-related variables: intensity, duration, and pack-years of smoking (N=6857). Odds ratios were adjusted for age, sex, education, occupation, area of residence, heart diseases, lung diseases, hypertension, metabolic and oncological diseases, contact with COVID-19 cases, living area, crowding index, and living with at-risk cohabitants. Dots and vertical lines indicate adjusted odds ratios and 95% CIs, respectively. cig: cigarettes.



Discussion

Principal Findings

This study evaluated the association between smoking habits and the odds of receiving positive SARS-CoV-2 molecular tests and infection severity in an Italian adult population recruited online during the first national lockdown. We found that current smoking was associated with a significant risk reduction of having a positive SARS-CoV-2 test and of developing a severe infection in a dose-response relationship, even after taking into account all the available confounding factors.

In our sample, the percentage of positive tests in participants was 24.7% (1691/6857), close to the positive test ratio shown by Romagnani and colleagues, who reported, at the beginning of April 2020, an overall percentage of positive tests of 18.6% for Italy, with a marked regional difference ranging from 38.5% in Lombardy to 7.5% in Lazio [29]. The relatively high percentage of positive tests reflects the initial phase of the pandemic spread, during which, in Italy, molecular tests were reserved for clinically relevant cases. This is in keeping with the low percentage of asymptomatic subjects in our sample: 2.3% of the overall evaluated sample and 9.2% among confirmed SARS-CoV-2 infection cases. Although 70.5% of participants had a university degree or higher and the female gender was predominant (65.9%), the prevalence of smoking habits in our sample was quite similar to that of the Italian general population. Indeed, we found that 63.2% of the included participants had never smoked, 21.3% were former smokers, and 15.5% were current smokers. In Italy, the prevalence of former smokers is 23.0%, while active smokers represent 18.4% of the population and those who never smoked represent 57.4% of the population [30].

When compared to those who never smoked, current smokers had a lower prevalence of chronic conditions (50.8% vs 55.4%), including those known to be influenced by smoking habits, such as CVD (2.5% vs 4.5%) and hypertension (13.5% vs 16.7%). Former smokers were older and more frequently retired compared to those who never smoked and they were, as expected, more affected by chronic diseases, such as CVD (5.2%) and hypertension (22.3%). This finding is consistent with the successful smoking cessation achieved by subjects affected by hypertension and myocardial infarction [31]. Current smokers had significantly fewer COVID-19–like symptoms and were less frequently hospitalized for COVID-19 than those who never smoked and former smokers; this is in agreement with a previous meta-analysis study showing a lower prevalence of current smokers among hospitalized COVID-19 patients [19].

We found that current smoking was associated with reduced odds of a positive NPS test by 46%. Analogously, Israel and colleagues [16] found reduced odds by 53% for the association between current smoking and fatal or severe disease in a population-based study among over 3,000,000 adults in Israel. Similar results were observed in a study on middle-aged veterans in the United States in which smokers were less likely to test positive for COVID-19 (OR 0.43), although there was no significant difference in hospitalization [17]. In a large cohort study of 17,278,392 adults from the general population in the United Kingdom, current smoking was associated with an increased risk of COVID-19–related death when controlling for age and sex. However, after adjustment for multiple adjusted covariates (eg, chronic respiratory diseases), the authors found that smoking was associated with a risk lowered by 11% [32]. A negative association between smoking prevalence and COVID-19 occurrence at the population level was also found in an ecological study conducted in 38 European countries, although the authors cautioned that this association might not imply a causal relationship [14].

In our study, we also observed a significant dose-response relationship between smoking habits and NPS test results. In the fully adjusted logistic model, mild smokers had a 24% lower probability of a positive NPS test, whereas moderate smokers and heavy smokers had, respectively, 44% and 62% lower probabilities compared to those who never smoked. Conversely, among former smokers, we did not find a significant effect of the time interval (≤10 years or >10 years) on NPS test results. A French study evaluating smoking habits among symptomatic COVID-19 inpatients and outpatients showed that, in both groups, active smokers were less frequently infected by COVID-19 when compared with the general population [33].

When we analyzed the association between smoking habits and SARS-CoV-2 infection severity, we found that active smokers were less likely to develop a severe infection. Furthermore, by evaluating participants with positive NPS test results in relation to their reported infection severity (ie, asymptomatic, mild, or severe infection), being a current smoker reduced the odds of a severe infection by 50%, 35%, and 73%, respectively. Likewise, regarding the dose-response effect found for positive NPS test results, heavy smokers showed a lower risk of developing different severity levels of SARS-CoV-2 infection, in particular severe COVID-19 (80% odds reduction). The link between smoking and infection severity is highly controversial in the literature. For example, in the previously cited meta-analysis, Farsalinos and colleagues showed that, although the risk for current smokers to be hospitalized was lower than for nonsmokers, current smokers were more likely to have an adverse outcome during their hospital admission [19]. In a population of over 2.4 million UK users of the Zoe COVID-19 Symptom Study app, Hopkinson found a statistically significant OR of 1.14 for the self-reporting of a triad of three symptoms (ie, fever, persistent cough, and shortness of breath) for current smokers; although to some extent this was also attributable to constipation or normal flu, the authors identified it as suggestive of COVID-19. On the contrary, when analyzing the stronger endpoint of a positive SARS-CoV-2 test, they observed a lower smoking rate (7.4% among positive tests vs 9.3% among negative tests), leading to a reduced aOR of 0.7 that they considered not generalizable to their general population, due to the physiological difference between tested and untested individuals [34]. In their systematic review, Vardavas and Nikitara concluded that smoking was associated with disease progression and increased adverse outcomes in COVID-19–positive patients [35]. This was the case even though, in both meta-analyses, the authors acknowledged that their studies were conducted with limited availability of data, the included studies came mostly from hospital contexts, and their analyses were not adjusted for confounding factors. Similar methodological limitations have been reported in the meta-analysis conducted by Patanavanich, who found that smoking was a risk factor for the progression of COVID-19 [36]; conversely, Lippi and Henry did not observe any association [37].

Our findings, which highlight the existence of a negative association of current smoking with SARS-CoV-2 infection and its severity, drive the focus to possible suggestive explanations. Since ACE2 is necessary for infection of cells by SARS-CoV-2 [38], the risk of contracting a severe SARS-CoV-2 infection, as well as the risk of a disadvantageous clinical

outcome, could be influenced by the number of available ACE2 receptors and by the receptor-ligand interaction of ACE2 and the SARS-CoV-2 spike protein [39]. Regarding the number of ACE2 receptors, nicotine seems to have a controversial role. Recent evidence indicates that a higher number of receptors are expressed in the lung tissues of smokers [40]. On the other hand, it has been suggested that nicotine downregulates the expression and/or the activity of ACE2 [41]. However, a better disease outcome was associated with an overexpression of ACE2, which was able to compensate for the negative effects of the ACE2 downregulation induced by the cell entry of SARS-CoV-2 [42]. Moreover, a direct role of nicotine in disrupting spike protein glycosylation could, in turn, directly affect the ability of SARS-CoV-2 to infect [43]. A recent study performed on a mouse model proposes the modulation of the renin-angiotensin pathway as a therapeutic target to protect individuals with SARS-CoV-2 infection from developing acute severe lung failure and acute respiratory distress syndrome [44]. In addition to that, nicotine might exert an anti-inflammatory effect by protecting against the *cytokine-storm syndrome* that is responsible for severe SARS-CoV-2 infections [21,45]. It has also been hypothesized that the cytokine storm, with excessive production of proinflammatory molecules, could be more easily triggered in individuals who never smoked rather than in smokers, whose immune systems are more tolerant and less reactive [46].

Another potential mechanism of action involves nitric oxide produced during smoking that, due to its reported antiviral effect, might inhibit virus replication and entry in the cells [21,47].

Alternatively, from a behavioral perspective, we cannot exclude that smokers, considering themselves at higher risk of developing the disease, were more careful than those who never smoked in adopting preventative measures, such as physical distancing, hand hygiene, covering coughs, wearing masks when appropriate, having fewer social relationships, etc [48].

Limitations and Strengths

This study has some limitations. Firstly, because of the observational nature of the study and the cross-sectional design, we cannot infer any causal relationship between smoking habits and COVID-19. In addition, misclassification of the outcome of severity may exist, since patients' conditions in some cases—although numerically limited—might have worsened a few days after the survey, with a subsequent potential distortion of measures of association. Secondly, smoking habits were self-reported; therefore, recall bias might have led to misclassification of the exposure. Thirdly, the sample was self-selected and not entirely representative of the Italian population because it was restricted to relatively younger, female, highly educated, and relatively healthy participants; therefore, results should be treated with caution when generalized to different populations [49]. Moreover, the low percentage of asymptomatic subjects in our sample may have influenced the evaluation of the effects of smoking habits on asymptomatic subjects with positive NPS test results. Nevertheless, in a previous study, smokers were proportionally represented among asymptomatic patients [50]. Lastly, although we controlled for several potential confounders, we cannot completely rule out the possibility of residual confounding due to unmeasured factors (eg, passive smoking). Our study also has several strengths. The first one is that evaluating the effect of smoking was the primary goal of the work. The presence in our study sample of subjects from a general population with negative NPS test results allows for an internal control group (ie, individuals with negative NPS test results). The web survey reached a large sample of adults with an acceptable geographical coverage reflecting the distribution of SARS-CoV-2 infection during the study period [24] and a proportion of smokers that almost overlapped with the prevalence of current smoking in the Italian population. Finally, and contrary to previously published work, we recorded factors that are not easy to obtain from medical records of inpatients, such as exhaustive details regarding smoking habits (ie, distinguishing between former smokers, active smokers, or those who never smoked) and factors suspected to be confounders in the observed association (ie, socioeconomic status as well as clinical, behavioral, and environmental characteristics).

Conclusions

In summary, we are aware that our findings must be carefully evaluated. This article takes as its premise the need to strengthen preventive actions against the most powerful human carcinogen known, which is also a heavy risk factor for many noncommunicable diseases [51] and disease progression in COVID-19 patients. However, we are now facing a second pandemic wave requiring the consideration of each issue that is still unresolved regarding the possible role played by smoking in COVID-19 disease. Further research on the mechanisms of interaction between tobacco smoke exposure and SARS-CoV-2 infection is warranted to fill this knowledge gap.

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Authors' Contributions

FP, FB, FA, and FC conceived, designed, and planned the study. FP and FA were responsible for the study procedures. FP conducted the statistical analysis and prepared a first draft of the manuscript. FB, GD, SR, FA, and FC contributed to drafting the manuscript. FB, FA, and FC supervised the study. GD, SR, AS, NJ, MG, AG, SMolinaro, LB, SMaggi, MN, and RAI critically edited and revised the manuscript for important intellectual content. All authors have approved the submitted version and any substantially modified version that involves each author’s contribution to the study. The corresponding author, FP, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary materials.
[DOCX File , 36 KB - publichealth_v7i4e27091_app1.docx]

Multimedia Appendix 2
Study survey.
[DOCX File , 36 KB - publichealth_v7i4e27091_app2.docx]

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Abbreviations

ACE2: angiotensin-converting enzyme 2
aOR: adjusted odds ratio
CVD: cardiovascular disease
EPICOVID19: Italian National Epidemiological Survey on COVID-19
EU GDPR: European Union General Data Protection Regulation
NPS: nasopharyngeal swab
OR: odds ratio

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Original Paper

Effects of Age, Gender, Health Status, and Political Party on COVID-19–Related Concerns and Prevention Behaviors: Results of a Large, Longitudinal Cross-sectional Survey

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Abstract

Background: With conflicting information about COVID-19, the general public may be uncertain about how to proceed in terms of precautionary behavior and decisions about whether to return to activity.

Objective: The aim of this study is to determine the factors associated with COVID-19–related concerns, precautionary behaviors, and willingness to return to activity.

Methods: National survey data were obtained from the Democracy Fund + UCLA Nationscape Project, an ongoing cross-sectional weekly survey. The sample was provided by Lucid, a web-based market research platform. Three outcomes were evaluated: (1) COVID-19–related concerns, (2) precautionary behaviors, and (3) willingness to return to activity. Key independent variables included age, gender, race or ethnicity, education, household income, political party support, religion, news consumption, number of medication prescriptions, perceived COVID-19 status, and timing of peak COVID-19 infections by state.

Results: The data included 125,508 responses from web-based surveys conducted over 20 consecutive weeks during the COVID-19 pandemic (comprising approximately 6250 adults per week), between March 19 and August 5, 2020, approved by the University of California, Los Angeles (UCLA) Institutional Review Board for analysis. A substantial number of participants were not willing to return to activity even after the restrictions were lifted. Weighted multivariate logistic regressions indicated the following groups had different outcomes (all P<.001): individuals aged ≥65 years (COVID-19–related concerns: OR 2.05, 95% CI 1.93-2.18; precautionary behaviors: OR 2.38, 95% CI 2.02-2.80; return to activity: OR 0.41, 95% CI 0.37-0.46 vs 18-40 years); men (COVID-19–related concerns: OR 0.73, 95% CI 0.70-0.75; precautionary behaviors: OR 0.74, 95% CI 0.67-0.81; return to activity: OR 2.00, 95% CI 1.88-2.12 vs women); taking ≥4 medications (COVID-19–related concerns: OR 1.47, 95% CI 1.40-1.54; precautionary behaviors: OR 1.36, 95% CI 1.20-1.555; return to activity: OR 0.75, 95% CI 0.69-0.81 vs <3 medications); Republicans (COVID-19–related concerns: OR 0.40, 95% CI 0.38-0.42; precautionary behaviors: OR 0.45, 95% CI 0.40-0.50; return to activity: OR 2.22, 95% CI 2.09-2.36 vs Democrats); and adults who reported having COVID-19

(COVID-19–related concerns: OR 1.24, 95% CI 1.12-1.39; precautionary behaviors: OR 0.65, 95% CI 0.52-0.81; return to activity: OR 3.99, 95% CI 3.48-4.58 vs those who did not).

Conclusions: Participants' age, party affiliation, and perceived COVID-19 status were strongly associated with their COVID-19–related concerns, precautionary behaviors, and willingness to return to activity. Future studies need to develop and test targeted messaging approaches and consider political partisanship to encourage preventative behaviors and willingness to return to activities.

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KEYWORDS

COVID-19; prevention; behavior; advice; health care provider; economy; health information; concern; survey

Introduction

On January 20, 2020, the first US case of a novel virus was detected [1], and it was later named SARS-COV-2 [2,3]. The coronavirus is spread primarily via exposure to oral and nasal secretions when a person is in close contact with someone who has COVID-19 [4], and it is known to cause critical illness and substantial mortality in a subset of the infected population [5]. As of August 27, 2020, a total of 24,234,340 confirmed cases and 827,110 deaths due to COVID-19 were reported worldwide [6], of which over 5,752,653 cases and 177,759 deaths were reported in the United States alone [7]. These high numbers are in part because SARS-COV-2 is highly contagious [8], and about 44% (95% CI 30%-57%) of the confirmed cases are due to presymptomatic transmission [9-11].

Without a vaccine or an effective treatment, the COVID-19 pandemic could easily overwhelm hospitals. Actions undertaken at the individual level, such as washing hands, social distancing [12], and wearing face masks [13], can slow the spread of the disease [14]. Government measures to curtail the spread started with international travel restrictions [15]. California was the first to issue state-wide stay-at-home orders [16], followed by most, but not all (8 states did not), states [17]. The states with stay-at-home orders successfully reduced the contagion compared to states that did not enforce these orders [18]. Stay-at-home policies have significant economic and social consequences [19]; federal, state, and local officials now struggle to protect American lives while also recovering the economy by enabling people to go back to work [20].

Multiple factors influence COVID-19 precautionary and return-to-activity behaviors. For example, knowledge about COVID-19 and its risks are associated with a high-risk behavior, such as attending large gatherings and not wearing masks [21]. Additionally, the risk of getting severely ill from COVID-19 increases with age and coexisting conditions [22], and the risk is higher in men than in women [23,24]. Among some racial and ethnic groups in specific contexts, evidence points to higher rates of hospitalization and death due to COVID-19, and this is especially true in vulnerable populations such as migrants and undocumented individuals [25-27]. Political orientation and environment also are associated with COVID-19 response recommendations [21,28]. Finally, income disparities can result in situations that pit physical distancing against meeting basic needs [29].

With conflicting statements in the media from medical and political leaders, the general public lives with considerable uncertainty about the disease and the impact of their behaviors on their health and the health of the community. Understanding the factors affecting adults' willingness to engage in precautionary behavior or to return to normal activities could improve messaging among those with trusted voices and potentially aid economic recovery [30]. Using cross-sectional, national, population-based surveys conducted across time, this exploratory study examines major factors associated with COVID-19 precautionary behaviors, willingness to return to typical activities when told it is safe to do so by public health officials, and the levels of concern about the virus in order to inform preventive efforts and determine key populations that may benefit from reinforced messaging from health care providers. Our hypothesis was that the identification of political party affiliation would have as large an effect as other traditional covariates such as age, gender, race or ethnicity, health (ie, number of prescriptions), education, information, income, COVID-19 status, and religion with regard to three key outcomes: (1) COVID-19–related concerns, (2) precautionary behaviors, and (3) willingness to return to activity.

Methods

The Democracy Fund + UCLA Nationscape Project

Data were obtained from 20 weeks of the ongoing Democracy Fund + UCLA Nationscape Project, a weekly survey comprising 6250 people ([31], Multimedia Appendix 1). The sample was provided by Lucid, a market research platform. Web-based surveys were administered. UCLA staff set quotas for sample acquisition and generated weights to produce a nationally representative sample of the adult American population. Additional information on the survey methodology and the data's comparability to population targets are available [31]. Nationscape is well suited to examine the impact of COVID-19 due to its size and geographic scope. The wording of questions and response options are available on the internet [32]. This project was approved by the University of California, Los Angeles (UCLA) Institutional Review Board (IRB #19-000897).

Key Outcome Variables

Three outcomes were considered: (1) COVID-19–related concerns, (2) precautionary behaviors, and (3) willingness to return to activity. Not all outcomes were asked in each survey wave; therefore, the sample size varies among outcomes.

