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Original Paper

Implementation of the World Health Organization Global Antimicrobial Resistance Surveillance System in Uganda, 2015-2020: Mixed-Methods Study Using National Surveillance Data

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Abstract

Background: Antimicrobial resistance (AMR) is an emerging public health crisis in Uganda. The World Health Organization (WHO) Global Action Plan recommends that countries should develop and implement National Action Plans for AMR. We describe the establishment of the national AMR program in Uganda and present the early microbial sensitivity results from the program.

Objective: The aim of this study is to describe a national surveillance program that was developed to perform the systematic and continuous collection, analysis, and interpretation of AMR data.

Methods: A systematic qualitative description of the process and progress made in the establishment of the national AMR program is provided, detailing the progress made from 2015 to 2020. This is followed by a report of the findings of the isolates that were collected from AMR surveillance sites. Identification and antimicrobial susceptibility testing (AST) of the bacterial isolates were performed using standard methods at both the surveillance sites and the reference laboratory.

Results: Remarkable progress has been achieved in the establishment of the national AMR program, which is guided by the WHO Global Laboratory AMR Surveillance System (GLASS) in Uganda. A functional national coordinating center for AMR has been established with a supporting designated reference laboratory. WHONET software for AMR data management has been installed in the surveillance sites and laboratory staff trained on data quality assurance. Uganda has progressively submitted data to the WHO GLASS reporting system. Of the 19,216 isolates from WHO GLASS priority specimens collected from October 2015 to June 2020, 22.95% (n=4411) had community-acquired infections, 9.46% (n=1818) had hospital-acquired infections, and 68.57% (n=12,987) had infections of unknown origin. The highest proportion of the specimens was blood (12,398/19,216, 64.52%), followed by urine (5278/19,216, 27.47%) and stool (1266/19,216, 6.59%), whereas the lowest proportion was urogenital

swabs (274/19,216, 1.4%). The mean age was 19.1 (SD 19.8 years), whereas the median age was 13 years (IQR 28). Approximately 49.13% (9440/19,216) of the participants were female and 50.51% (9706/19,216) were male. Participants with community-acquired infections were older (mean age 28, SD 18.6 years; median age 26, IQR 20.5 years) than those with hospital-acquired infections (mean age 17.3, SD 20.9 years; median age 8, IQR 26 years). All gram-negative (*Escherichia coli, Klebsiella pneumoniae*, and *Neisseria gonorrhoeae*) and gram-positive (*Staphylococcus aureus and Enterococcus* sp) bacteria with AST showed resistance to each of the tested antibiotics.

Conclusions: Uganda is the first African country to implement a structured national AMR surveillance program in alignment with the WHO GLASS. The reported AST data indicate very high resistance to the recommended and prescribed antibiotics for treatment of infections. More effort is required regarding quality assurance of laboratory testing methodologies to ensure optimal adherence to WHO GLASS–recommended pathogen-antimicrobial combinations. The current AMR data will inform the development of treatment algorithms and clinical guidelines.

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KEYWORDS

antimicrobial resistance; surveillance; microbiology; laboratory; Uganda; implementation; WHO; collection; analysis; data; antimicrobial; progress; bacteria; feasibility; resistance; antibiotic

Introduction

Background

Antimicrobial resistance (AMR) is associated with increased morbidity and mortality and is recognized as an emerging global health threat. If left unchecked, by 2050, AMR may contribute up to 10 million deaths per year [1]. In low- and middle-income countries (LMICs), particularly in Africa, data on drug-resistant infections are extremely scarce [2]. A few available reports indicate that resistance to commonly prescribed antibiotics is prevalent, but the methodology for the generation and reporting of AMR data is suboptimal [3,4]. A systematic review targeting policy makers in East Africa found significant knowledge gaps in AMR and recommended strengthening antimicrobial stewardship and AMR surveillance in the region [5].

In Uganda, early efforts against AMR identified the critical gap as a lack of routine surveillance systems with limited data, making it difficult to track the AMR burden [6]. Moreover, a substantial proportion of methicillin-resistant *Staphylococcus aureus* and gram-negative organisms in different sample types has been reported [7]. Another study at a Ugandan regional referral hospital (RRH) on antimicrobial-resistant infections among postpartum mothers recommended increased microbiological testing [8]. This informs appropriate antibiotic use, development of antimicrobial stewardship programs, and strengthening of infection prevention and control practices as top priorities. Notably, through an ongoing sentinel surveillance program, microbiology capacity has been enhanced in selected RRHs that contribute significantly toward bacterial ID and antimicrobial susceptibility testing (AST) in Uganda [9]. In addition, Uganda is among the few African countries that have adopted and established a quality-assured World Health Organization (WHO) Enhanced Gonococcal Antimicrobial Surveillance Program and reported data locally and globally [10,11].

In 2015, the WHO launched the Global Laboratory AMR Surveillance System (GLASS) and initiated its implementation in the human health sector [12]. The GLASS program provides national guidance on AMR, focusing on different surveillance methods for adoption and priority specimens, pathogens, and pathogen-antibacterial combinations for use within national surveillance programs. GLASS enables monitoring of emerging AMR profiles at the country level and facilitates the development of hospital-based antibiograms to inform clinical treatment decisions.

In line with global calls to enhance support for AMR systems in LMICs, development partners are currently supporting Uganda's national laboratory system and, more recently, the National Action Plan (NAP) for AMR [13] using a system-strengthening approach [14]. Since 2015, the United States with the help of the Centers for Disease Control and Prevention has been supporting the laboratory capacity at national and regional referral levels to enhance sample transportation systems for microbiology samples. In 2018, the Fleming Fund of the United Kingdom initiated support to the Government of Uganda to strengthen national coordination efforts for AMR using the One Health approach. The efforts are targeting to expand the microbiology testing capacity at the national level and selected RRHs and generate quality-assured AMR data. With the support of these and other partners, Uganda is implementing its NAP for AMR, which was formally launched in 2019.

Objective

In this paper, we highlight the progress on the implementation of GLASS in Uganda from October 2015 to June 2020 and describe laboratory-based AMR surveillance data obtained from selected surveillance sites in the same period. The data include corresponding participant characteristics (sex and age), source of bacterial infection for surveillance hospital-acquired infections (HAIs), bacterial recovery rates, and resistance profiles.

Methods

Overview

A mixed methodology was used to obtain data presented in this study. Qualitative methods were used for the program setup, whereas quantitative methods were used to generate the AMR

surveillance isolate data. A situational analysis report by the Uganda National Academy of Sciences was reviewed to understand the existing national AMR capacity and provide important information to guide program development [15]. To develop a sustainable national AMR surveillance program, the Ministry of Health (MoH) benchmarked on international guidance, using the approach first described in the WHO GLASS manual for the early implementation [12] and later interpreted according to the road map for participation in GLASS by Seale et al [16]. These recommendations were implemented under the cognizance of the local context of Uganda's health systems. A systematic stepwise capacity-building approach [17] was used to set up and implement the program. The approach focused on setting up structures, systems, and roles at national and subnational levels; addressing staffing and infrastructure needs; and providing skills and tools to health workers. Stakeholders' engagement was undertaken to ensure a supportive environment for the implementation of AMR surveillance. The partners supporting the national AMR surveillance program include the Centers for Disease Control and Prevention, the Fleming Fund, the World Bank, and academic institutions, including Makerere University and Mbarara University of Science and Technology. Using the outline by Seale et al [16], we describe the steps taken and the achievements of developing the national AMR surveillance program and later present the AMR data obtained from the program under the *Results* section.

Key Achievements

Enrollment of Uganda in GLASS

In 2015, Uganda responded to the WHO call for countries to enroll in the GLASS program. By enrolling in the GLASS program, Uganda committed to collecting and sharing national AMR surveillance data. As part of this process, the country also acquired the WHONET software [18] used to report AMR surveillance data. A WHO GLASS focal person was designated by the MoH to support the coordination of AMR data validation, quality assurance, and the reporting process. Uganda now participates in the annual AMR data submissions to GLASS, and the country AMR data are part of the WHO global AMR surveillance reports [19].