COVID-19–Related Concerns

Concerns about COVID-19 were coded as four categories: "Not at all concerned," "Not very concerned," "Somewhat concerned," and "Very concerned."

Precautionary Behaviors

Precautionary behaviors included individual items on washing hands, wearing a face mask, limiting visits to family members, quarantining oneself, and cancelling travel plans. Respondents were asked whether they had performed each of these activities in response to the spread of COVID-19 (response options: yes or no). In surveys conducted after May 28, 2020, respondents were specifically asked whether they had worn a face mask when going out in public within the last week. The return to activity component evaluated the respondents' routine activities, including having dinner with friends, attending a funeral, attending a wedding, attending church, getting a haircut, visiting a dentist, going to a shopping mall, sending a child to school, going to school oneself, taking a flight, going to the movies, using public transit, attending a sporting event, and attending a concert. Respondents were asked whether they would return to a given activity if the restrictions on doing so were lifted on the advice of public health officials (response options: yes or no). Individuals who reported that they "would not have done this activity before the COVID-19 pandemic" for a given activity were excluded from further analyses.

Key Independent Variables

Key independent variables included age (age range: 18-39, 40-64, and ≥65 years), gender (male or female), race or ethnicity (Hispanic, White, Black, Asian or Pacific Islander, or other), education (high school or lower, some college, and college and beyond), household income (by tercile), political party they support (Democrat, Independent, or Republican), religion (Protestant, Catholic, Jewish, Mormon, other, or not religious), evangelical (evangelical or not evangelical), political news consumption (0-2, 3-6, or ≥7 news sources), number of prescription medications (0-3 or ≥4), COVID-19 status (believes they had COVID-19 or not), and the timing of COVID-19 infections by state (early peak, later peak, or no peak or low rate). For the last variable, "early peak" states were those that reached a threshold of 30 confirmed cases per 100,000 residents before June 1, 2020; "later peak" states were those that failed to reach this threshold by June 1, 2020, but eventually reached at least 10 cases per 100,000.

Data Analysis

The data included 125,508 interviews conducted between March 19 and August 5, 2020. Across the different survey waves, of those respondents selected to be interviewed, 13% (22,115/174,690) declined immediately, and 10% (17,517/174,690) dropped off elsewhere during the survey without completing it. An additional 5% (9550/174,690) were removed after quality control checks. This results in a response yield of 72% (125,508/174,690) of the initially invited sample. Most sample proportions were within a few points of the target population before weights were applied (Table 1, Multimedia Appendix 2). The data were weighted to age, race, ethnicity, gender, education, partisanship, income, and region, among other items; thus, any differences observed here were further minimized after weighting.

Weighted proportions were calculated with R statistical software (version 3.6.1) based on data collected from March to August 2020. Weighted multivariate logistic regression analyses were used to calculate odds ratios (ORs). The survey wave was included as a fixed effect. Additionally, weighted difference-in-means tests assessed whether the trends shown in Multimedia Appendix 3 were statistically significant. These tests compared weighted proportions from the April 16, 2020 wave to the June 11, 2020 wave—both overall and for each subgroup. The reference categories are described in Multimedia Appendix 4. To demonstrate the effect of gender, partisanship, and having contracted COVID-19, the average probabilities of the population engaging in each dependent variable were calculated as if the respondents were all either men or women, Republicans or Democrats, and sick or not sick (leaving other characteristics unchanged) [33]. The difference between the probabilities when everyone was assigned the propensity of men compared to women, for example, illustrates the differences in likelihood due to gender.

Table 1. Unweighted and weighted characteristics of the sample population (N=125,508).

Characteristics	Unweighted, n (%)	Weighted (%)
Age (years)		
18-39	52,413 (41.8)	37.7
40-64	54,330 (43.3)	41.8
65+	18,768 (15.0)	20.5
Gender		
Female	66,918 (53.3)	51.7
Male	58,590 (46.7)	48.3
Race or ethnicity		
Asian or Pacific Islander	8,913 (7.1)	8.0
Black	12,513 (10.0)	11.2
Hispanic	17,835 (14.2)	15.5
Some other race	2,352 (1.9)	1.9
White	83,898 (66.8)	63.4
Education		
High school or lower	31,983 (25.5)	32.3
Some college	42,723 (34.0)	36.9
College and above	50,805 (40.5)	30.9
Income		
1st tercile (US $0-34,999)	42,048 (33.5)	20.3
2nd tercile (US $34,999-79,999)	44,655 (35.6)	35.5
3rd tercile (≥US $79,999)	38,808 (30.9)	44.2
State-level COVID-19 trend		
Early peak state	24,939 (19.9)	19.7
Late peak state	93,516 (74.7)	75.1
Low rate	6,663 (5.3)	5.2
Prescriptions		
0-3	47,076 (79.6)	79.4
≥4	12,090 (20.4)	20.6
Perceived as having contracted COVID-19		
Self	8,106 (6.5)	5.2
Family	10,080 (8.1)	7.5
Work	114,300 (15.1)	14.0
Other	105,369 (32.4)	32.0
Political party support		
Democrat	55,947 (44.6)	44.9
Independent	18,561 (14.8)	16.9
Republican	50,856 (40.6)	38.1
News from Facebook		
No	35,244 (28.1)	31.9
Yes	90,267 (71.9)	68.1
News sources		
0-2	31,254 (24.9)	25.9

Characteristics	Unweighted, n (%)	Weighted (%)
3-6	68,286 (54.4)	55.2
≥7	25,971 (20.7)	18.9

Results

The data included responses from 125,508 interviews conducted between March 19 and August 5, 2020, approved by the UCLA Institutional Review Board for analyses. Unless otherwise noted, all ORs presented were significant at $P<.001$, with 95% CIs presented.

COVID-19–Related Concerns

About 57.3% (unweighted: 69,556/122,798) of the respondents were "very" concerned (vs "somewhat," "a little," or "not at all" concerned) about COVID-19. Groups more likely to be *very concerned* about COVID-19 were those involving participants aged ≥65 years (OR 2.05, 95% CI 1.93-2.18 vs those aged 18-40 years); Asian or Pacific Islander (OR 1.48, 95% CI 1.38-1.59), Black (OR 1.33, 95% CI 1.25-1.42), or Hispanic participants (OR 1.29, 95% CI 1.22-1.36) versus White participants; participants with college education (OR 1.15, 95% CI 1.1-1.21 vs those with high-school education or lower); participants who took ≥4 medications (OR 1.47, 95% CI 1.40-1.54 vs those who took <3 medications); participants who thought they had contracted COVID-19 (OR 1.24, 95% CI 1.12-1.39 vs those who did not think they had contracted COVID-19); and participants who received news from ≥7 sources (OR 2.37, 95% CI 2.23-2.52 vs those who received news from 0-2 sources). Groups less likely to be *very concerned* about COVID-19 were men (OR 0.73, 95% CI 0.70-0.75 vs women), Independents (OR 0.54, 95% CI 0.51-0.57 vs Democrats), Republicans (OR 0.40, 95% CI 0.38-0.42 vs Democrats), and those who lived in later-peak states (OR 0.83, 95% CI 0.79-0.87 vs those who lived in early-peak states). More detailed results are available in Multimedia Appendix 5.

Precautionary Behaviors

The majority of individuals (>70%) reported engaging in precautionary behaviors, ranging from 71.9% (unweighted: 43,646/61,844) to 92.2% (unweighted: 56,820/61,987) depending on the specific behavior (Figure 1). For example, the following groups were more likely to wear a face mask (Figures 1 and 2 and Multimedia Appendix 5): older (≥65 years) individuals (OR 2.38, 95% CI 2.02-2.80 vs 18-40 years); Asian or Pacific Islander (OR 2.10, 95% CI 1.71-2.58), Black (OR 1.22, 95% CI 1.03-1.44), and Hispanic participants (OR 1.87, 95% CI 1.60-2.20) versus White participants; those taking ≥4 medications (OR 1.36, 95% CI 1.20-1.55 vs <4 medications); those receiving political news from a greater number (≥7) of sources (OR 2.06, 95% CI 1.75-2.43 vs ≤2 sources), and those with household incomes over US $80,000 annually (OR 1.51, 95% CI 1.31-1.71 vs those with incomes less than $40,000 annually).

The following groups were less likely to wear a mask: men (OR 0.74, 95% CI 0.67-0.81] vs women); people who believe they have had COVID-19 (OR 0.65, 95% CI 0.52-0.81 vs those who do not believe so); participants in late-peak states (OR 0.64, 95% CI 0.55-0.73 vs those in early-peak states); Independents (OR 0.50, 95% CI 0.43-0.57 vs Democrats); or Republicans (OR 0.45, 95% CI 0.40-0.50 vs Democrats).

Figure 1. Percentage of the sample population that has undertaken precautions and will return to activities.

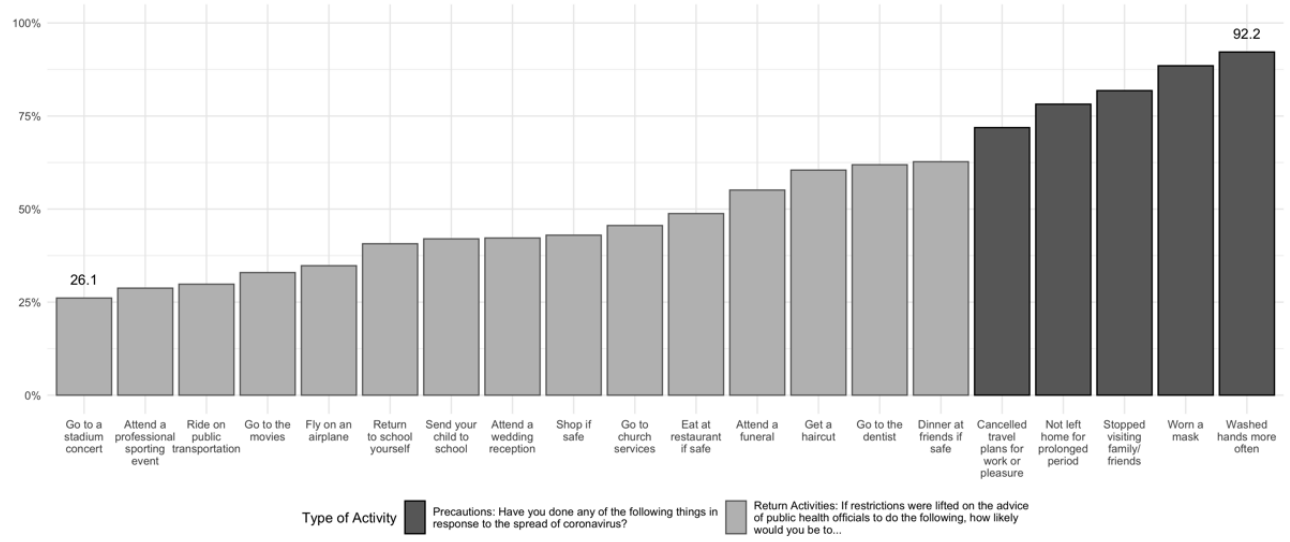
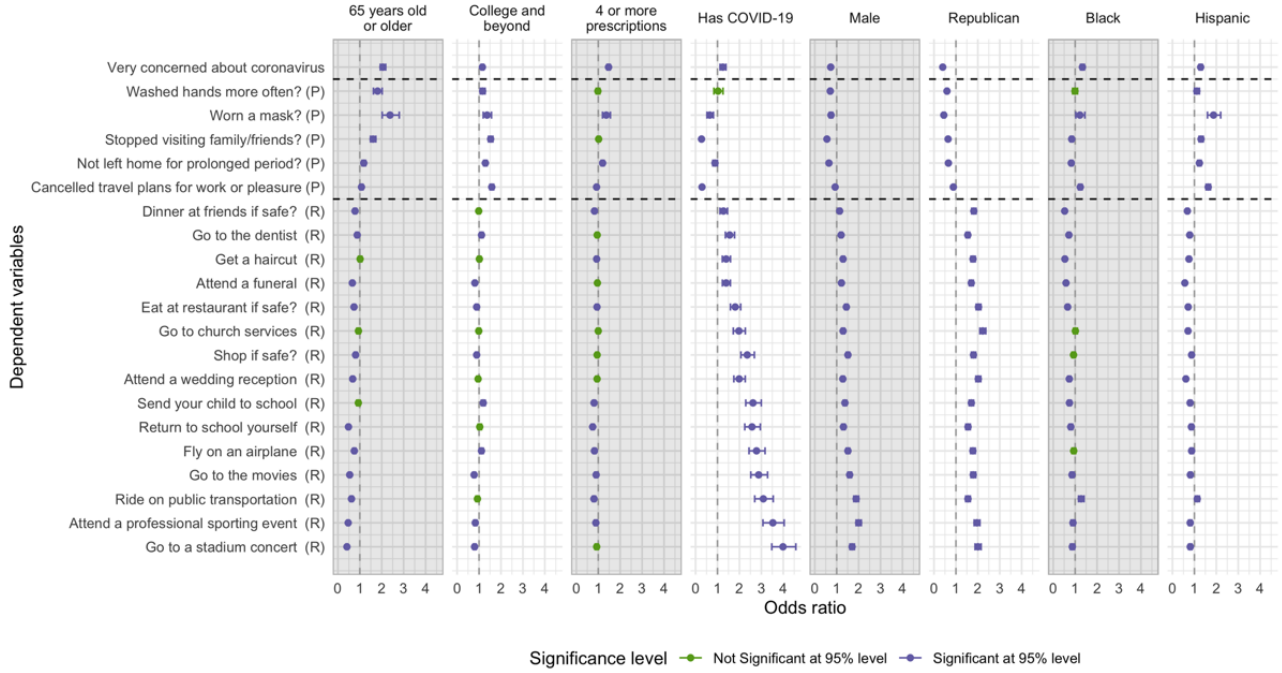


Figure 2. Key predictors of COVID-19–related concerns, taking precautions, and returning to activities. Results control for variables in Multimedia Appendix 4. Unless noted, all controls are at median values. For dependent variables (y-axis), "P" indicates "precaution" and "R" indicates "return activity." Sample size and date range vary by model, see Multimedia Appendix 5 for details. Data are from The Democracy Fund + UCLA Nationscape Project [31].



Willingness to Return to Activities

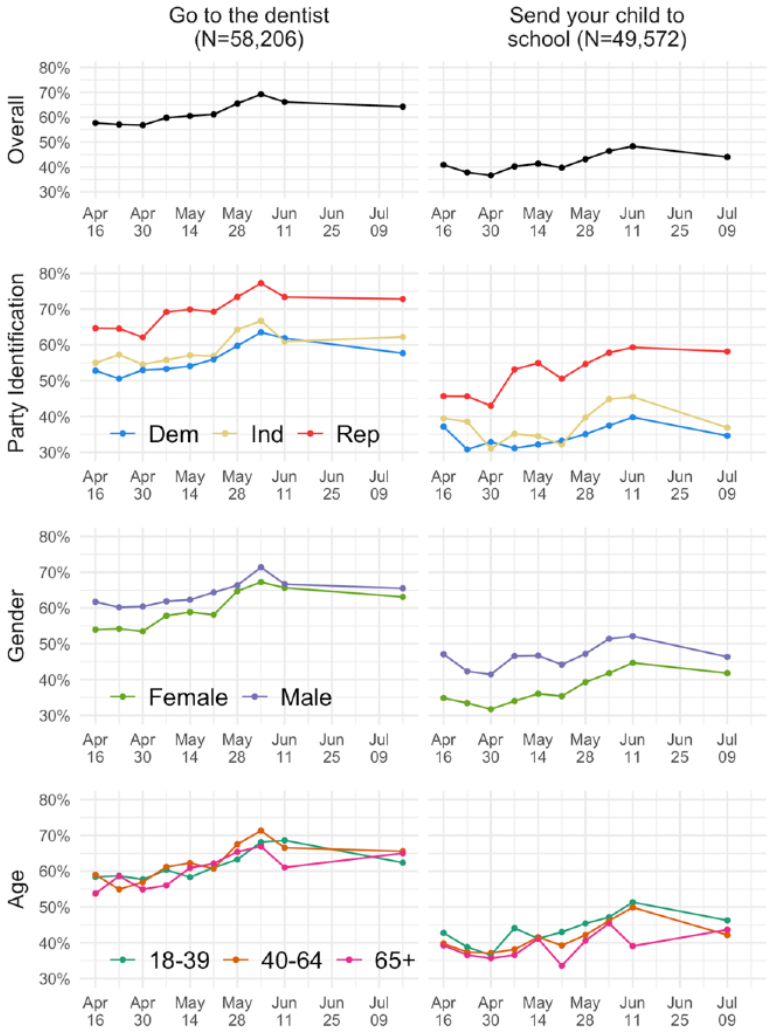
A large number of participants would not be willing to return to activities they engaged in before COVID, ranging from 26.1% (unweighted: 15,082/51,773) to 62.7% (unweighted: 37,471/58,504), even after the restrictions are lifted and public health officials declare it is safe to return to such activities (Figure 1). The following groups tended to be less likely to report willingness to return to activities across the board (Figures 1 and 2 and Multimedia Appendix 5): older (≥65 years) individuals (OR 0.41, 95% CI 0.37-0.46 to OR 0.93, 95% CI 0.88-0.98 vs 18-40 years); Asian or Pacific Islander (OR 0.52, 95% CI 0.46-0.59 to OR 0.88, 95% CI 0.80-0.96); Black (OR 0.52, 95% CI 0.48-0.57 to OR 0.90, 95% CI 0.81-1.0), and Hispanic participants (OR 0.56, 95% CI 0.53-0.61 to OR 0.87, 95% CI 0.81-0.95) compared with White participants, except in the use of public transportation among Black participants (OR 1.27, 95% CI 1.16-1.40 vs White participants) and Hispanic participants (OR 1.13, 95% CI 1.04-1.23; $P<.01$ vs White participants); and those taking 4 or more medications (OR 0.75, 95% CI 0.69-0.81 to OR 0.94, 95% CI 0.89-1.00 vs those taking <4 medications).