Establishment of the AMR National Coordinating Center

The National Coordinating Center (NCC) at the MoH has been set up to oversee the national AMR surveillance program in human health, including the collection and aggregation of data from surveillance sites. The NCC works in collaboration with the Uganda National AMR Sub-Committee (UNAMRsC) of the One Health approach to provide strategic oversights of the national AMR program. The UNAMRsC has also been established as part of the governance structure for AMR in the country. The membership of the UNAMRsC also includes representation from other relevant line ministries, such as animal health, wildlife, and the environment. The mandate of the UNAMRsC includes defining the national AMR surveillance objectives; developing and disseminating protocols; coordinating data collection, analysis, and reporting; and reviewing data before reporting to GLASS. To date, the NCC has supported the development of key AMR surveillance documents, including national AMR surveillance plans, protocols, guidelines, curricula, and microbiology standard operating procedures.

Finalization of the NAP for AMR

The WHO requested all member countries to develop multisectoral-wide NAPs that are aligned with the Global Action Plan for AMR to support the implementation of the national AMR programs. Working with partners, the UNAMRsC completed the development of the Uganda AMR NAP [13], which was launched in November 2018 and now supports the implementation of priority activities in the NAP for AMR.

Designation of the National Microbiology Reference Laboratory

Initially, the Department of Medical Microbiology Laboratory at Makerere University was designated as the AMR Surveillance Laboratory. However, the capacity of the Central Public Health Laboratories has been built gradually, and it is now the designated national microbiology reference laboratory for AMR surveillance. The capacity built at Central Public Health Laboratories includes human resource development, quality management systems toward accreditation, isolate transportation, enhanced biorepository, and enrollment of laboratories in an External Quality Assurance scheme. In addition, the state-of-the-art Becton and Dickson–manufactured equipment, including matrix assisted laser desorption/ionization time of flight [20] and Phoenix M50 [21], has been installed at the reference laboratories and BACTEC blood culture systems, including FX 200 and FX40 [22], at selected RRH laboratories. These results support bacterial ID and AST.

Selection and Capacity Building for AMR Surveillance Sites

In 2016, the AMR NCC designated different facilities as AMR surveillance sites. The sites were selected to ensure a balanced geographic, demographic, and socioeconomic distribution. They offer both outpatient and inpatient services, as per GLASS recommendations. However, the capacity of health facilities to conduct AMR surveillance varied between the different health facilities. As a result, selected sites have reported AMR surveillance data to the WHO and the capacity of the surveillance sites has been gradually developed. The Medicines and Therapeutics Committees oversee the implementation of the AMR surveillance program at the surveillance sites, which have been trained in collecting, analyzing, and reporting epidemiological, clinical, and laboratory data. The Medicines and Therapeutics Committee is usually headed by a senior consultant (Internal medicine, Gynecology, Surgery, and Pediatrics) who leads the stewardship of the AMR program at the site. On the basis of the clinician's request for bacterial ID and AST as part of patient care, samples are collected according to the clinical protocols appropriate for the clinical presentation of patients and sent to the microbiology laboratory. The samples mainly include blood, urine, stool, and urogenital swabs and are accompanied by a microbiology laboratory request form that captures epidemiological information such as patient demographics and clinical presentation. The bacterial ID and AST data in this report were collected from 10 surveillance site microbiology laboratories between October 2015 and June 2020.

The surveillance sites included Department of Medical Microbiology, Mbarara University of Science and Technology, Arua RRH, Kabale RRH, Mbarara RRH, Mubende RRH, Fort Portal RRH, Hoima RRH, Jinja RRH, Mbale RRH, and Soroti RRH (Figure 1). The surveillance sites have microbiology laboratories with the capacity to isolate, identify, and conduct microbial sensitivity testing for GLASS priority pathogens.

Figure 1. Geographic locations of the sentinel sites participating in the National Antimicrobial Resistance surveillance program.

Bacterial ID and AST

In the laboratory, bacterial ID and AST for the different samples were collected, and subsequently isolates were performed in accordance with the standardized microbiology protocols and standard operating procedures. Blood culture vials were placed in a BACTEC 9050 or FX40 blood culture system (Becton-Dickinson) according to the manufacturer's instructions. Samples from flagged positive vials were subjected to Gram staining and then cultured on blood agar, chocolate agar, and MacConkey agar culture plates. The culture plates were incubated for 18 to 24 hours at 35°C to 37°C, with recovered colonies undergoing conventional biochemical testing to confirm ID. For stool samples, a loop full of emulsified sample was inoculated on deoxycholate citrate agar, or Xylose Lysine Deoxycholate agar, and MacConkey agar and incubated at 35°C to 37°C in ambient air for 18 to 24 hours. Isolation and ID of growth was performed using conventional methods. Urine samples were gently mixed and inoculated on MacConkey agar and blood agar using an appropriate calibrated loop and incubated in ambient air overnight for 18 to 24 hours at 35°C to 37°C. Isolation, conventional ID, and colony counting were performed where applicable. Both urine and stool were examined macroscopically and microscopically (Gram staining). All urogenital swabs were inoculated on selective modified Thayer Martin and nonselective chocolate agar culture plates and then incubated at 35°C to 37°C in 5% CO_2-enriched humid conditions. ID of gonococci colonies was based on the growth of the colonies with typical morphology in the modified Thayer Martin medium with a positive oxidase test [23]. AST was performed using the Kirby-Bauer disk diffusion method according to the Clinical and Laboratory Standards Institute [24]. We followed the WHO GLASS pathogen-antimicrobial combinations to set the antibiotics for susceptibility testing [12]. Preliminary culture results were immediately sent to the hospital wards to help clinicians optimize patient management, whereas the final results were shared later.

Submission of AMR Data for National and WHO GLASS Reporting

All laboratory results (bacterial ID and AST), patient demographics, and clinical data were entered into the microbiology register. These data were then entered into the WHONET software program [18] on a weekly basis for data analysis to generate facility-based AMR surveillance reports. The AMR surveillance subcommittee technical working committee representatives conducted data quality assessments on a quarterly basis to inform key performance indicators and reports submitted to NCCs. Uganda has been consistently

submitting data to GLASS reporting since its enrollment in 2016 [19].

Statistical Analysis

Summary statistics were calculated for key demographic characteristics of participants from whom samples were collected and stratified by the origin of the samples. Age was summarized as a continuous variable and categorized with age groups defined. *P* values based on chi-square tests were calculated for each variable to provide a sense of differences in demographic characteristics among different origins. For each specimen type, the percentage recovery for all bacterial pathogens and GLASS priority pathogens was expressed as the proportion of samples with a positive culture result out of the total samples cultured. Similarly, for each pathogen, resistance was expressed as the proportion of isolates with resistant or intermediate results out of the total number of isolates tested for susceptibility to a specific antibiotic. The binomial 95% CIs for the proportions of recovery and resistance were calculated using the Wilson method. The frequency of infection with resistant pathogens could not be calculated because data on the population at risk were unavailable. In addition, because of potential sampling bias, no statistical analysis was performed to identify any associations or risk factors for the occurrence of resistant pathogens. The analysis was performed using Excel (Microsoft), R version 3.6 (R Foundation for Statistical Computing), and WHONET.

Results

Demographics of Participants

Of the 19,216 participants involved in the surveillance program, 22.95% (4411/19,216) had community-acquired infections, 9.46% (1818/19,216) had HAIs, and 68.57% (12,987/19,216) had infections of unknown origin (Table 1). The mean age was 19.1 years (SD 19.8 years), whereas the median was 13 years (IQR 28 years). Approximately 49.13% (9440/19,216) of the participants were female, and 50.51% (9706/19,216) were male. Participants with community-acquired infection were older (mean age 28 years, SD 18.6 years; median age 26 years, IQR 20.5 years) than those with HAIs (mean age 17.3 years, SD 20.9 years; median age 8 years, IQR 26 years).

Table 1. Characteristics of participants in the antimicrobial resistance surveillance program from 10 surveillance sites from October 2015 to June 2020.