Respondents who were more likely to report willingness to return to activities included those who believe they had contracted COVID-19 (OR 1.27, 95% CI 1.11-1.45 to OR 3.99, 95% CI 3.48-4.58 vs those who believe they did not); men (OR 1.13, 95% CI 1.08-1.19 to OR 2.00, 95% CI 1.88-2.12 vs women); and Republicans (OR 1.55, 95% CI 1.46-1.63 to OR 2.22, 95% CI 2.09-2.36 vs Democrats). Those who are highly educated (college education or beyond) were significantly less likely to consider participating in activities such as going to the movies, concert, or sporting event (OR 0.77, 95% CI 0.72-0.83 to OR 0.83, 95% CI 0.76-0.90 vs those who have less than or up to high school–level education), but they were more likely to send their children to school (OR 1.19, 95% CI 1.11-1.28), visit a dentist (OR 1.11, 95% CI 1.04-1.19), or travel by air (OR 1.11, 95% CI 1.03-1.19).

Longitudinal Analysis

We conducted a series of weighted difference-in-means tests assessing whether the trends illustrated in Figure 3 changed over time. Specifically, we compared the percentage from the survey wave of April 16, 2020, to that from the survey wave of June 11, 2020. This was the final wave where all outcome variables were collected. These tests were run both for the overall trends for going to the dentist and sending your child to school as well as for each of the subgroups presented in Figure 3. The trends were found to be generally statistically significant (see longitudinal analysis results shown in Multimedia Appendix 3). More people were willing to return to these activities every week between April and June 2020. In June and July, however, the increases generally tapered off, as shown in Figure 3. The rate of increases was similar across gender and age groups, although there was a more pronounced separation noted between Democrats (who were less willing) and Republicans (who were more willing) in July than in April, suggesting a slower rate of increase to return to activities for Democrats, particularly with respect to sending a child to school.

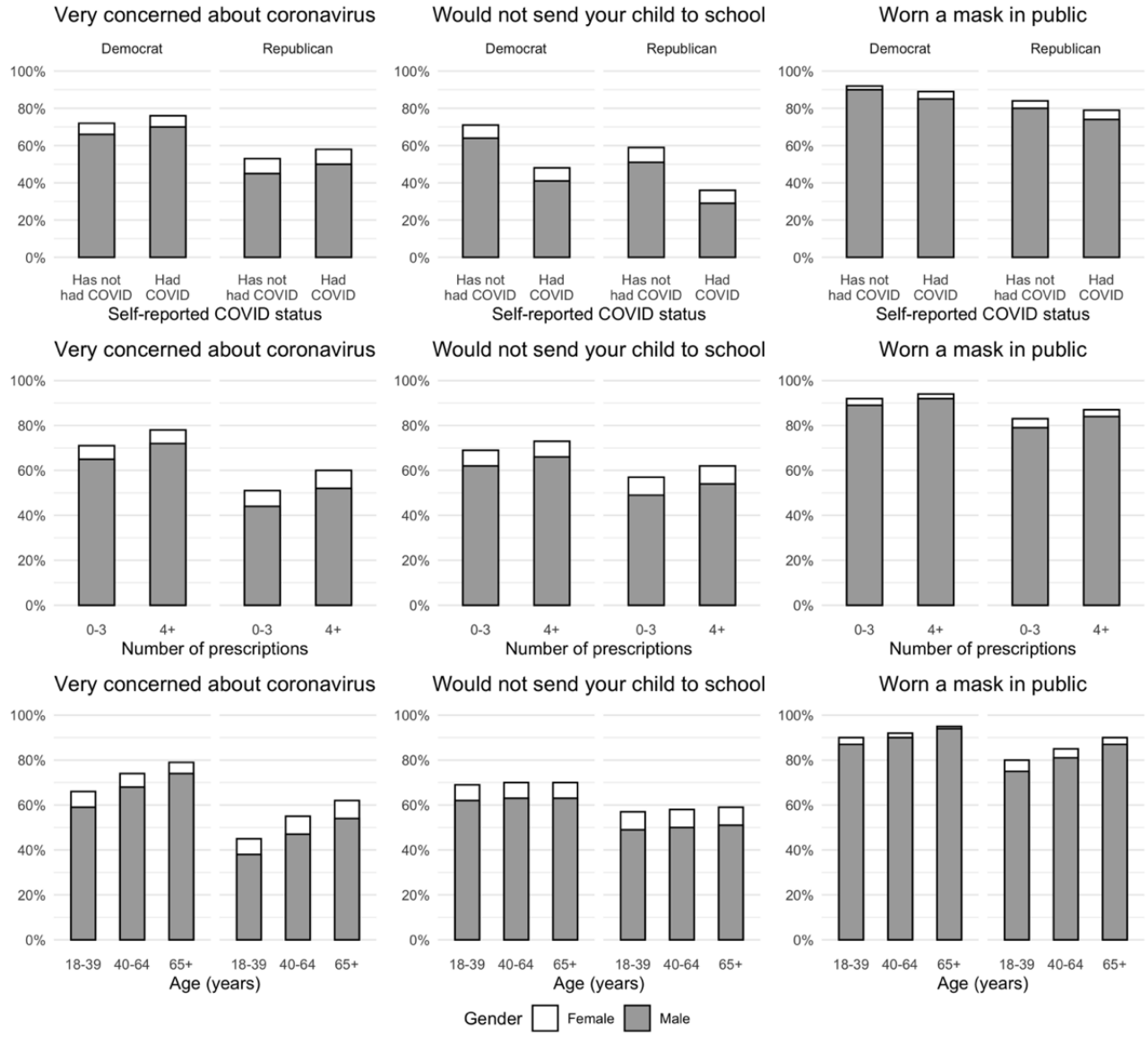
Figure 3. Longitudinal data for two recovery behaviors (going to the dentist and sending your child to school) overall and by political party affiliation, gender, and age.



Predicted Probabilities for Specific Groups

Several patterns appeared in these analyses. The most concerned group of people were older adults, women, Democrats (with an 80% chance of being concerned), as shown in Figure 4. To understand how age, gender, and political party affiliation come together to shape a person's orientation toward COVID-19, we compared this group to younger, Republican men, whose chances of being concerned about COVID-19 were found to be the lowest, just under 40%. A similar pattern was observed for sending a child to school and for wearing a mask. Democratic women who took 4 or more medications were 30 points more likely to keep their child home and not send them to school than Republican men who took fewer medications. Similarly, Republicans who thought they have had COVID-19 were 30 points less likely to wear a mask in public than Democrats who did not think they had contracted the infection.

Figure 4. Predicted probabilities of outcomes for key groups.



Discussion

The data from our analyses provide considerable evidence that the majority of Americans have rapidly adopted new preventive behaviors in the face of the deadly COVID-19 pandemic. On average, more than 8 in 10 report wearing a mask outside (unweighted: 70,802/80,624), and most have avoided meeting family and cancelled travel plans. In addition, these data shed light on the challenges that cities and states face as society reopens. Even after public health officials declare activities to be safe to engage in, more than half the survey respondents reported that they will not send a child to school or travel by air, and only 61.9% will visit a dentist (unweighted: 36,540 /58,206). It is unclear whether projected caution is related to the inconsistent messaging or the source of information requires greater exploration than we can provide here and needs to be further evaluated. This may also be related to public uncertainty and trust in the messenger or the message itself [34]. There is significant politicization that casts doubt on public health warnings and in the accuracy of statements from public officials in the recommendations associated with preventive behaviors and how to ramp-up the economy [35,36]. Politicization of COVID-19 preventive behaviors is not limited to the United States, but it is also observed in other countries such as the United Kingdom and Brazil [37,38]. Confusion and mixed messaging (alongside variations in protocols implemented by 50 state governors) calls on the physician to provide guidance that is based on science and perceived as trustworthy by patients [39,40].

Despite the generally high rates of reported precautionary behaviors, the 10%-20% nonadherence rate may exceed the thresholds needed to quell the virus spread [13,41-43]. It is also noteworthy that these rates are likely high estimates because our survey questions asked about whether the behavior was practiced at all, but not how often or how consistently. It should alarm health care providers that small, but possibly substantial, groups of patients are not following public health rules (which may have limited evidence-based data), suggesting that behavioral intention concerning the contagion should be explored with patients. Several studies have shown that level of concern and risk perception is linked to adoption of precautionary behaviors [44-46], which is augmented by varying

infection fatality rates [47]. Reinforcing preventive messages is particularly needed for patients who have recovered from COVID-19 infection. Such individuals are less likely to engage in precautionary behaviors, which may be the reason they contracted the virus. It is likely, however, that recovered patients also have developed some immunity against reinfection. This demonstrates the risk of inadequate testing, false-positive serological testing, and assumptions around T-cell immunity in creating a false sense of security that in turn encourages permissive behavior [48-50].

The analyses identified clear patterns in the levels of concern, precautionary behaviors, and willingness to resume activities after the restrictions are lifted. Despite controlling for all other factors, party affiliation was a significant factor for being *very concerned* about COVID-19, engaging in preventive measures, and returning to activities, to an extent not observed in other major disease outbreaks or prior pandemics [51-55]. The group most likely to be concerned about COVID-19 (ie, older adults, female participants, and Democrats) was also more likely to engage in preventive behaviors and less willing to resume activities. A second group (ie, younger adults, male participants, less well-educated participants, and Republicans) reported lower levels of concern about COVID-19, were less likely to report precautionary behaviors, and more willing to return to activities. Previous studies have suggested that people trust medical experts more than political leaders [56,57]. However, it would be short-sighted to neglect how the lens of political party affiliation informs attitudes and how patients process information given the prior evidence that political party influences health domains such as obesity, end-of-life management, and vaccine adoption [58]. Our findings are consistent with those of other studies that highlight the political polarization of preventive health behavior with regard to COVID-19 and in general [21,28,59,60].

This study's limitations deserve mention. First, this study focused primarily on readily observable factors. However, such factors (eg, gender) are not explanatory by themselves. Relatedly, most health behaviors involve multiple determinants, and the determinants evince substantial interindividual variability. Reliable mask-wearing might result from concern for others' health, risk aversion, respect for the relevant science, high motivation to comply with rules, among other factors. Evidence for the malleability of risk perceptions, prosocial motivation, and other contributors to health-promoting behaviors point toward promising targets for change [61-64]. Our research group and others [65] are working to identify such malleable targets. The present survey did not collect data on occupation and work-related subsidies. Second, the cross-sectional nature of the data does not allow for definitive interpretation of findings regarding across-time stability and change; however, the sampling strategy and large sample lend confidence to the findings. Third, measures of precautionary behaviors were author-constructed in a way that may overestimate their extent. Fourth, the questions about COVID-19 status did not differentiate between those individuals who had symptoms versus a confirmed laboratory test, yet the construct of believing that one has had COVID-19 is clinically relevant. Finally, in this study, we could not compare the sample population to an international sample to analyze the effect of the prosperity of a country or differences in national health care insurance plans [66,67].

Health care providers have a significant role to play both in managing the pandemic and ensuring adherence to prevention and recovery behaviors. This implies not only making masks mandatory in clinical settings but also strongly counseling patients to wear face coverings [68] in high-risk environments and avoiding high-risk activities. For providers and public health officials to serve as facilitators, they need to understand the attitudes and perceptions of their patients and tailor messages to move them toward both prevention and recovery. This is critical because recovery represents a set of behaviors that impact not just economic health but also the personal health of patients, many of whom have also been deferring the care of their chronic medical illnesses as well as routine but important health maintenance and prevention. Future studies need to develop and test targeted messaging approaches, including those with respect to political party, to encourage preventative behaviors and willingness to return to activities.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist.
[PDF File (Adobe PDF File), 45 KB - publichealth_v7i4e24277_app1.pdf]

Multimedia Appendix 2
Representativeness table.

[PDF File (Adobe PDF File), 107 KB - publichealth_v7i4e24277_app2.pdf]

Multimedia Appendix 3
Longitudinal analysis of data shown in Figure 2: Difference in means over time for willingness to send children to school and visit the dentist.
[PDF File (Adobe PDF File), 75 KB - publichealth_v7i4e24277_app3.pdf]

Multimedia Appendix 4
Median values for regression analysis.
[PDF File (Adobe PDF File), 123 KB - publichealth_v7i4e24277_app4.pdf]

Multimedia Appendix 5
Regression tables.
[PDF File (Adobe PDF File), 87 KB - publichealth_v7i4e24277_app5.pdf]

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Abbreviations

OR: odds ratio
UCLA: University of California, Los Angeles

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Original Paper

Surveillance of the Second Wave of COVID-19 in Europe: Longitudinal Trend Analyses

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Abstract

Background: The COVID-19 pandemic has severely impacted Europe, resulting in a high caseload and deaths that varied by country. The second wave of the COVID-19 pandemic has breached the borders of Europe. Public health surveillance is necessary to inform policy and guide leaders.

Objective: This study aimed to provide advanced surveillance metrics for COVID-19 transmission that account for weekly shifts in the pandemic, speed, acceleration, jerk, and persistence, to better understand countries at risk for explosive growth and those that are managing the pandemic effectively.

Methods: We performed a longitudinal trend analysis and extracted 62 days of COVID-19 data from public health registries. We used an empirical difference equation to measure the daily number of cases in Europe as a function of the prior number of cases, the level of testing, and weekly shift variables based on a dynamic panel model that was estimated using the generalized method of moments approach by implementing the Arellano-Bond estimator in R.

Results: New COVID-19 cases slightly decreased from 158,741 (week 1, January 4-10, 2021) to 152,064 (week 2, January 11-17, 2021), and cumulative cases increased from 22,507,271 (week 1) to 23,890,761 (week 2), with a weekly increase of 1,383,490 between January 10 and January 17. France, Germany, Italy, Spain, and the United Kingdom had the largest 7-day moving averages for new cases during week 1. During week 2, the 7-day moving average for France and Spain increased. From week 1 to week 2, the speed decreased (37.72 to 33.02 per 100,000), acceleration decreased (0.39 to –0.16 per 100,000), and jerk increased (–1.30 to 1.37 per 100,000).

Conclusions: The United Kingdom, Spain, and Portugal, in particular, are at risk for a rapid expansion in COVID-19 transmission. An examination of the European region suggests that there was a decrease in the COVID-19 caseload between January 4 and January 17, 2021. Unfortunately, the rates of jerk, which were negative for Europe at the beginning of the month, reversed course and became positive, despite decreases in speed and acceleration. Finally, the 7-day persistence rate was higher during week 2 than during week 1. These measures indicate that the second wave of the pandemic may be subsiding, but some countries remain at risk for new outbreaks and increased transmission in the absence of rapid policy responses.

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KEYWORDS

SARS-CoV-2 surveillance; wave two; second wave; global COVID surveillance; Europe Public Health Surveillance; Europe COVID; Europe surveillance metrics; dynamic panel data; generalized method of the moments; Europe econometrics; Europe SARS-CoV-2; Europe COVID surveillance system; European COVID transmission speed; European COVID transmission acceleration; COVID transmission deceleration; COVID transmission jerk; COVID 7-day lag; SARS-CoV-2; Arellano-Bond estimator; GMM; Albania; Andorra; Austria; Belarus; Belgium; Bosnia and Herzegovina; Bulgaria; Croatia; Czech Republic; Denmark; Estonia; Finland; France; Germany; Greece; Greenland; Hungary; Iceland; Ireland; Isle of Man; Italy; Latvia; Liechtenstein; Lithuania; Luxembourg; Moldova; Monaco; Montenegro; Netherlands; Norway; Poland; Portugal; Romania; San Marino; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Ukraine; United Kingdom; Vatican City

Introduction

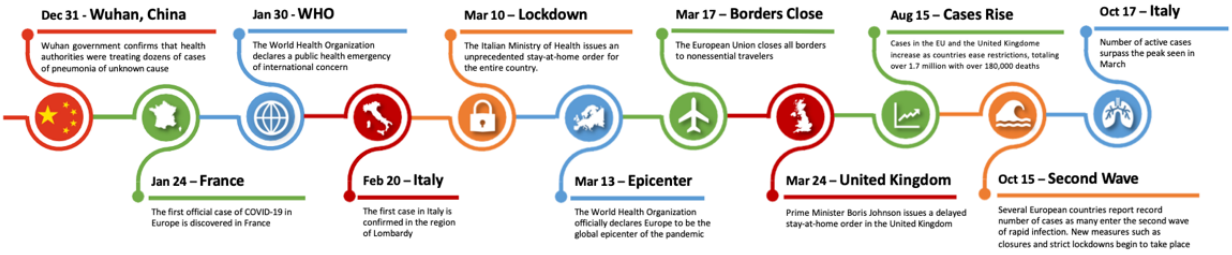
Background

The first European COVID-19 case was reported on January 24, 2020, in France, with subsequent cases confirmed in Germany and Finland days later [1]. On March 11, 2020, the World Health Organization (WHO) declared that the spread of the novel coronavirus had exceeded the threshold of a pandemic [2] and, on March 13, 2020, the WHO declared Europe as the global epicenter, when their caseload and deaths exceeded the combined caseload in the rest of the world [1] (See Figure 1). The European Union (EU) closed all external borders on March 17, 2020 [1]. Although the EU coordinated the COVID-19 response between member countries, individual governments enacted separate national policies and made individual decisions regarding border closure and quarantine measures [3]. COVID-19 caseloads decreased for most European countries after peaking in April and May [4].

At present, European countries are experiencing a second wave of COVID-19 [5-11]. The WHO has warned that the death counts in Europe could surpass the peak observed in April 2020 [12]. Nations worldwide are struggling to control COVID-19 transmission by imposing social isolation and economic restrictions, with leaders reluctant to shut down businesses and quarantine citizens again [13,14]. As of February 9, 2021, the WHO reported 106,125,682 confirmed COVID-19 cases and 2,320,497 deaths worldwide [15]. Collectively, 33,534,153 COVID-19 cases have been reported in the EU and the United Kingdom, which have resulted in 740,733 deaths [4].

The World Bank (WB), a global partnership dedicated to reducing poverty and increasing sustainable prosperity in developing nations, divides the world into regions based on shared geographical, development, and cultural or historical features [16]. The Global SARS-CoV-2 Surveillance Project: Policy, Persistence, & Transmission provides surveillance data [17] based on these WB-defined regions. The focus of this study is on the spread of COVID-19 specifically within the Western European region, including Albania, Andorra, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Greenland, Hungary, Iceland, Ireland, Isle of Man, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Moldova, Monaco, Montenegro, the Netherlands, Norway, Poland, Portugal, Romania, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, the United Kingdom, and Vatican City.