Characteristics	Origin			Total (N=19,216)	*P* value
	Community acquired (n=4411)	Hospital acquired (n=1818)	Unknown (n=12,987)		
Value, mean (SD)	28.0 (18.6)	17.3 (20.9)	15.9 (19.0)	19.1 (19.8)	N/A[a]
Value, median (IQR)	26 (20.5)	8 (26)	6 (27)	13 (28)	N/A
Age (years), n (%)					<.001
<1	230 (5.21)	192 (10.56)	1753 (13.49)	2175 (11.32)	
1-4	365 (8.27)	485 (26.68)	3003 (23.12)	3853 (20.05)	
05-14	372 (8.43)	459 (25.25)	1600 (12.32)	2431 (12.65)	
15-24	909 (20.61)	149 (8.19)	1042 (8.02)	2100 (10.92)	
25-34	1083 (24.55)	168 (9.24)	1267 (9.76)	2518 (13.1)	
35-44	572 (12.97)	120 (6.6)	748 (5.76)	1440 (7.49)	
45-54	350 (7.93)	88 (4.84)	463 (3.56)	901 (4.69)	
55-64	170 (3.85)	37 (2.04)	268 (2.06)	475 (2.47)	
65-80	149 (3.38)	60 (3.3)	229 (1.76)	438 (2.28)	
>81	52 (1.18)	30 (1.65)	51 (0.39)	133 (0.69)	
Unknown	159 (3.6)	30 (1.65)	2563 (19.74)	2752 (14.32)	
Sex, n (%)					<.001
Female	2413 (54.72)	836 (45.98)	6191 (47.67)	9440 (49.13)	
Male	1974 (44.75)	980 (53.91)	6752 (51.99)	9706 (50.51)	
Unknown	24 (0.54)	2 (0.11)	44 (0.34)	70 (0.36)	
Facility, n (%)					<.001
Arua RRH[b]	1026 (23.26)	384 (21.12)	1049 (8.08)	2459 (12.79)	
DMM MUST[c]	480 (10.88)	35 (1.92)	2351 (18.13)	2866 (14.91)	
Fort Portal RRH	390 (8.84)	270 (14.85)	99 (0.76)	759 (3.95)	
Hoima RRH	7 (0.16)	2 (0.11)	164 (1.26)	173 (0.9)	
Jinja RRH	88 (1.99)	336 (18.48)	4398 (33.86)	4822 (25.09)	
Kabale RRH	699 (15.84)	106 (5.83)	2191 (16.87)	2996 (15.59)	
Mbale RRH	653 (14.8)	163 (8.97)	692 (5.33)	1508 (7.85)	
Mbarara RRH	392 (8.89)	277 (15.24)	132 (1.02)	801 (4.17)	
Mubende RRH	312 (7.07)	153 (8.42)	1464 (11.27)	1929 (10.04)	
Soroti RRH	364 (8.25)	92 (5.06)	447 (3.44)	903 (4.69)	
Department, n (%)					<.001
Inpatient	1186 (26.89)	1509 (83)	4527 (34.86)	7222 (37.58)	
Outpatient	2850 (64.61)	181 (9.96)	3289 (25.32)	6320 (32.89)	
Unknown	375 (8.5)	128 (7.04)	5171 (39.82)	5674 (29.53)	

[a]N/A: not applicable.

[b]RRH: regional referral hospital.

[c]DMM MUST: Department of Medical Microbiology, Mbarara University of Science and Technology.

A total of 19,216 WHO GLASS priority specimens were collected for microbiological testing from 10 surveillance sites over a period of 4 years and 6 months, from October 2015 to June 2020. The highest proportion of the specimens was blood (12,398/19,216, 64.52%), followed by urine (5278/19,216, 27.47%) and stool (1266/19,216, 6.59%), whereas the lowest proportion was that of urogenital swabs (274/19,216, 1.43%).

Recovery Rates and Distribution of Pathogens

The overall recovery rate of the GLASS priority pathogens from the GLASS priority specimens was 7.4% (1429/19,216; Table 2). The recovery rates from the different samples were as follows: urogenital swabs 17.9% (49/274), urine 12.1% (637/5278), stool 7.74% (98/1266), and blood 5.2% (645/12,398). The highest percentage of GLASS priority pathogens identified were *Escherichia coli* (652/1429, 45.62%), followed by *S aureus* (337/1429, 23.58%), with the lowest being *Acinetobacter baumannii* (6/1429, 0.42%).