Figure 1. Timeline of COVID-19–related events and decisions made (2020). EU: European Union; WHO: World Health Organization.



Outbreak and Governance

Policies and Culture

Analysis of COVID-19 cumulative incidence indicates that the drastic measures undertaken by the Italian government slowed the spread of the disease to lower than the expected 7-10 days after restrictions were implemented [18]. The rapid transmission was likely due to high population density [19], and the high case-fatality rate is associated with the older age distribution in Italy, wherein approximately 23% of the Italian population was aged 65 years or older in 2019 [20].

Other factors that influenced the severity of the COVID-19 were family structures, which likely increased interaction among family members [21]. Additionally, Southern European countries engage in physical greetings, with kisses on the cheek and friendly hugs being common in Italy, Spain, and France [22]. These cultural practices may be a contributing factor to the increased transmission of COVID-19 and related mortality in the Southern European countries listed above, where the virus spread very rapidly and yielded severe adverse effects [23].

In contrast, in Northern European countries such as Sweden, children tend to leave home earlier and frequently move farther away from their parents, often to pursue higher education. A “post-nuclear family structure” has developed more rapidly, and children in these countries may have less frequent contact with their families from an earlier age than those in the more traditional Southern European countries [21]. Additionally,

personal space is valued to a higher degree, and kissing is less commonly used as a greeting compared to shaking hands or other less physical forms of greeting [24]. Sweden enacted less strict policies than Southern European countries did and saw similar results as countries that enacted late-onset stringent mandates [25]. It is worth noting that Sweden's per capita COVID-19 death rate far outpaces that of its Scandinavian neighbors, decreasing confidence in their mitigation strategies [26]. At the other extreme lie countries such as Hungary, where the Prime Minister pushed through legislation that allowed him to rule by decree for however long the pandemic continues and mandates jail time for the spread of disinformation, leading to concerns about restrictions on human rights and media freedoms [27].

The United Kingdom, physically and organizationally separated from its European neighbors since leaving the European Union, took a delayed and somewhat hesitant approach to controlling the spread of the virus. The first two COVID-19 cases in the nation were confirmed on January 31, 2020. The Department of Health and Social Care's coronavirus action plan was approved on March 3, 2020, outlining the country's plan to deploy four phased actions to deal with the pandemic: Contain, Delay, Research, and Mitigate [28]. The government moved from the Contain phase to the Delay phase on March 12, 2020, after Italy had already locked down, and emphasized testing in hospital settings and not communities, with unrestricted entry to the country via ports and airports [28]. On March 19, 2020, COVID-19 was reclassified from level 4 to a milder threat level (ie, level 3) by the Advisory Committee on Dangerous Pathogens, allowing hospital infection control requirements to be lowered [28]. Finally, on March 24, 2020, the Prime Minister declared an enforceable lockdown across the nation [28], but COVID-19 spread rapidly throughout the United Kingdom, leading Europe in COVID-19–related deaths at over 43,579 [4]. Many European countries are experiencing a second wave of infections, with surging daily case numbers in France, Spain, the Netherlands, and the United Kingdom, and the WHO warning that, within the coming months, daily death counts could surpass the April peak observed in Europe [12]. National governments are struggling to control the infection due to increased pushback from local governments who are reluctant to shut down businesses and quarantine citizens a second time after being allowed to open up [13].

Economics and Food Insecurity

An important impact of the pandemic is the risk of food insecurity in vulnerable nations such as Ukraine and Moldova [29]. Much of the population in Ukraine lacks the ability to buy a sufficient amount of healthy food and often resides in conflict-affected areas of the country. Moreover, the current pandemic threatens to impact Ukraine's wheat exportation and livestock processing, which could create even more scarcity in affordable food for its citizens [30,31]. Ukraine responded with early restrictive policies in response to widespread fear among citizens, and the country ended up reporting fewer cases than Russia and Belarus, indicating that its response was most likely effective in slowing disease transmission [32]. However, economic growth in Ukraine was stable at 3.2% in 2019, but the pandemic has forced a sudden slowdown in economic activity; the future of the economy will be dependent on the country's ability to support investment and diversify exports after the pandemic subsides [33].

Economic growth in Moldova had already declined sharply to 0.2% in late 2019, and the unemployment rate saw an increase compared to 2018 [33]. Many citizens of Moldova rely heavily on food self-provisioning or food sharing within village networks [34]. Poverty is expected to increase in response to the COVID-19 pandemic, and the effects will likely impact households with inadequate insurance mechanisms. The maintenance of food security and economic stability will depend on the government's ability to alleviate food shortages and compensate for lost income, as well as to support jobs and growth when the crisis subsides [33].

Surveillance

Public health surveillance informs policy on "flattening the curve" of COVID-19 spread [17,35-37]. Epidemiologists have utilized various modeling techniques to forecast COVID-19 case numbers and attributed deaths [38-42]. The European Center for Disease Control, the WHO, and the Center for Systems Science and Engineering at Johns Hopkins University have developed tracking tools [11,38]. Although helpful, these static metrics are limited by incomplete case ascertainment and data contamination [17,36]. Existing surveillance is a proxy for the true COVID-19 caseload because public health surveillance systems tend to pick up the most severe cases [43,44], which is especially problematic when tracking SARS-CoV-2 infections because most carriers are asymptomatic or presymptomatic or may have mild symptoms [45-48]. Therefore, public health surveillance that can control for these limitations are needed. Moreover, metrics that detect the speed of transmission of the novel coronavirus, shifts in the pandemic, and acceleration of the speed and persistence of COVID-19 based on prior infections are needed to supplement existing measures.

Significance

Ideally, the development of a more advanced methodology for tracking and estimating COVID-19 transmission in regions within Europe will allow for a more reliable analysis of which policies are effective and what other factors may be associated with transmission rates. Public health departments, in addition to several universities and media outlets, are tracking COVID-19 metrics by using raw data, including the number of new cases, diagnostic tests, positive results, transmission rates and deaths, in addition to other measures such as local hospital capacity [4,49-57]. To remove temporal effects, many surveillance systems have shifted to 7-day moving averages to counter the dearth of reporting during holidays and weekends. Although moving averages temper volatility of data and testing or reporting affects, surveillance is still limited by missing cases. General public health surveillance is helpful and provides a proxy of the pandemic, but surveillance data are still limited by significant bias due to undercounts, reporting delays, testing errors, dearth of testing, asymptomatic carriers, and other types of data contamination. In fact, surveillance systems are predicated on the fact that they tend to include only the more severe cases, whereas mild cases and undiagnosed infections and deaths are excluded [43,44].

To that end, the objective of our study is to use a longitudinal trend analysis study design in concert with *Dynamic Panel Modeling* and *Method of Moments* to correct for existing surveillance data limitations [17,36]. Specifically, we will measure significant weekly shifts in the increase, decrease, or plateaued transmission of COVID-19. We will also measure the underlying causal effect from the previous week that persists through the current week, with a 7-day persistence rate to explain a clustering-declustering effect. The 7-day persistence represents an underlying disease transmission wave, wherein a large number of transmissions 7 days ago that resulted in a large number of infections today then *echoes* forward into a large number of new transmissions and, hence, a large number of new cases 7 days forward. An example of the 7-day lag would be large sporting events in the United Kingdom that drew huge crowds weekend after weekend even after new COVID-19 cases were confirmed in the country. Other potential "superspreader" events such as the exportation of COVID-19 cases from a popular ski town in the Austrian Alps back in March 2020 [58], would certainly contribute to this persistence effect as well. In summary, we will measure negative and positive shifts in the transmission of SARS-CoV-2 or the acceleration or deceleration rates. Our surveillance metric will provide public health surveillance data to inform governments in decision-making regarding disease control, mitigation strategies, and reopening policies as they continue to manage this unprecedented situation.

Methods

Our World in Data [59] compiles data from multiple sources on the web. Data for the most recent 7 weeks were accessed from the GitHub repository [60]. This resulted in a panel of 39 countries in Western Europe with 62 days in each panel (n=2418). Based on published reports [16,61], an empirical difference equation was specified in which the number of new positive cases in each country at each day is a function of the prior number of cases, the level of testing, and weekly shift variables that measure whether the contagion was growing faster, at the same speed, or slower than in the previous weeks. This resulted in a dynamic panel model that was estimated using the generalized method of moments (GMM) approach by implementing the Arellano-Bond estimator in R [17,36].

Results

Country Regression Results

Regression results are presented for 39 European countries in Table 1. Weekly surveillance data presented in Tables 2-6 are based in part on these regressions. Data for 44 European countries were collected, but data for 5 countries were excluded in the regression analysis due to missing data. The regression Wald statistic is significant (X^2_8=4980; P<.001). The Sargan test was not significant, failing to reject the validity of overidentifying restrictions (X^2_{511}=39; P=.39).

The coefficient for the 7-day lag was positive and statistically significant (0.90, P<.001), indicating the number of infections 7 days prior to the study had a positive relationship that echoed forward 7 days later. The shift parameter 14 days ago was negative and statistically significant (coefficient –0.30, P<.001), suggesting that exogenous shift events had a negative effect on total case numbers (Table 1).

Table 1. Arellano-Bond dynamic panel data model of COVID-19 dynamics at the country level in Europe.

Variable	Coefficient	*P* value
7-day lag	0.90	<.001
Cumulative tests	–0.000	.42
7-day lag shift	–0.30	<.001
Weekend	–2.1	.02

Table 2. Static surveillance metrics for European countries for the week of January 4-10, 2021.

Country	New weekly COVID-19 cases	Cumulative COVID-19 cases	7-day moving average of new COVID-19 cases	Infection rate per 100,000 population	New weekly deaths	Cumulative deaths due to COVID-19	7-day moving average of new COVID-19–related deaths	Deaths rate per 100,000 population
Albania	562	63,595	593.86	19.53	8	1241	6.86	0.28
Andorra	0	8586	56.29	0.00	0	85	0.14	0
Austria	1651	380,722	2136.29	18.33	36	6723	57	0.40
Belarus	1833	212,201	1748.43	19.40	10	1517	9.43	0.11
Belgium	1569	664,263	2036	13.54	40	20,078	53.86	0.35
Bosnia & Herzegovina	254	115,633	426.86	7.74	25	4330	28.43	0.76
Bulgaria	105	208,511	780	1.51	29	8126	64	0.42
Croatia	646	219,993	1005	15.74	26	4368	42.29	0.63
Czech Republic	8449	831,165	12,954.86	78.90	137	13,115	165	1.28
Denmark	1246	182,161	1829	21.51	28	1571	28.14	0.48
Estonia	427	33,516	626.43	32.19	5	283	5.57	0.38
Finland	198	38,590	259.71	3.57	0	586	3.57	0
France	159,44	2,840,864	18,269.86	24.43	151	67,885	388.71	0.23
Germany	948	1,929,410	20,787.71	1.13	339	40,936	877.86	0.40
Greece	445	144,738	662.71	4.27	36	5263	43.71	0.35
Hungary	1778	342,237	2034.57	18.41	94	10,648	109.14	0.97
Iceland	10	5890	19.43	2.93	0	35	0	0
Ireland	6886	147,613	6532.29	139.46	8	2344	12.14	0.16
Italy	18,625	2,276,491	17,292.14	30.80	361	78,755	489.00	0.60
Latvia	616	49,568	1010.14	32.66	31	849	24.14	1.64
Lithuania	1492	159,672	1862.14	54.81	26	2197	79.14	0.96
Luxembourg	0,	47,744	189.86	0.00	0	527	4.57	0.00
Malta	184	14,396	187.71	41.67	1	233	1.86	0.23
Moldova	298	149,391	502.57	7.39	9	3139	14.57	0.22
Netherlands	6655	885,098	7485.14	38.84	55	12,461	107.71	0.32
Norway	555	55,474	679.71	10.24	0	472	5.14	0
Poland	9133	1,385,522	9565.71	24.13	178	31,189	295.71	0.47
Portugal	7502	483,689	8062.14	73.57	102	7803	97.86	1.00
Romania	3082	671,284	4407.86	16.02	62	16,654	96.43	0.32
San Marino	0	2628	28.57	0.00	0	64	0.71	0
Serbia	3564	359,689	2259.86	40.79	69	3582	36.71	0.79
Slovakia	2973	208,209	2963.71	54.45	82	2919	85.86	1.50
Slovenia	763	139,281	2027.86	36.70	25	2998	27.86	1.20
Spain	0	2,050,360	17,442.14	0	0	51,874	148.14	0
Sweden	0	489,471	7441.71	0	0	9433	100.86	0.00
Switzerland	0	477,983	3669.57	0	14	8267	74.29	0.16
Ukraine	5322	1,150,265	6161.14	12.17	115	20,641	144.43	0.26
United Kingdom	55,026	3,081,368	59,809.86	81.06	567	81,567	918.57	0.84
Europe	158,741	22,507,271	208,581.43	26.52	2669	524,758	4649.43	0.45

Table 3. Static surveillance metrics for European countries for the week of January 11-17, 2021.

Country	New weekly COVID-19 cases	Cumulative COVID-19 cases	7-day moving average of new COVID-19 cases	Infection rate per 100,000 population	New weekly deaths	Cumulative deaths due to COVID-10	7-day moving average of new COVID-19–related deaths	Deaths rate per 100,000 population
Albania	474	67,690	585	16.47	7	1277	5.14	0.24
Andorra	45	9083	71	58.24	0	91	0.86	0
Austria	1267	393,778	1865.14	14.07	29	7082	51.29	0.32
Belarus	1924	22,5461	1894.29	20.36	9	1582	9.29	0.10
Belgium	1630	678,839	2082.29	14.06	39	20,435	51	0.34
Bosnia & Herzegovina	0	11,7011	196.86	0	0	4411	11.57	0
Bulgaria	77	211,813	471.71	1.11	9	8483	51	0.13
Croatia	379	224,954	708.71	9.23	28	4616	35.43	0.68
Czech Republic	5253	889,159	8284.86	49.05	123	14,338	174.71	1.15
Denmark	889	189,767	1086.57	15.35	28	1776	29.29	0.48
Estonia	388	37,079	509	29.25	5	325	6	0.38
Finland	236	40,337	249.57	4.26	0	618	4.57	0
France	37,405	2,969,091	18,318.14	57.31	329	70,422	362.43	0.50
Germany	11,484	2,050,129	17,245.57	13.71	437	46,901	852.14	0.52
Greece	237	148,607	552.71	2.27	28	5469	29.43	0.27
Hungary	1241	351,828	1370.14	12.85	77	11,341	99	0.80
Iceland	0	5956	9.43	0	0	35	0	0
Ireland	2946	172,726	3587.57	59.66	13	2608	37.71	0.26
Italy	125,44	2,381,277	14,969.43	20.75	377	82,177	488.86	0.62
Latvia	567	55,664	870.86	30.06	17	978	18.43	0.90
Lithuania	836	167,516	1120.57	30.71	31	2445	35.43	1.14
Luxembourg	0	48,630	126.57	0	0	549	3.14	0
Malta	141	15,588	170.29	31.93	1	239	0.86	0.23
Moldova	214	152,854	494.71	5.30	5	3250	15.86	0.12
Netherlands	5643	925,355	5751	32.93	41	13,107	92.29	0.24
Norway	206	58,651	453.86	3.80	0	517	6.43	0.00
Poland	5970	1,435,582	7151.43	15.77	142	33,355	309.43	0.38
Portugal	10,385	549,801	9444.57	101.85	152	8861	151.14	1.49
Romania	2156	693,644	3194.29	11.21	57	17,221	81	0.30
San Marino	0	2778	21.43	0	0	65	0.14	0
Serbia	1317	372,533	1834.86	15.07	20	3750	24	0.23
Slovakia	573	223,325	2159.43	10.50	57	3475	79.43	1.04
Slovenia	569	149,125	1406.29	27.37	40	3180	26	1.92
Spain	0	2,252,164	28,829.14	0	0	53,314	205.71	0
Sweden	0	523,486	4859.29	0	0	10,323	127.14	0
Switzerland	0	495,228	2463.57	0	7	8682	59.29	0.08
Ukraine	6398	1,198,512	6892.43	14.63	130	21,767	160.86	0.30
United Kingdom	38,670	3,405,740	46,338.86	56.96	682	89,429	1123.14	1
Europe	152,064	23,890,761	17,7288	25.40	2920	558,494	4819.43	0.49

Table 4. Novel surveillance metrics for European countries for the week of January 4-10, 2021.

Country	Speed[a] (weekly average of new daily cases per 100,000 population)	Acceleration[b] (weekly average, per 100,000 population)	Jerk[c] (per 100,000 population)	7-day persistence effect on speed (number of new daily cases per 100,000 population attributed to new cases 7 days ago)
Albania	20.64	0.57	0.67	9.48
Andorra	72.85	–4.81	–13.68	41.13
Austria	23.72	0.29	–1.11	13.20
Belarus	18.50	–604,7296.00	0.20	11.98
Belgium	17.57	0.90	–0.47	8.23
Bosnia & Herzegovina	13.01	–1.08	–3.08	7.71
Bulgaria	11.23	–0.14	–0.25	6.58
Croatia	24.48	–0.17	–4.16	16.75
Czech Republic	120.97	4.58	–8.31	55.90
Denmark	31.58	0.17	–0.15	22.78
Estonia	47.22	0.92	–0.90	24.14
Finland	4.69	0.08	–0.24	2.78
France	27.99	0.75	–2.90	12.66
Germany	24.81	–1.60	-3.64	12.81
Greece	6.36	0.08	–0.66	3.82
Hungary	21.06	0.70	–1.23	10.58
Iceland	5.69	0.42	–0.13	1.78
Ireland	132.29	5.57	1.38	27.34
Italy	28.60	1.03	–0.89	15.27
Latvia	53.55	0.36	–6.12	28.01
Lithuania	68.40	1.33	0.57	50.47
Luxembourg	30.33	0	0	16.50
Malta	42.51	3.20	–1.88	14.69
Moldova	12.46	0.42	0.46	9.59
Netherlands	43.68	–0.67	0.38	29.34
Norway	12.54	0.28	0.33	5.78
Poland	25.27	1.26	–0.15	13.75
Portugal	79.07	5.77	–2.97	27.46
Romania	22.91	0.04	–2.35	10.96
San Marino	84.20	0	0	49.73
Serbia	25.86	2.61	5.73	17.46
Slovakia	54.28	4.59	–1.52	31.29
Slovenia	97.54	0.14	-10.14	42.36
Spain	37.31	0	–203.00	13.43
Sweden	73.69	0	0	35.06
Switzerland	42.40	0	0	23.85
Ukraine	14.09	0.14	0.23	9.96
United Kingdom	88.10	–0.03	–0.50	46.37
Region	37.72	0.39	–1.30	18.97

[a]Speed: Daily positive cases per 100,000 population.

[b]Acceleration: day-to-day change in the number of positive cases per day.

[c]Jerk: week-over-week change in acceleration.

Table 5. Novel surveillance metrics for the week of January 11-17, 2021.

Country	Speed[a] (weekly average of new daily cases per 100,000 population)	Acceleration[b] (weekly average per 100,000 population)	Jerk[c] (per 100,000 population)	7-day persistence effect on speed (number of new daily cases per 100,000 population attributed to new cases 7 days ago)
Albania	20.33	–0.44	–0.07	12.37
Andorra	91.89	8.32	9.24	43.68
Austria	20.71	–0.61	0.27	14.22
Belarus	20.05	0.14	–0.11	11.10
Belgium	17.97	0.08	–0.08	10.53
Bosnia & Herzegovina	6	–1.11	0.89	7.80
Bulgaria	6.79	–0.06	0.27	6.73
Croatia	17.26	–0.93	1.29	14.68
Czech Republic	77.36	–4.26	0.82	72.54
Denmark	18.76	–0.88	1.25	18.93
Estonia	38.37	–0.42	–0.88	28.32
Finland	4.50	0.10	0.44	2.81
France	28.06	4.70	9.05	16.78
Germany	20.58	1.80	3.16	14.88
Greece	5.30	–0.29	0.11	3.81
Hungary	14.18	–0.79	1.10	12.63
Iceland	2.76	–0.42	0.13	3.41
Ireland	72.66	–11.40	–6.74	79.33
Italy	24.76	–1.44	–0.57	17.15
Latvia	46.17	–0.37	0.68	32.11
Lithuania	41.16	-3.44	–0.71	41.02
Luxembourg	20.22	0	0	18.19
Malta	38.57	–1.39	0.87	25.49
Moldova	12.26	–0.30	–0.13	7.47
Netherlands	33.56	–0.84	0.87	26.19
Norway	8.37	–0.92	–0.39	7.52
Poland	18.90	–1.19	0.11	15.16
Portugal	92.62	4.04	1.98	47.41
Romania	16.60	–0.69	0.19	13.74
San Marino	63.15	0	–4.63	50.49
Serbia	21	–3.67	–5.95	15.51
Slovakia	39.55	–6.28	–0.98	32.55
Slovenia	67.64	–1.33	1.07	58.49
Spain	61.66	0	0	22.37
Sweden	48.12	0	0	44.18
Switzerland	28.47	0	0	25.42
Ukraine	15.76	0.35	–0.63	8.45
United Kingdom	68.26	–3.44	0.49	52.83
Europe	33.02	–0.16	1.37	22.62

[a]Speed: Daily positive cases per 100,000 population.

[b]Acceleration: day-to-day change in the number of positive cases per day.

[c]Jerk: week-over-week change in acceleration.

Table 6. Difference in 7-day persistence between the two study weeks.

Rank	Week 1 (January 4-10, 2021)		Week 2 (January 11-17, 2021)	
	Country	Difference	Country	Difference
1	Czech Republic	55.90	Ireland	79.33
2	Lithuania	50.47	Czech Republic	72.54
3	San Marino	49.73	Slovenia	58.49
4	United Kingdom	46.36	United Kingdom	52.83

Interpretation: Europe Regression Results

The lagging indicators and shift parameters suggested recent changes in disease transmission in Europe between November 30, 2020, and January 17, 2021. The shift in the most recent 14 days, or 2 weeks, was negative and statistically significant (*P*<.001). The coefficient for *weekend* was negative and statistically significant (–2.1, *P*<.02), as shown in Table 1.

Surveillance Results

Tables 2-6 display static and novel dynamic surveillance measures for the weeks of January 4-10, 2021, and January 11-17, 2021. Information pertaining to the prior weeks can be found in Tables S1-S8 of Multimedia Appendix 1. Static measures include the number of new cases during the first day of a given week, cumulative cases, the 7-day moving average of new cases, rate of infection, new deaths during the first day of a given week, cumulative deaths, the 7-day moving average of new deaths, and the rate of deaths (see Tables 2 and 3). The dynamic measures include a temporal element to better understand how past cases affect the present ones and how present cases affect the future ones. Dynamic measures (see Tables 4 and 5) include (1) speed—the number of new observed COVID-19 cases per day per 100,000, averaged over a week; (2) acceleration—the change in speed from the prior week to the current week; (3) jerk—the week-over-week change in acceleration as a function of time over the course of 2 weeks between January 4 and 17, 2021; and (4) the 7-day persistence effect on speed—the average of the number of new cases per day in a given week that are statistically attributable to new cases reported 7 days earlier.

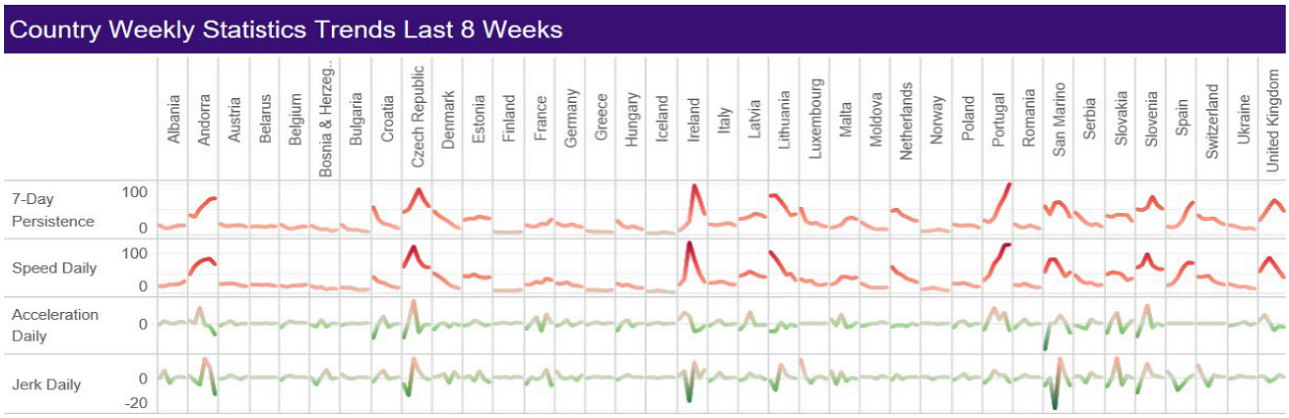
Static measures in Europe for the week of January 4-10, 2021, are presented in Table 2 and those for the week of January 11-17, 2021, are presented in Table 3. New European cases slightly decreased from 158,741 to 152,064 during the first day of each week, with only cumulative cases increasing from 22,507,271 to 23,890,761, which is a weekly increase of 1,383,490 from January 10 to January 17, 2021. Cumulative deaths due to COVID-19 in Europe reached 558,494 by January 17, 2021. The 7-day moving average of new cases totaled 208,581 in the first week and 177,288 in the second week.

France, Germany, Italy, Spain, and the United Kingdom had the largest 7-day moving averages for new cases of infection at 18,269, 20,787, 17,292, 17,442, and 59,809 during the week of January 4-10, 2021. In the second week (January 11-17, 2021), 7-day moving averages increased to 18,318 and 28,829 for France and Spain, respectively. The 7-day moving average for Germany, Italy, and the United Kingdom decreased to 17,245, 14,969, and 46,338, respectively. The infection rate per 100,000 people during the week of January 4-10, 2021, was the highest in Ireland and the United Kingdom at 139.5 and 81.06, respectively. The Czech Republic, Portugal, and Lithuania reported the next highest rates at 78.90, 73.59, and 54.81 per 100,000 population. These 5 countries with the highest infection rates reported a change for the week of January 11-17, 2021, thereby also changing the ranking and magnitude of rates. The top 5 countries by infection rate in week 2 were Portugal at 101.85, Ireland at 59.66, Andorra at 58.24, France at 57.31, and the United Kingdom at 56.94 per 100,000 population.

During the week of January 4-10, 2021, the highest death rates were reported in Latvia, Slovakia, and the Czech Republic at 1.64, 1.50, and 1.28 per 100,000 population. The following week, the European countries with the highest death rates were Slovenia, Portugal, and the Czech Republic at 1.92, 1.49 and 1.15 per 100,000 population.

Tables 4 and 5 and Figure 2 (data sourced from The Global SARS-CoV-2 Surveillance Project [62]) display the dynamic metrics that offer a more temporal view of these data. Novel metrics are also displayed in Multimedia Appendices 2-4. From the week of January 4-10 to the week of January 11-17, 2021, in Europe, the dynamic measures of speed decreased (37.72 to 33.02 per 100,000), acceleration decreased (0.39 to –0.16 per 100,000), and jerk increased (–1.30 to 1.37 per 100,000). Speed was the highest and decreasing in Ireland (132.29 to 72.66 per 100,000), the Czech Republic (120.97 to 77.36 per 100,000), and Slovenia (97.54 to 67.64 per 100,000) during both weeks. Acceleration was the highest in Portugal, Ireland, and Slovakia in the week of January 4-10, 2021, at 5.77, 5.57, and 4.59 per 100,000 population, respectively. Only Ireland had a positive jerk during this time. Andorra, France, and Portugal had the largest acceleration rates during the week of January 4-10, with reported increases to 8.32, 4.70, and 4.04 per 100,000 population, respectively. Jerk was the highest in Serbia, Ireland, and Albania during the week of January 4-10, 2021, at 5.73, 1.38, and 0.67 per 100,000 population. Andorra, France, and Germany reported the highest jerk rates per 100,000 in the week January 11-17, 2021, at 9.24, 9.05, and 3.16, respectively.

Figure 2. Weekly SARS-CoV-2 trends by country in Europe (December 7, 2020, to January 17, 2021; data source: [62]).



The 7-day persistence difference in Table 6 demonstrates the changes in 7-day persistence for the top 4 European countries between January 4-10 and January 11-17, 2021, suggesting an underlying shift that significantly increased persistence for some countries but significantly decreased persistence for other countries during the week of January 11-17. Only two of the countries were in the top 4 for both weeks (ie, the Czech Republic and United Kingdom). Lithuania and San Marino were in the top 4 for the first week, but Lithuania decreased to 41.01 in the second week. San Marino slightly increased from 49.73 to 50.49, but did not make it into the top 4 for the second week.

Among the top 5 countries by population (Table 7), Germany and France remained relatively stable, and the United Kingdom had the highest indicators of cause for alarm, with positive increases in speed and persistence but slightly negative decreases in acceleration and jerk. Smaller countries such as the Czech Republic, Ireland, Andorra, and Portugal reported higher positive increases in speed, acceleration, jerk, and persistence.

Table 7. Most populous European countries.

Country	Population as of 2020
Germany	83,783,942
United Kingdom	67,886,011
France	65,273,511
Italy	60,461,826
Spain	46,754,778

Discussion

Principal Results

Thus far, European COVID-19 infection surveillance has depended on static metrics with limited insight into longitudinal pandemic progression. Dynamic metrics provide an additional lens for surveillance that better captures the evolving prevalence of disease. After combining static and dynamic metrics, some European countries stand out as with the highest risk for uncontrolled growth. These high-risk countries must maintain transmission mitigating policies if they are to protect their citizens and the citizens of neighboring countries.

Europe, as a region, is still experiencing high COVID-19 case rates, but these appear to be trending downward as the region emerges from its second wave. The 7-day moving average of new cases showed a substantial decrease from 208,581 to 177,288 between January 4 and January 17, 2021. The 7-day moving average of COVID-19–related deaths, however, increased from the week of January 4-10 to the week of January 11-17, 2021. Speed of transmission in the region decreased and acceleration shifted from positive to negative from week 1 to week 2, suggesting that case rates may continue to trend downward in coming weeks. This shift in acceleration implies that the speed was increasing at the beginning of the study period but entered a downward trajectory by the end. However, jerk shifted from negative to positive during these two weeks, indicating that the downward trend in acceleration was slowing toward the end of the study period. Interventions and continued precautions will be necessary to maintain a decreasing 7-day moving average of new cases and to continue the downward trajectory of speed and acceleration.

Infection rates show the countries that were the hardest hit at the time of data collection. The top 5 most populous countries in Europe are Germany, the United Kingdom, France, Italy, and Spain. Unsurprisingly, these 5 countries also had the largest 7-day moving averages for new infections during the study period. The United Kingdom had the second highest infection rate per 100,000 people during week 1 of the data collection, along with the largest 7-day moving average of new cases. This finding indicates that the United Kingdom may be at risk of increasing transmission, but the infection rate per 100,000 people decreased from 81.06 during week 1 to 56.94 in week 2, which is reassuring. Both the speed of virus transmission and acceleration in the United Kingdom decreased over the recorded period as well, but jerk actually increased from –0.49 to 0.50, and the country's 7-day persistence was the fourth highest in Europe during both weeks, indicating that the United Kingdom

does need to stay vigilant and ensure proper enforcement of policies to reduce transmission in order to avoid another outbreak.

France and Germany both reported increases in acceleration over the two weeks, and the jerk transitioned from a negative value to a positive value, putting both countries at risk of experiencing increased growth in the coming weeks. Additionally, Spain had increasing speed and jerk, and its 7-day persistence effect increased over the 2-week period, indicating an increase in forward echoes of COVID-19 cases present in the country. Fortunately, Italy's speed and acceleration both decreased over the recorded period, and the jerk was negative during both weeks, implying that mitigation strategies are currently proving to be effective in Italy—the country that was initially one of the hardest hit. These 5 most populous countries are responsible for a very significant portion of the total cases in the European region, and they will likely require regional policy coordination for optimal control of virus transmission.

Some smaller countries in the region have also demonstrated dynamic metrics that warrant concern, such as Andorra. The speed increased from week 1 to week 2, and jerk and acceleration both dramatically increased from negative to positive values, indicating that more intense restrictions are likely necessary to slow the spread. Ireland had the highest infection rate per 100,000 people during week 1 of data collection and the second highest infection rate during week 2. Additionally, Ireland had the largest speed and jerk and the second largest acceleration during week 1, thereby increasing concern for a potential future outbreak in the country. However, all of these dynamic metrics decreased dramatically during week 2 (January 11-17, 2021), with acceleration and jerk actually transitioning to negative values, supporting the idea that Ireland's mitigation strategy is proving to be effective, at least during the time period in question.

Portugal was also at high risk of increased transmission, with a transmission rate per 100,000 people in the top 5 countries of the region during both weeks. With respect to novel dynamic metrics, Portugal had the largest positive acceleration in the region during week 1 and the third largest in week 2. Additionally, the country's jerk increased from a negative value to a positive value and the 7-day persistence effect almost doubled from week to week. This finding indicates that Portugal should consider implementing new policies to reduce transmission and specifically to restrict the evolution of superspreader events, given the increase in 7-day persistence and the fact that Portugal had the second highest death rate per 100,000 people in the region during week 2 (January 11-17, 2021). Residents of Portugal were not only highly likely to contract COVID-19 during this time period, but they were also more likely to die of the disease than residents of most other European countries.

Although some European countries showed signs of uncontrolled growth for the near future, many demonstrate decreasing dynamic metrics that provide reassurance that transmission is being controlled appropriately. However, based on these results, countries with increasing dynamic metrics that are most at risk of outbreaks include Andorra, Portugal, and Spain. Fortunately, Andorra's population is relatively small for the region, potentially insulating regional policy makers and agencies from an overwhelming surge in COVID-19 cases. In contrast, Spain and Portugal are relatively large countries. Their caseloads and positive dynamic metrics suggest that these two countries would require substantial effort to control the COVID-19 spread. Regional coordination would be essential given the size of these countries from a population and economic perspective. Additionally, some countries such as the Czech Republic have very high 7-day persistence effects but decreasing speed and acceleration, indicating that the overall transmission in the country may be decreasing, but focused policy targeted toward preventing superspreader events may be helpful.

Europe experienced a surge in COVID-19 transmission due to the second wave of the pandemic [11,63-65]. Because infection rates had significantly increased across Europe, many governments imposed strict lockdowns shutting down European economies again. Since SARS-CoV-2 cases were first reported in Europe earlier in 2020, COVID-19–related research has kept pace and, consequently, fewer deaths have been reported [61]. The virus is still just as contagious and deadly, but targeted therapies have resulted in attenuation of death rates across countries [61].

Limitations

Data are limited by granularity and collection method. Data were collected at the country level, which precludes local analysis of surveillance trends. Moreover, data collection mechanisms differ by country and may even differ by region within a given country. These different methods lead to weekend effects, missing data points, and other contamination.

Comparison With Prior Work

This study is part of a broader research program at Northwestern Feinberg School of Medicine, The Global SARS-CoV-2 Surveillance Project: Policy, Persistence, & Transmission. This research program developed novel surveillance metrics to include speed, acceleration, jerk, and 7-day persistence at the country level [17,66]. We have also derived surveillance metrics for all global regions.