Table 2. Bacterial recovery rates from priority specimens collected from 10 surveillance sites, October 2015 to June 2020.

Variable	Value, n (%)	Odds ratio (95% CI)
Samples cultured (n=19,216)		N/A[a]
Blood	12,398 (64.52)	
Urogenital swabs	274 (1.43)	
Stool	1266 (6.59)	
Urine	5278 (27.47)	
Samples with bacterial growth (n=4471)		23.3 (22.7-23.9)
Blood	1520 (33.99)	12.3 (11.7-12.9)
Urogenital swabs	174 (3.89)	63.5 (57.7-69.0)
Stool	491 (10.98)	38.8 (36.1-41.5)
Urine	2286 (51.13)	43.3 (42.0-44.6)
Samples yielding the GLASS[b] priority pathogens (n=1429)		7.4 (7-7.8)
Blood	645 (45.14)	5.2 (4.8-5.6)
Urogenital swabs	49 (3.43)	17.9 (13.8-22.9)
Stool	98 (6.86)	7.7 (6.3-9.3)
Urine	637 (44.58)	12.1 (11.3-13.0)
GLASS priority pathogens recovered (n=1429)		N/A
Escherichia coli	652 (45.62)	
Staphylococcus aureus	337 (23.58)	
Salmonella spp	237 (16.58)	
Klebsiella pneumoniae	109 (7.63)	
Neisseria gonorrhoeae	49 (3.43)	
Shigella spp	21 (1.47)	
S pneumoniae	18 (1.26)	
Acinetobacter baumannii	6 (0.42)	

[a]N/A: not applicable.

[b]GLASS: Global Laboratory Antimicrobial Resistance Surveillance System.

Pathogen Resistance

Resistance patterns for the most commonly isolated gram-negative bacteria, that is, *E coli*, *Neisseria gonorrhoeae*, *Shigella* sp, and *Salmonella* sp are shown in Table 3, with all gram-negative bacteria showing resistance to each of the tested antibiotics. High resistance of *E coli* was noted among commonly used antibiotics, with 52.7% (95% CI 46.8%-58.5%) resistance to ceftriaxone, 18.8% (95% CI 14.9%-23.4%) resistance to imipenem, and 52% (95% CI 47.5%-56.6%) resistance to ciprofloxacin. High resistance of *Klebsiella pneumoniae* was noted among the commonly used antibiotics. High resistance of *N gonorrhoeae* was noted among the commonly used antibiotics, with 10% (95% CI 1.8%-40.4%) resistance to ceftriaxone and 71.4% (95% CI 45.4%-88.3%) resistance to ciprofloxacin. High resistance of *Salmonella* and *Shigella* was noted among the commonly used antibiotics, including resistance to meropenem, ceftriaxone, and ciprofloxacin.

Table 3. Antimicrobial resistance profiles of selected gram-negative bacteria from 10 surveillance sites from October 2015 to June 2020.