Conclusion

Static and dynamic public health surveillance tools provide a more complete picture of the progression of the COVID-19 pandemic across countries and regions. Although static measures, including infection rates and death rates, capture data at a given point in time, they are less successful in assessing population health over a period of weeks or months. By including speed, acceleration, jerk, and 7-day persistence, public health officials may design policies with an eye to the future. According to surveillance data, all countries in Europe that were at the highest risk during the second wave of the COVID-19 pandemic shared a number of characteristics. The United Kingdom, Spain, and Portugal demonstrated high infection rates, jerk, and 7-day persistence rates. Looking ahead, policy makers in these countries and the region at large should be concerned about growth in the already substantial number of COVID-19 cases over the short term. Given the substantial 7-day persistence rates in large countries such as the United

Kingdom, Spain, and the Czech Republic, it is imperative that efforts be made to target superspreader events. Analysis of subsequent surveillance data using both static and dynamic tools can help confirm the efficaciousness of new policies.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Tables S1-S10. Static and novel surveillance metrics for specific weeks.
[DOCX File , 54 KB - publichealth_v7i4e25695_app1.docx]

Multimedia Appendix 2
Map showing global weekly explosive growth potential of COVID-19 cases.
[PNG File , 511 KB - publichealth_v7i4e25695_app2.png]

Multimedia Appendix 3
Map showing weekly speed of virus transmission by country in Europe.
[PNG File , 689 KB - publichealth_v7i4e25695_app3.png]

Multimedia Appendix 4
Map showing weekly acceleration/jerk by country in Europe.
[PNG File , 807 KB - publichealth_v7i4e25695_app4.png]

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Abbreviations

EU: European Union
GMM: generalized method of moments
WB: World Bank
WHO: World Health Organization

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Original Paper

Use of a Telemedicine Risk Assessment Tool to Predict the Risk of Hospitalization of 496 Outpatients With COVID-19: Retrospective Analysis

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Abstract

Background: Risk assessment of patients with acute COVID-19 in a telemedicine context is not well described. In settings of large numbers of patients, a risk assessment tool may guide resource allocation not only for patient care but also for maximum health care and public health benefit.

Objective: The goal of this study was to determine whether a COVID-19 telemedicine risk assessment tool accurately predicts hospitalizations.

Methods: We conducted a retrospective study of a COVID-19 telemedicine home monitoring program serving health care workers and the community in Atlanta, Georgia, with enrollment from March 24 to May 26, 2020; the final call range was from March 27 to June 19, 2020. All patients were assessed by medical providers using an institutional COVID-19 risk assessment tool designating patients as Tier 1 (low risk for hospitalization), Tier 2 (intermediate risk for hospitalization), or Tier 3 (high risk for hospitalization). Patients were followed with regular telephone calls to an endpoint of improvement or hospitalization. Using survival analysis by Cox regression with days to hospitalization as the metric, we analyzed the performance of the risk tiers and explored individual patient factors associated with risk of hospitalization.

Results: Providers using the risk assessment rubric assigned 496 outpatients to tiers: Tier 1, 237 out of 496 (47.8%); Tier 2, 185 out of 496 (37.3%); and Tier 3, 74 out of 496 (14.9%). Subsequent hospitalizations numbered 3 out of 237 (1.3%) for Tier 1, 15 out of 185 (8.1%) for Tier 2, and 17 out of 74 (23%) for Tier 3. From a Cox regression model with age of 60 years or older, gender, and reported obesity as covariates, the adjusted hazard ratios for hospitalization using Tier 1 as reference were 3.74 (95% CI 1.06-13.27; P=.04) for Tier 2 and 10.87 (95% CI 3.09-38.27; P<.001) for Tier 3.

Conclusions: A telemedicine risk assessment tool prospectively applied to an outpatient population with COVID-19 identified populations with low, intermediate, and high risk of hospitalization.

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KEYWORDS

COVID-19; SARS-CoV-2; nonhospitalized; risk assessment; outpatient; outcomes; telemedicine

Introduction

In March 2020, the identification of SARS-CoV-2 in the United States led to the rapid closure of elective medical care at many health care institutions, with redeployment of personnel to address the rising burden of COVID-19. In the US state of Georgia, the cumulative number of cases reported by the Department of Public Health rose from 84 cases on March 15, 2020, to 4231 cases by March 31, 2020.

It was recognized from early reports that the severity of COVID-19 varies from asymptomatic to life-threatening [1,2] and that most patients have mild illness and do not require hospitalization [3]. For these patients, the recommendation is to isolate at home and monitor symptoms under the care of a medical provider [4,5]. Many US medical centers have employed telemedicine and remote monitoring programs to provide this care [6-8]. Monitoring programs require investment and staffing [7]; it may be appropriate to focus these resources on those at highest risk of hospitalization for severe COVID-19. While it is recognized that certain groups (eg, older adults and patients with diabetes) have higher rates of hospitalization [9-12], there are no validated risk assessment tools that stratify risk for outpatients undergoing home monitoring [13]. The tools in existence often require in-person criteria (eg, vital signs, labs, and imaging) that are not available by telemedicine [13,14].

In order to better target care for outpatients with COVID-19, we created a risk assessment tool to assign patients a *risk tier* by incorporating age, comorbidities, symptom severity and course, and the ability to isolate—criteria highlighted in the initial US Centers for Disease Control and Prevention (CDC) guidance for home monitoring of patients with COVID-19 [4]. We prospectively applied this risk tool during the telemedicine assessment of outpatients recently diagnosed with COVID-19 in a home monitoring program. Patients were followed with regular phone calls until clinical improvement or hospitalization. In this retrospective study, we analyzed patient data gathered systematically at telemedicine intake visits, including patient characteristics and assigned risk tier, and used an outcome of hospitalization related to COVID-19. We hypothesized that the multifactorial tool would predict hospitalization rates.

Methods

Ethical Approval and Consent

The study was approved by the Emory University Institutional Review Board, which granted a waiver of consent and a waiver of Health Insurance Portability and Accountability Act authorization. The study was carried out in accordance with the principles embodied in the Declaration of Helsinki.

Study Setting and Population

The study is a retrospective cohort investigation of outpatients with confirmed COVID-19 at Emory Healthcare, the largest academic health system in Georgia, serving the greater Atlanta metropolitan area. Testing was scheduled through a central COVID-19 hotline and performed at one screening clinic and one drive-through site, in addition to the emergency departments (EDs) at four hospitals. The test used was real-time reverse transcription–polymerase chain reaction (RT-PCR) detection of SARS-CoV-2 by nasopharyngeal swab. During the study period, testing for COVID-19 was available for symptomatic adults and prioritized (1) health care workers, (2) university students on campus, and (3) patients who were older or had medical comorbidities. Testing and monitoring of children (aged <18 years) was not available at Emory Healthcare. Patients with positive RT-PCR results were called by a dedicated result notification nurse team to provide self-care advice and refer for enrollment in the home monitoring program, named the Virtual Outpatient Monitoring Clinic (VOMC). Characteristics of the first 208 patients in VOMC [15] and the symptom course of VOMC patients [16] have been previously described.

The VOMC intake team included 14 physicians and 3 advanced practice providers (APPs) from two primary care clinics. VOMC follow-up call teams included 19 redeployed registered nurses (RNs) and 20 APPs. All intake providers were trained in the use of the risk assessment tool in a 1-hour webinar and conducted a median of 25 intake visits during the study period (IQR 36.5; range 5-99).

Enrollment criteria for this study included the following: (1) completion of new patient VOMC visit during the period of March 24 to May 26, 2020, and (2) documentation of positive RT-PCR result for SARS-CoV-2. Exclusion criteria included the following: (1) hospitalization prior to VOMC enrollment and (2) immediate discharge from VOMC—no follow-up calls—due to meeting CDC criteria for ending home isolation (≥14 days from symptom onset with resolution of fever and improvement in respiratory symptoms).

Exposure

VOMC intake visits comprised a 40-minute nurse intake (ie, initial data entry) followed by a 40-minute physician or APP telemedicine visit including risk assessment. The clinical care pathway for outpatients with COVID-19 in the VOMC is outlined in Multimedia Appendix 1. The risk assessment tool used by the VOMC was created based on published data about risk factors for severe COVID-19 and the natural history of disease available in March 2020. Patients were assigned to a baseline *risk tier 1 to 3* by the provider upon completion of the VOMC intake visit that determined the planned frequency and duration of monitoring. Low-risk patients (Tier 1) received calls every other day for a minimum of 7 days from symptom onset. Intermediate-risk patients (Tier 2) received daily calls for a minimum of 14 days from symptom onset. High-risk patients (Tier 3) were called twice daily for a minimum of 21 days from symptom onset. There was no limit on duration of care, and calls would continue for all patients until symptom improvement or hospitalization, regardless of tier.

Details of the tier assignment by the VOMC risk assessment tool are in Multimedia Appendix 2. Tier 1 patients must meet *all* of the following criteria: aged <60 years; no comorbidities known to increase risk of severe COVID-19; no lower respiratory tract symptoms, except mild cough; and able to self-isolate. Tier 2 included patients aged 60 to 69 years without comorbidities and patients aged less than 60 years with moderate-risk comorbidities or with persistent symptoms (ie, no improvement) into the second week of illness. Tier 3 included

patients meeting *any* of the following criteria: aged ≥70 years, younger age with specific high-risk comorbidity or multiple comorbidities, new or worsening lower respiratory symptoms, or uncertain ability to self-isolate. Providers were instructed to lower the risk tier by one level for patients whose intake visit occurred during the second week of illness if they reported improving symptoms, even if older age or comorbidities were present.

Outcome

Hospitalization was the primary study outcome, consistent with the stated purpose of the risk assessment tool. ED visits and observation admissions were not included as events. Hospitalization at four Emory Healthcare acute care hospitals was determined by Emory Clinical Data Warehouse (CDW) queries, last performed on July 6, 2020. External hospitalizations were identified by chart review in (1) VOMC clinical notes, (2) administrative messages, and (3) hospitalization documentation in the Emory Healthcare electronic health record per data sharing agreements with other health systems. Loss to follow-up was minimal because VOMC patients were followed until symptom improvement and for specified minimum intervals—7, 14, and 21 days for Tiers 1, 2, and 3, respectively—whichever was longer.

Covariates

Risk assessment data were obtained for all patients enrolling in the VOMC during an intake telemedicine visit utilizing synchronous two-way audio-video communication, with a telephone call as a backup option. VOMC providers completed a standard note template, including comorbidities (ie, past medical history and specific conditions with elevated COVID-19 severity risk), symptom description (ie, onset, severity, and course), social support and ability to isolate, and clinician-assigned risk tier using the risk assessment tool (Multimedia Appendix 2). These data were extracted from the completed VOMC intake notes by CDW query. Missing data were included by manual chart review by the authors (JO and GO) of provider free-text documentation in the intake note. Only data recorded at intake visits with initial risk tier were used; subsequent changes in illness severity and tier reassignments, based on worsening or improvement, were not used in the analysis. Actual age, BMI (calculated as weight in kilograms divided by height in meters squared), and race were obtained with a second CDW query of demographics and height and weight records. If a BMI of 30 or greater was recorded by the provider in the comorbidity portion the VOMC note, it was considered *reported obesity*. If a BMI of 30 or greater was identified by either the VOMC note or the inclusion of height and weight records, we considered this *corrected obesity* for analysis. As we observed underreporting of BMI values of 30 or greater in provider notes compared to height and weight records, we conducted sensitivity analyses to determine if preference for one metric or another substantially influenced results.

Statistical Methods

Survival analysis was used to determine factors associated with hospitalization to evaluate the risk tier model. Initial unadjusted hazard ratios (HRs) were calculated using a Cox proportional hazards model. A multivariable model was then constructed using a Cox proportional hazards model. Time-varying covariates were identified by individual evaluation of covariates looking at Kaplan-Meier curves and testing for a statistically significant time-variable interaction. Covariates with *P* values less than .05 for the time interaction term were considered time-varying.

The models developed by backward and forward selection were then manually checked by adding and removing individual variables and assessing model fit. Cases with missing data were not included in analysis during the exploratory phase. The final model did not have any missing data. To provide odds ratios (ORs) for comparison, logistic regression was performed with the same variables as the Cox regression analysis. All analyses were conducted using SPSS statistical software, version 26 (IBM Corp).

Proposed Simplified Tier Model

We considered covariates for a streamlined risk assessment model to simplify the tier-assignment process for more practical use.

Results

Participant Characteristics

We identified 551 patients completing a new VOMC visit from March 24, 2020, through May 26, 2020. We included 496 patients in the analysis after excluding 7 patients without a positive RT-PCR result, 25 patients hospitalized for COVID-19 prior to their VOMC visit, 2 patients sent to the ED and hospitalized at their first VOMC visit, 1 patient with a blank form, and 20 patients who met criteria for discharge—by duration of symptoms and improvement—and were, thus, not placed into a tier. During the study period—testing dates March 15 to May 22, 2020—the following number of nonhospitalized patients tested positive for SARS-CoV-2 by RT-PCR at Emory Healthcare: 730 in the outpatient setting and 170 in the ED. We do not have data on the patients who did not complete a VOMC intake visit.

The timing of the initial VOMC visit was similar between tiers (mean 9.3 days from symptom onset), and the mean follow-up was shorter for Tier 1 (mean 9.5 days, 95% CI 8.6-10.4) compared to the overall cohort (mean 13.1, 95% CI 12.2-13.9) (Table 1). The majority of the patients were female (330/496, 66.5%), 252 (50.8%) were Black, and 383 (77.2%) were under 60 years of age. Only 174 patients out of 496 (35.1%) reported no high-risk comorbidities, with hypertension (175/496, 35.3%) and reported BMI greater than 30 (147/496, 29.6%) as the most frequent comorbidities. Most patients (316/496, 63.7%) had mild symptoms or no symptoms at the time of the visit.

Table 1. Characteristics of outpatients with COVID-19 by assigned risk tier in a retrospective cohort from a telemedicine monitoring program in Atlanta, Georgia, with enrollment between March 24 and May 26, 2020.

Characteristic	All patients (N=496)	Tier 1[a] (n=237)	Tier 2[a] (n=185)	Tier 3[a] (n=74)
Age (years), mean (95% CI)	47.6 (46.3-48.9)	41.5 (39.8-43.2)	52.5 (50.6-54.4)	54.9 (51.4-58.4)
Days from first symptom to intake visit, mean (95% CI)	9.3 (8.5-10.0)	8.9 (8.2-9.7)	10.0 (8.4-11.6)	8.4 (6.9-9.8)
Days from COVID-19 test to intake visit, mean (95% CI)	3.7 (3.4-3.9)	3.9 (3.4-4.4)	3.5 (3.0-3.9)	3.3 (2.7-4.0)
Follow-up duration (days from intake), mean (95% CI)	13.1 (12.2-13.9)	9.5 (8.6-10.4)	16.3 (14.8-17.7)	16.7 (14.0-19.3)
Age category (years), n (%)				
18-29	78 (15.7)	65 (27.4)	10 (5.4)	3 (4.1)
30-39	84 (16.9)	49 (20.7)	26 (14.1)	9 (12.2)
40-49	106 (21.4)	50 (21.1)	39 (21.1)	17 (23.0)
50-59	115 (23.2)	48 (20.3)	50 (27.0)	17 (23.0)
60-69	84 (16.9)	21 (8.9)	45 (24.3)	18 (24.3)
≥70	29 (5.8)	4 (1.7)	15 (8.1)	10 (13.5)
Race, n (%)				
Black	252 (50.8)	109 (46.0)	102 (55.1)	41 (55.4)
White	97 (19.6)	47 (19.8)	36 (19.5)	14 (18.9)
Other	147 (29.6)	81 (34.2)	47 (25.4)	19 (25.7)
Gender, n (%)				
Female	330 (66.5)	156 (65.8)	125 (67.6)	49 (66.2)
Male	166 (33.5)	81 (34.2)	60 (32.4)	25 (33.8)
Comorbidities, n (%)				
Asthma	73 (14.7)	18 (7.6)	37 (20.0)	18 (24.3)
Cancer or malignancy	37 (7.5)	9 (3.8)	21 (11.4)	7 (9.5)
Chronic obstructive pulmonary disease	5 (1.0)	0 (0)	4 (2.2)	1 (1.4)
Coronary artery disease	24 (4.8)	1 (0.4)	11 (5.9)	12 (16.2)
Diabetes	69 (13.9)	10 (4.2)	35 (18.9)	24 (32.4)
Drug abuse or addiction	4 (0.8)	0 (0)	4 (2.2)	0 (0)
Heart failure	10 (2.0)	2 (0.8)	4 (2.2)	4 (5.4)
Hypertension	175 (35.3)	42 (17.7)	91 (49.2)	42 (56.8)
Immune suppression	30 (6.0)	9 (3.8)	11 (5.9)	10 (13.5)
Lung disease	17 (3.4)	3 (1.3)	9 (4.9)	5 (6.8)
Reported obesity[b]	147 (29.6)	52 (21.9)	63 (34.1)	32 (43.2)
Corrected obesity[c]	212 (42.7)	87 (36.7)	85 (45.9)	40 (54.1)
Renal disease	16 (3.2)	3 (1.3)	6 (3.2)	7 (9.5)
Number of diagnoses, n (%)				
0 (healthy)	174 (35.1)	129 (54.4)	35 (18.9)	10 (13.5)
1	158 (31.9)	81 (34.2)	65 (35.1)	12 (16.2)
2	91 (18.3)	19 (8.0)	48 (25.9)	24 (32.4)
≥3	73 (14.7)	8 (3.4)	37 (20.0)	28 (37.8)
Ability to self-isolate safely, n (%)				

Characteristic	All patients (N=496)	Tier 1[a] (n=237)	Tier 2[a] (n=185)	Tier 3[a] (n=74)
Adequate	409 (82.5)	205 (86.5)	156 (84.3)	48 (64.9)
Inadequate	9 (1.8)	1 (0.4)	3 (1.6)	5 (6.8)
Unknown	78 (15.7)	31 (13.1)	26 (14.1)	21 (28.4)
Severity of symptoms, n (%)				
None or mild	316 (63.7)	204 (86.1)	102 (55.1)	10 (13.5)
Moderate	134 (27.0)	18 (7.6)	69 (37.3)	47 (63.5)
Severe	9 (1.8)	0 (0)	0 (0)	9 (12.2)
Unknown	37 (7.5)	15 (6.3)	14 (7.6)	8 (10.8)
Symptoms course, n (%)				
Improving	264 (53.2)	156 (65.8)	90 (48.6)	18 (24.3)
Stable	155 (31.3)	61 (25.7)	65 (35.1)	29 (39.2)
Worsening	31 (6.3)	0 (0)	14 (7.6)	17 (23.0)
Unknown	46 (9.3)	20 (8.4)	16 (8.6)	10 (13.5)

[a]Risk tiers: Tier 1 = low risk, Tier 2 = intermediate risk, and Tier 3 = high risk (Multimedia Appendix 2).

[b]BMI ≥30 recorded in Virtual Outpatient Monitoring Clinic (VOMC) intake note by provider; BMI is calculated as weight in kilograms divided by height in meters squared.

[c]BMI ≥30 determined by height and weight data in electronic medical record or recorded in VOMC intake note; BMI is calculated as weight in kilograms divided by height in meters squared.

Univariate Analysis

We identified 35 VOMC patients requiring hospitalization and 461 patients who did not require hospitalization during the follow-up period. There were no deaths during VOMC care at home; 2 patients died during hospitalization and a third died shortly after hospitalization while in hospice care. Statistically significant factors for hospitalization included risk tier, age, coronary artery disease, diabetes mellitus, heart failure, reported obesity (BMI ≥30), two comorbidities, three or more comorbidities, severe symptom rating, and worsening symptom course (Table 2). Of the patients initially categorized as Tier 3, 17 out of 74 (23%) were hospitalized in the course of their care, compared with 15 out of 185 (8.1%) Tier 2 patients and 3 out of 237 (1.3%) Tier 1 patients. Among 35 hospitalized patients, the median days to admission from symptom onset was 8 in Tier 3, 11 in Tier 2, and 13 in Tier 1. Tier level had the highest unadjusted HR of all factors, with 5.29 for Tier 2 and 16.24 for Tier 3 in comparison to Tier 1.

Table 2. Characteristics of patients by outcome of hospitalization in a retrospective cohort from a telemedicine monitoring program in Atlanta, Georgia, with enrollment between March 24 and May 26, 2020.

Characteristic	Nonhospitalized patients (n=461)	Hospitalized patients (n=35)	Unadjusted hazard ratio (95% CI)	*P* value
Age (years), mean (95% CI)	46.7 (45.4-48.1)	59.1 (55.2-63.1)	N/A[a]	<.001[b]
Days from first symptom to visit, mean (95% CI)	9.4 (8.6-10.2)	7.4 (5.2-9.6)	N/A	.16[b]
Days from COVID-19 test to visit, mean (95% CI)	3.7 (3.4-4.0)	2.7 (1.9-3.5)	N/A	.09[b]
Follow-up duration (days), mean (95% CI)	13.4 (12.6-14.3)	8.5 (5.0-12.1)	N/A	.003[b]
Age category (years), n (%)				
18-29 (n=78)	78 (16.9)	0 (0)	N/A	—[c]
30-39 (n=84)	81 (17.6)	3 (8.6)	Reference	—
40-49 (n=106)	103 (22.3)	3 (8.6)	0.71 (0.14-3.53)	.68
50-59 (n=115)	105 (22.8)	10 (28.6)	2.16 (0.59-7.85)	.24
60-69 (n=84)	68 (14.8)	16 (45.7)	4.89 (1.42-16.79)	.01
≥70 (n=29)	26 (5.6)	3 (8.6)	2.32 (0.47-11.52)	.31
Race, n (%)				
Other (n=147)	141 (30.6)	6 (17.1)	Reference	—
Black (n=252)	234 (50.8)	18 (51.4)	1.59 (0.63-4.01)	.33
White (n=97)	86 (18.7)	11 (31.4)	2.59 (0.96-7.01)	.06
Gender, n (%)				
Female (n=330)	311 (67.5)	19 (54.3)	Reference	—
Male (n=166)	150 (32.5)	16 (45.7)	1.76 (0.91-3.43)	.10
Comorbidities, n (%)				
Asthma (n=73)	67 (14.5)	6 (17.1)	1.07 (0.44-2.59)	.88
Cancer or malignancy (n=37)	34 (7.4)	3 (8.6)	1.07 (0.33-3.50)	.91
Chronic obstructive pulmonary disease (n=5)	4 (0.9)	1 (2.9)	2.58 (0.35-18.84)	.35
Coronary artery disease (n=24)	18 (3.9)	6 (17.1)	3.71 (1.54-8.96)	.004
Diabetes (n=69)	56 (12.1)	13 (37.1)	3.59 (1.81-7.12)	<.001
Drug abuse or addiction (n=4)	3 (0.7)	1 (2.9)	4.29 (0.59-31.45)	.15
Heart failure (n=10)	6 (1.3)	4 (11.4)	5.84 (2.06-16.55)	<.001
Hypertension (n=175)	157 (34.1)	18 (51.4)	1.75 (0.90-3.40)	.10
Immune suppression (n=30)	30 (6.5)	0 (0)	0.05 (0.00-16.22)	.30
Lung disease (n=17)	14 (3.0)	3 (8.6)	2.10 (0.64-6.88)	.22
Obesity reported[d] (n=147)	130 (28.2)	17 (48.6)	2.27 (1.17-4.41)	.02
Obesity corrected[e] (n=212)	186 (87.7)	26 (74.3)	3.83 (1.80-8.18)	<.001
Renal disease (n=16)	13 (2.8)	3 (8.6)	2.35 (0.72-7.71)	.16
Number of diagnoses, n (%)				
0 (healthy) (n=174)	170 (36.9)	4 (11.4)	Reference	—
1 (n=158)	148 (32.1)	10 (28.6)	2.61 (0.82-8.34)	.11
2 (n=91)	83 (18.0)	8 (22.9)	3.43 (1.03-11.40)	.04
≥3 (n=73)	60 (13.0)	13 (37.1)	6.77 (2.20-20.83)	<.001
Ability to self-isolate safely, n (%)				

Characteristic	Nonhospitalized patients (n=461)	Hospitalized patients (n=35)	Unadjusted hazard ratio (95% CI)	*P* value
Adequate (n=409)	383 (83.1)	26 (74.3)	Reference	—
Inadequate (n=9)	7 (1.5)	2 (5.7)	3.80 (0.90-16.05)	.07
Unknown (n=78)	71 (15.4)	7 (20.0)	Unknown	—
Severity of symptoms, n (%)				
None or mild (n=316)	301 (65.3)	15 (42.9)	Reference	—
Moderate (n=134)	121 (26.2)	13 (37.1)	1.79 (0.85-3.77)	.13
Severe (n=9)	6 (1.3)	3 (8.6)	6.82 (1.95-23.83)	.003
Unknown (n=37)	33 (7.2)	4 (11.4)	Unknown	—
Symptoms course, n (%)				
Improving (n=264)	253 (54.9)	11 (31.4)	Reference	—
Stable (n=155)	143 (31.0)	12 (34.3)	1.84 (0.81-4.17)	.15
Worsening (n=31)	24 (5.2)	7 (20.0)	5.43 (2.10-14.03)	<.001
Unknown (n=46)	41 (8.9)	5 (14.3)	Unknown	—
Tier, n (%)				
1 (n=237)	234 (50.8)	3 (8.6)	Reference	—
2 (n=185)	170 (36.9)	15 (42.9)	5.29 (1.53-18.32)	.009
3 (n=74)	57 (12.4)	17 (48.6)	16.24 (4.74-55.59)	<.001

[a]N/A: not applicable; unadjusted hazard ratio was not calculated.

[b]*P* value was based on a *t* test.

[c]Not calculated, either because the unadjusted hazard ratio value was not calculated or was unknown or because the characteristic was used as reference.

[d]BMI ≥30 recorded in Virtual Outpatient Monitoring Clinic (VOMC) intake note by provider; BMI is calculated as weight in kilograms divided by height in meters squared.

[e]BMI ≥30 determined by height and weight data in electronic medical record or recorded in VOMC intake note; BMI is calculated as weight in kilograms divided by height in meters squared.

Multivariable Analysis

The final model that predicts hospitalization among outpatients in VOMC includes (1) risk tier, (2) reported obesity, (3) aged ≥60 years, and (4) gender as strata (Table 3). This model had an overall fit that was statistically significant (*P*<.001). Covariates other than gender satisfied the proportional hazards assumption. Even though the risk tier rubric does take into account both age and obesity, both of these covariates remained statistically significant with HRs greater than 2 and so were retained in the final model (Multimedia Appendix 3). Gender was found to be a time-varying covariate (Multimedia Appendix 3) and was, therefore, analyzed by stratum [17]. The adjusted HRs for Tiers 2 and 3 compared to Tier 1 were 3.74 (95% CI 1.06-13.27; *P*=.04) and 10.87 (95% CI 3.09-38.27; *P*<.001), respectively. Age of 60 years or older had an adjusted HR of 2.53 (95% CI 1.27-5.02; *P*=.008) and reported obesity had an adjusted HR of 2.09 (95% CI 1.06-4.13; *P*=.03). Survival curves (Figure 1) show days from symptom onset to hospitalization by tier. Males were hospitalized earlier and more often than females. Logistic regression performed with the same variables to shadow the Cox regression analysis found similar results with adjusted ORs of 4.87 for Tier 2 and 15.38 for Tier 3 compared to Tier 1. Age of 60 years or older and reported obesity both had adjusted ORs similar to their adjusted HRs (Table 3). Gender was not statistically significant but was kept in the logistic regression model for comparison to the survival analysis.

Table 3. Hazard ratios (HRs) and odds ratios (ORs) for variables with significant predictive value for hospitalization in the outpatient telemedicine cohort.

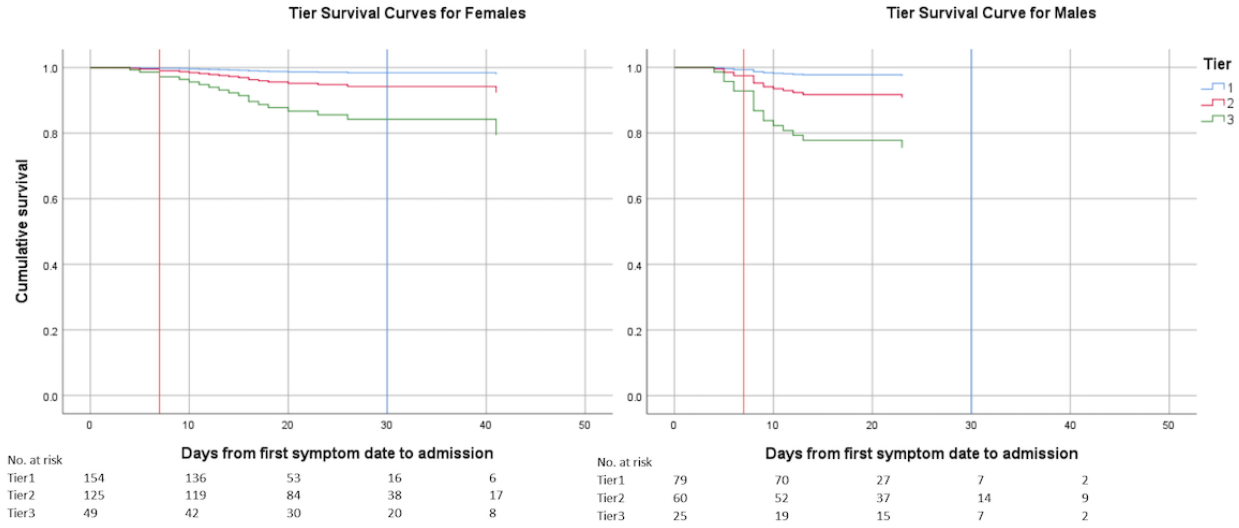
Variable	Unadjusted HR (95% CI)	*P* value	Adjusted HR[a] (95% CI)	*P* value	Adjusted OR[b] (95% CI)	*P* value
Tier 1	Reference	N/A[c]	Reference	N/A	Reference	N/A
Tier 2	5.29 (1.53-18.32)	.009	3.74 (1.06-13.27)	.04	4.87 (1.35-17.57)	.02
Tier 3	16.24 (4.74-55.59)	<.001	10.87 (3.09-38.27)	<.001	15.38 (4.21-56.20)	<.001
Aged ≥60 years	3.77 (1.94-7.34)	<.001	2.53 (1.27-5.02)	.008	2.94 (1.38-6.25)	.005
Reported obesity	2.27 (1.17-4.41)	.02	2.09 (1.06-4.13)	.03	2.17 (1.01-4.67)	.048
Male	1.76 (0.91-3.43)	.10	Analyzed by strata	N/A	1.94 (0.91-4.18)	.09

[a]Cox overall model of fit: χ^2_4=41.4; *P*<.001.

[b]Logistic regression overall model of fit: χ^2_5=50.8; *P*<.001.

[c]N/A: not applicable; *P* value was not calculated because the variable was used as the reference (in the case of Tier 1) or because the variable was analyzed by strata (in the case of gender).

Figure 1. Cox regression survival curves for hospitalization by risk tier in the outpatient telemedicine cohort.



Sensitivity Analysis

We performed sensitivity analysis for obesity to see if using the actual BMI (ie, corrected obesity) would be more predictive than reported obesity from the VOMC note. The adjusted HR for corrected obesity was 3.783 (95% CI 1.761-8.126; *P*<.001) with only minor changes in the HR and *P* values for tier and for age of 60 years or older (Multimedia Appendix 4).

Proposed Simplified Tier Model

We looked at factors associated with hospitalization to propose a streamlined risk assessment model to predict which patients in the VOMC setting will not require hospitalization during COVID-19 illness. Defining a new Tier 1 as age of less than 60 years, no high-risk comorbidities, able to self-isolate, symptom severity mild or none, and symptom course stable or improving, we find a model with no hospitalizations for proposed Tier 1 patients (Table 4).

Table 4. Proposed simplified risk assessment for *new Tier 1*[a] low-risk patients tested in the study cohort.

Tier	Hospital admission, n (%)	
	No	Yes
1 (n=114)	114 (100)	0 (0)
2 and 3 (n=382)	347 (90.8)	35 (9.2)

[a]The proposed four-criteria model for *new Tier 1* is as follows: (1) aged <60 years, (2) no at-risk comorbidities, (3) symptoms mild and stable or improving, and (4) able to self-isolate.

Data Sharing Statement

Deidentified data are available in a public, open access repository [18].

Discussion

Principal Findings

This study describes the outcomes of outpatients with confirmed COVID-19 who participated in a standardized telemedicine risk assessment and telephone monitoring program. We found that the *risk tiers* designated by a multifactorial tool predicts hospitalization rates more strongly than individual variables. We also found that age and obesity still remained significant predictors even though they were part of the risk assessment. It is likely that providers weighed initial symptom severity more in their assessment than either age or obesity, as initial symptom severity was not significant when risk tier was taken into account. Future iterations of the risk assessment tool should increase the relative weights of age and obesity. We note that many similar efforts to produce valid outpatient risk assessment tools are ongoing, but they have not yet been prospectively validated [13].

Comparison to Previous Studies

The overall hospitalization rate in this outpatient cohort was 7%, which is lower than that in other populations reported in New York (51.9%) [11] and Louisiana (39.7%) [19], likely because testing in these cohorts was concentrated in EDs, with lower numbers of patients in the outpatient setting. A more comparable cohort of outpatients monitored by text messaging in Pennsylvania reported a low rate of ED use at approximately 7% but with limited follow-up for hospitalization [20]. The individual risk factors for hospitalization in this study are similar to those identified in earlier cohort studies, particularly age, male sex, and elevated BMI [11,12], but these studies did not include any multifactorial provider risk assessment rubric.

Potential Applications

The identification of a small group of outpatients (ie, Tier 3) at the highest risk of hospitalization facilitates planning efforts for high-intensity outpatient monitoring with limited follow-up resources and may justify the expanded implementation of the risk assessment tool at the point of care. One question raised by a useful risk tier rubric is whether it can be codified into a computer-resident algorithm, an artificial intelligence (AI) application. We attempted models with tier as an output rather than input and using the objective and subjective notes and clinical observations as inputs. We were unable to develop such a model, evidently because the tier assignment includes several points where clinical judgment is required and applied. Incorporating that clinical judgment is necessary and is beyond our AI ability at this point.

The largest group identified by this risk assessment tool was Tier 1. These individuals were at low risk of hospitalization, with 3 admissions out of 237 patients. In order to rapidly identify individuals at low risk of hospitalization and, therefore, who require fewer monitoring resources, we were able to simplify criteria for a proposed *new Tier 1* four-item risk score. As additional remote monitoring tools become available (eg, automated text message surveys), this population may be appropriate to assign *as needed* follow-up instead of proactive monitoring calls.

Strengths and Limitations

While the overall study design is retrospective, our program implemented the risk assessment tool prospectively for all new patients with COVID-19, and we were able to follow all patients until clinical improvement or hospitalization because of the availability of redeployed providers (ie, RNs and APPs), minimizing gaps in data. Furthermore, we found that the risk tiers tool predicted hospitalization risk with highly significant results in multivariate analysis and time-to-hospitalization survival analysis. This supports our hypothesis that inclusion of multiple factors in patient assessment (ie, age, risk factors, symptoms, and social factors) would most effectively identify absolute hospitalization risk and time to hospital admission.

A primary limitation of this single-center study is generalizability to other populations. We had a high proportion of working-age individuals in the first wave of the pandemic, and relatively few older adults and socially disadvantaged individuals are included in the study population. This may explain the lower hospitalization rate compared to cities with larger outbreaks. Furthermore, the time to enrollment in the VOMC (9.3 days) reflects the real-world practice at our clinic, but limits generalizability to settings (eg, urgent care) where patients may present earlier in the disease course. Another limitation is the existence of different levels of observation (ie, frequency of telephone calls, provider type for calls, and duration of follow-up calls) based on assigned tier, which may have impacted outcomes. We cannot speculate if and how more frequent calls would affect the likelihood of hospitalization. We also acknowledge the possibility of loss to follow-up: patients could end VOMC care on request and we do not have direct data for outside hospitalizations, although we reviewed all charts for documentation of such.

The risk assessment tool itself has limitations. First, it was not derived from an outpatient cohort, since none existed at the time, and was instead designed based on limited data available from reports of COVID-19 in hospitalized patients. Second, due to the differential risk posed by age ranges and specific comorbidities, the risk tool is relatively complex and required skilled medical providers to gather the necessary data. We trained a dedicated provider group in its use, but this limits external validity. Even in the optimal setting, we encountered underreporting issues (eg, reported obesity vs actual BMI).

Future Directions

In subsequent waves of the pandemic, the majority of patients in our practice remain home during acute COVID-19. Telephone monitoring continues to provide care for high-risk patients without the ability to participate in automated programs. With the introduction of technologies such as wearable monitoring devices and advanced treatments (eg, monoclonal antibodies), the identification of high-risk patients who are most likely to benefit continues to be a high priority. In this context, the refinement and validation of risk assessment rubrics across

clinical sites and in diverse populations remains important to COVID-19 outpatient care. Future investigation may consider rapid tools (eg, automated identification of highest and lowest risk groups at the time of presentation for testing) as well as validation of provider assessment tools such as ours within other centralized telemedicine programs.

Conclusions

Our findings suggest that patients at low, intermediate, and high risk for hospitalization may be identified with a telemedicine risk assessment tool incorporating age, medical history, symptom severity, and social factors. The Tier 1 patients in our cohort had low hospitalization rates. We observed increasing odds of hospitalization in Tiers 2 and 3, respectively. External validation of these findings is necessary, but we also recognize that care delivery decisions need to be made immediately in the context of recently escalating cases in the COVID-19 pandemic. It is possible to use these data to create care models targeting the highest-risk patients during the highest-risk time periods, but further study of the safety and outcomes of this risk-based approach is needed. This study represents our initial experience with an outpatient telemedicine COVID-19 risk assessment tool. In the absence of clear guidelines on the risk stratification and duration of monitoring of outpatient COVID-19, these data may help guide resource allocation, planning of current care structures, and future research.

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Authors' Contributions

ET, DT, JO, and GO conceptualized the study. DT, JO, and GO obtained the data. ET and DT proposed the data analysis plan. DT performed data analysis and created all tables and figures, and TT performed data analysis and verification of initial model results. JO drafted the Introduction and Discussion sections, ET drafted the Results section, and DT drafted the Methods section. All authors reviewed the manuscript and provided revisions.

Conflicts of Interest

GO served on an advisory board of Eyepoint Pharmaceuticals in 2019; that role is unrelated to this work.

Multimedia Appendix 1
Clinical care pathway for Virtual Outpatient Management Clinic (VOMC).
[DOCX File , 22 KB - publichealth_v7i4e25075_app1.docx]

Multimedia Appendix 2
COVID-19 telemedicine risk tier assessment tool.
[DOCX File , 27 KB - publichealth_v7i4e25075_app2.docx]

Multimedia Appendix 3
Model building.
[DOCX File , 30 KB - publichealth_v7i4e25075_app3.docx]

Multimedia Appendix 4
Sensitivity analysis for obesity.
[DOCX File , 20 KB - publichealth_v7i4e25075_app4.docx]

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Abbreviations

AI: artificial intelligence
APP: advanced practice provider
CDC: US Centers for Disease Control and Prevention
CDW: Clinical Data Warehouse
ED: emergency department
HHS: US Department of Health and Human Services
HR: hazard ratio
HRSA: Health Resources and Services Administration
OR: odds ratio
RN: registered nurse
RT-PCR: reverse transcription–polymerase chain reaction
VOMC: Virtual Outpatient Monitoring Clinic

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Short Paper

Coinfection With SARS-CoV-2 and Influenza A(H1N1) in a Patient Seen at an Influenza-like Illness Surveillance Site in Egypt: Case Report

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Abstract

Background: Sentinel surveillance of influenza-like illness (ILI) in Egypt started in 2000 at 8 sentinel sites geographically distributed all over the country. In response to the COVID-19 pandemic, SARS-CoV-2 was added to the panel of viral testing by polymerase chain reaction for the first 2 patients with ILI seen at one of the sentinel sites. We report the first SARS-CoV-2 and influenza A(H1N1) virus co-infection with mild symptoms detected through routine ILI surveillance in Egypt.

Objective: This report aims to describe how the case was identified and the demographic and clinical characteristics and outcomes of the patient.

Methods: The case was identified by Central Public Health Laboratory staff, who contacted the ILI sentinel surveillance officer at the Ministry of Health. The case patient was contacted through a telephone call. Detailed information about the patient's clinical picture, course of disease, and outcome was obtained. The contacts of the patient were investigated for acute respiratory symptoms, disease confirmation, and outcomes.

Results: Among 510 specimens collected from patients with ILI symptoms from October 2019 to August 2020, 61 (12.0%) were COVID-19–positive and 29 (5.7%) tested positive for influenza, including 15 (51.7%) A(H1N1), 11 (38.0%) A(H3N2), and 3 (10.3%) influenza B specimens. A 21-year-old woman was confirmed to have SARS-CoV-2 and influenza A(H1N1) virus coinfection. She had a high fever of 40.2 °C and mild respiratory symptoms that resolved within 2 days with symptomatic treatment. All five of her family contacts had mild respiratory symptoms 2-3 days after exposure to the confirmed case, and their symptoms resolved without treatment or investigation.

Conclusions: This case highlights the possible occurrence of SARS-CoV-2/influenza A(H1N1) coinfection in younger and healthy people, who may resolve the infection rapidly. We emphasize the usefulness of the surveillance system for detection of viral causative agents of ILI and recommend broadening of the testing panel, especially if it can guide case management.

(JMIR Public Health Surveill 2021;7(4):e27433) doi:10.2196/27433

KEYWORDS

influenza-like Illness; pandemic; SARS-CoV-2; COVID-19; influenza; virus; case study; Egypt; flu; coinfection; infectious disease; surveillance; outcome; demographic

Introduction

COVID-19 Epidemic Situation

COVID-19 is caused by the virus SARS-CoV-2. As of September 7, 2020, a total of 27,314,629 confirmed COVID-19 cases and 893,474 related deaths had been reported worldwide [1]. In Egypt, a total of 99,863 confirmed COVID-19 cases and 5530 related deaths had been reported as of September 7, 2020 [2].

Egypt Influenza-like Illness Surveillance

Influenza-like illness (ILI) sentinel surveillance in Egypt started in 2000 at 8 sentinel sites geographically distributed all over the country. Patients presenting to the outpatient clinics in the participating hospitals with fever and cough within the last 10 days are required to provide throat swabs to be maintained in viral transport media, stored in a nitrogen tank at –80 C and shipped on a weekly basis to the Central Public Health Laboratory (CPHL) in Cairo for testing for influenza type and subtype by reverse transcriptase–polymerase chain reaction (RT-PCR). Demographic and clinical data of the patients are collected in a special database that is regularly analyzed. Reports of the rate of influenza positivity and prevalent influenza types and subtypes are provided to decision makers and relevant stakeholders on a weekly basis.

Modifications to the ILI Surveillance Scheme During the COVID-19 Pandemic

Since the beginning of the COVID-19 pandemic, the Egyptian Ministry of Health and Population (MoHP) requested that all patients with acute respiratory symptoms at all governmental hospitals be assessed by the emergency department (ED). Accordingly, ILI surveillance teams were requested to enroll the first 2 patients with ILI symptoms every day in the ED and follow the usual surveillance methodology for data and sample collection. The MoHP requested that SARS-CoV-2 be added to the testing panel at all ILI surveillance sites.

Early in the pandemic, CPHL was the only laboratory approved by the MoHP for SARS-CoV-2 testing. Because of resource constraints, testing for influenza was placed on hold starting in October 2019, and specimens collected from ILI patients were archived at –70 °C for subsequent testing when possible. As the number of COVID-19 patients in Egypt started to decline in August 2020, CPHL began to test the archived specimens collected at ILI sites.

Study Objectives

On August 16, 2020, CPHL notified the MoHP surveillance department of a case with mixed SARS-CoV-2 and influenza A(H1N1) virus infection. This report aims to describe how the case was identified and to describe the patient's demographic and clinical characteristics and outcomes.

Methods

ILI Surveillance Methods: Case Detection

The influenza virological surveillance was implemented in Egypt in 2000 at 8 outpatient clinics in 6 governorates across Egypt. Participants enrolled in the virological surveillance (2-3 ILI subjects per day, 6 days per week) are interviewed to obtain their demographic information. The World Health Organization surveillance standards for ILI are used to recruit patients, including abrupt onset of fever ≥38 ºC with respiratory manifestations of cough with onset within the last 10 days [3].

While testing routine ILI samples, CPHL staff noted a case of coinfection of SARS-CoV-2 and influenza A(H1N1), confirmed by PCR testing.

Case Investigation

The CPHL staff contacted a surveillance officer, who investigated the case through a telephone call. The clinical picture, disease course, severity risk factors, other clinical investigations and disease outcome were investigated for the case patient and her contacts. Surveillance data were entered in a real-time web-based database at MoHP, and laboratory data were entered at CPHL to be merged automatically with the surveillance data. ILI data from October 2019 to August 2020 were extracted and analyzed for influenza and SARS-CoV-2 as well as their coinfection.

Laboratory and Clinical Investigations

A nasopharyngeal swab was collected from the patient, and nucleic acid extraction for the clinical sample was performed using the chemagic 360 instrument (PerkinElmer Inc). SARS-CoV-2 RNA (ORF1ab) was detected using a VIASURE SARS-CoV-2 Real-Time PCR Detection Kit (Certest Biotec SL). The RT-PCR runs were performed in triplicate and according to the manufacturer's recommendations, and the samples were confirmed to be positive for SARS-CoV-2 using a cobas 6800 system (Roche Holding AG). Moreover, influenza A(H1N1) was tested by real-time PCR using the US Centers for Disease Control protocol [4]. A complete blood count (CBC) and computed tomography (CT) images of the chest were obtained for the patient.

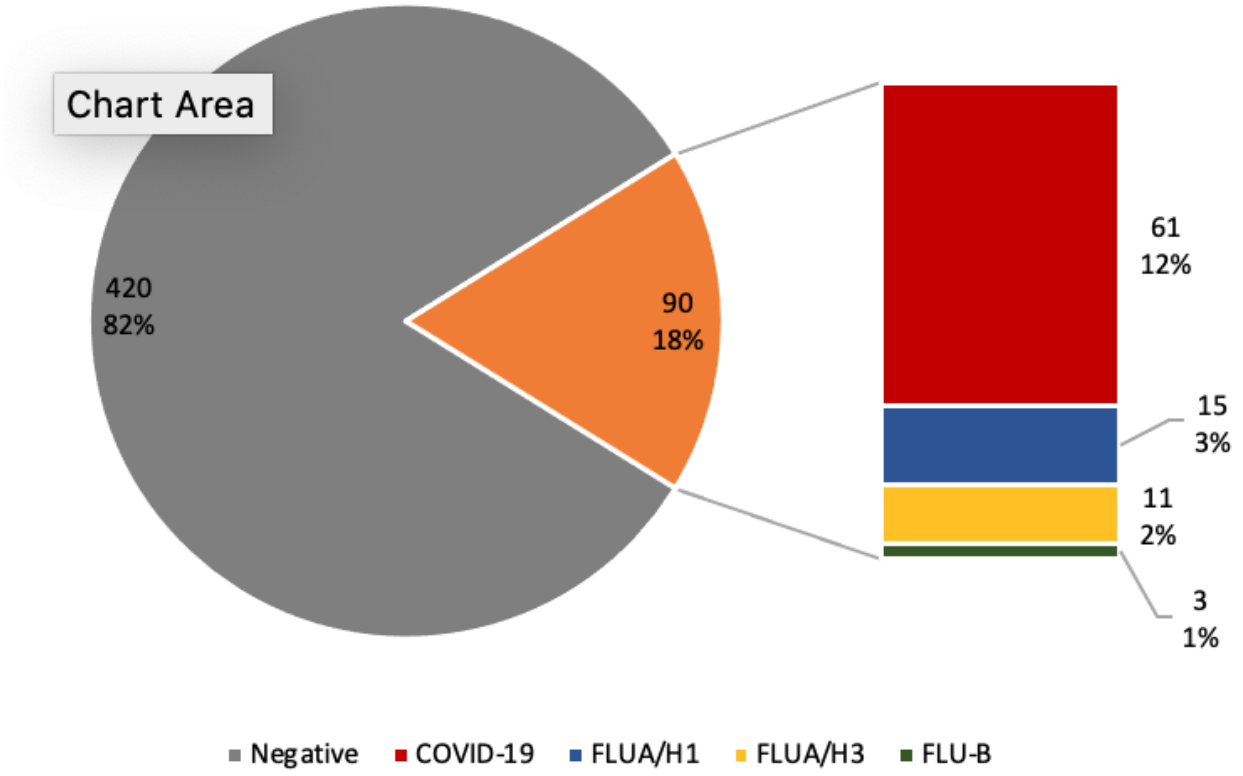
Results

ILI Surveillance Virological Results

Among 510 specimens collected from patients with ILI symptoms from February to August 2020, 29 (5.7%) were positive for influenza. Of those, 15 (51.7%) were positive for A(H1N1), 11 (38.0%) for A(H3N2), and 3 (10.3%) for influenza B. The first case of COVID-19 in Egypt was announced on February 14, whereas the ILI surveillance identified its first COVID-19 case 2 weeks later, announcing the beginning of community transmission of the disease in Egypt. Of the 510 specimens tested, 61(12.0%) were COVID-19–positive (Figure

1). One case was confirmed to have both SARS-CoV-2 and influenza A(H1N1).

Figure 1. Viral causes of 510 specimens collected from influenza-like illness sentinel surveillance in Egypt from October 2019 to September 2020. FLUA/H1: influenza A(H1N1); FLUA/H3: influenza A(H3N2); FLU-B: influenza B.



Case Investigation Results

The case patient presented to the outpatient clinic of one of the ILI surveillance sites that serves Helwan, a semiurban area in Cairo, on May 2020. She was a 21-year-old female student complaining of fever, cough, fatigue, and malaise for 2 days with no other symptoms or associated comorbidities. She presented with a high fever of 40.2°C, and her chest was free on auscultation. The patient's CBC was normal and her chest CT imaging was clear, indicating that she had no lower respiratory tract infection. The patient was swabbed and sent home for treatment; she was given symptomatic treatment in the form of an antipyretic, an antitussive, and oral cefadroxil 2 g per day. Her symptoms persisted for 2 days, followed by full recovery. At home, no isolation was performed for the case patient, and 4 of her 5 family contacts had mild respiratory symptoms 2-3 days after exposure to the confirmed case. Secondary cases included the 2 parents (both 49 years of age) and 2 brothers (9 and 16 years of age); all of them recovered within 2-3 days except for the case patient's father, who experienced hypertension and recovered in 2 weeks. None of the case patient's contacts sought health care, and they all recovered without treatment.

Laboratory and Clinical Investigation Results

The patient tested positive by RT-PCR for both SARS-CoV-2 and influenza A(H1N1). The main cycle threshold (Ct) value for the SARS-CoV-2 N gene was 16.1, and that for ORF1ab was 14.2 (Certest Biotec SL); also, the main Ct value for the SARS-CoV-2 ORF1ab gene was 14.9 and that for the E gene was 15.6 (cobas 6800, Roche Holding AG) as a confirmatory method. At the same time, the main Ct value for influenza A was 32.6, that for swFluA was 32.2, and that for swH1 was 31.6. The case patient's CBC was normal, and her chest CT imaging was clear.

Discussion

Coinfection of SARS-CoV-2 and Influenza A(H1N1)

This study illustrates the characteristics of the first case of SARS-CoV-2 and influenza A(H1N1) coinfection with mild ILI symptoms in Egypt and highlights the benefit of a surveillance system for codetection of respiratory viruses.

Coinfection of other coronaviruses and influenza A viruses has been reported [5]. During the current COVID-19 pandemic, coinfection of SARS-CoV-2 and influenza A(H1N1) was reported in case studies conducted in many countries, including China, Italy, Iran, and Japan [6-9].

Predominant Viral Cause

The abrupt symptom of high fever, short secondary incubation period, and mildness and short course of disease suggest that influenza was the main causative agent [10]. Interestingly, the Ct values in the specimen of this patient indicate that the viral load of SARS-CoV-2 infection was much higher than that of influenza A(H1N1). Studies suggest that the viral load of SARS-CoV-2 peaks around symptom onset or a few days later [11]. This suggests that influenza infection occurred earlier and competitively suppressed replication of SARS-CoV-2 [12].

How the Egyptian Case Compares to Cases Reported From Other Countries

Demographics

The case patient reported in Egypt was a young woman, whereas most of the patients reported from other countries were older. In a mini-review by D'Abramo et al [7] that describes 37 patients with SARS-CoV-2 and influenza coinfection, it was found that 66.7% of patients were ≥50 years of age, and 56.5% were male.

Disease Course and Severity

Most of the cases of coinfection reported from other countries had a prolonged course of the disease, and all of them were admitted to hospital [6-10]. Although the case patient reported from Egypt had mild symptoms, she was detected during routine ILI surveillance activities. She had a short disease course of 4 days with home treatment, and her CBC and CT chest imaging were normal. Her contacts had even milder symptoms; therefore, they did not seek any medical advice.

Predisposing Factors

Most of the reported cases with coinfection had predisposing factors reducing their immunity, and many of them required mechanical ventilation or intensive care unit (ICU) admission [6-9,13]. It was found that more than 60% of patients with coinfection had comorbidities, 33% needed artificial ventilation, and 29% were admitted to the ICU. To date, the case reported from Egypt is the only one from any country with mild upper respiratory symptoms. This could be related to the patient's age and gender in addition to the absence of predisposing comorbidities.

The results of ILI patient testing indicated that more than 80% of cases were negative for both SARS-CoV-2 and influenza. Broader viral testing may be needed to identify the etiology, particularly if it would affect patient treatment [13].

Conclusion

Egypt is reporting a case of SARS-CoV-2 and influenza A(H1N1) co-infection with mild ILI symptoms. This finding suggested that coinfection can occur in people of younger age with no comorbidities. The report showed that patient immunity can overcome both infections, leading to full recovery in a short period with no need for medical procedures. ILI surveillance proved effective in the detection of the viral causes of patients with ILI symptoms. Broadening of the testing panel is recommended, especially if it could guide improvement of case management guidelines.

Conflicts of Interest

None declared.

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Abbreviations

CBC: complete blood count
CPHL: Central Public Health Laboratory
Ct: cycle threshold
CT: computed tomography
ICU: intensive care unit
ILI: influenza-like illness
MoHP: Ministry of Health and Population
RT-PCR: reverse transcriptase–polymerase chain reaction

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