Bacteria name	Antibiotic name	Number	R+I[a] (95% CI; %)
Escherichia coli			
	Amikacin	52	7.7 (3-18.2)
	Amoxicillin	25	88 (70-95.8)
	Amoxicillin and clavulanic acid	232	75 (69.1-80.1)
	Ampicillin	359	91.6 (88.3-94.1)
	Cefoxitin	27	25.9 (13.2-44.7)
	Ceftazidime	77	45.5 (34.8-56.5)
	Ceftriaxone	277	52.7 (46.8-58.5)
	Cefuroxime	334	63.8 (58.5-68.7)
	Chloramphenicol	366	42.1 (37.1-47.2)
	Ciprofloxacin	455	52.1 (47.5-56.6)
	Clindamycin	54	88.9 (77.8-94.8)
	Erythromycin	100	92 (85-95.9)
	Gentamicin	403	38.2 (33.4-42.8)
	Imipenem	324	18.8 (14.9-23.4)
	Levofloxacin	35	5.7 (1.6-18.6)
	Meropenem	42	19 (10-33.3)
	Nalidixic acid	181	76.8 (70.1-82.3)
	Nitrofurantoin	266	30.8 (25.6-36.6)
	Penicillin G	71	97.2 (90.3-99.2)
	Piperacillin or tazobactam	33	36.4 (22.2-53.4)
	Tetracycline	226	78.8 (73-83.6)
	Trimethoprim-sulfamethoxazole	327	83.8 (79.4-87.4)
	Vancomycin	94	76.6 (67.1-84)
Klebsiella pneumoniae			
	Amoxicillin	50	86 (73.8-93)
	Ampicillin	79	97.5 (91.2-99.3)
	Ceftazidime	20	65 (43.3-81.9)
	Ceftriaxone	79	79.7 (69.6-87.1)
	Cefuroxime	63	77.8 (66.1-86.3)
	Chloramphenicol	78	53.8 (42.9-64.5)
	Ciprofloxacin	86	53.5 (43-63.7)
	Gentamicin	78	71.8 (61-80.6)
	Imipenem	63	1.6 (0.3-8.5)
	Meropenem	21	23.8 (10.6-45.1)
	Tetracycline	42	54.8 (39.9-68.8)
	Trimethoprim-sulfamethoxazole	67	82.1 (71.3-89.4)
Neisseria gonorrhoeae			
	Ceftriaxone	10	10 (1.8-40.4)
	Cefuroxime	13	46.2 (23.2-70.9)
	Ciprofloxacin	14	71.4 (45.4-88.3)
	Tetracycline	16	100 (80.6-100)

Bacteria name	Antibiotic name	Number	R+I[a] (95% CI; %)
Salmonella sp			
	Amikacin	37	5.4 (1.5-17.7)
	Amoxicillin	33	100 (89.6-100)
	Ampicillin	131	81.7 (74.2-87.4)
	Ceftazidime	66	13.6 (7.3-23.9)
	Ceftriaxone	98	17.3 (11.1-26)
	Cefuroxime	108	20.4 (13.9-28.9)
	Chloramphenicol	138	66.7 (58.4-74)
	Ciprofloxacin	116	24.1 (17.3-32.7)
	Gentamicin	52	17.3 (9.4-29.7)
	Imipenem	83	3.6 (1.2-10.1)
	Levofloxacin	60	1.7 (0.3-8.9)
	Nalidixic acid	127	15.7 (10.4-23.1)
	Tetracycline	96	87.5 (79.4-92.7)
	Trimethoprim-sulfamethoxazole	114	69.3 (60.3-77)
Shigella sp			
	Amikacin	15	93.3 (70.2-98.8)
	Ceftriaxone	19	15.8 (5.5-37.6)
	Cefuroxime	10	50 (23.7-76.3)
	Chloramphenicol	11	54.5 (28-78.7)
	Ciprofloxacin	20	30 (14.5-51.9)
	Gentamicin	13	23.1 (8.2-50.3)
	Nalidixic acid	12	33.3 (13.8-60.9)
	Tetracycline	12	50 (25.4-74.6)
	Trimethoprim-sulfamethoxazole	13	38.5 (17.7-64.5)

[a]R+I: Resistance + Intermediate.

Among gram-positive bacteria, high resistance of *S aureus* was noted among the commonly used antibiotics, with 42.9% (95% CI 28%-59.1%) resistance to cefoxitin, 30.9% (95% CI 21.2%-42.6%) resistance to oxacillin, 76.9% (95% CI 69%-83.2%) resistance to TMP-SMX, and 15.5% (95% CI 9.6%-24%) resistance to vancomycin (Table 4). High resistance of *Enterococcus* sp was noted among the commonly used antibiotics, with 81.8% (95% CI 61.5%-92.7%) resistance to ciprofloxacin and 50% (95% CI 33.6%-66.4%) resistance to vancomycin. A high resistance of *Streptococcus* sp was noted between vancomycin and ceftriaxone.

Table 4. Antimicrobial resistance profiles of selected gram-positive bacteria from 10 surveillance sites, from October 2015 to June 2020.

Bacteria name	Antibiotic name	Number	R+I[a] (95% CI; %)
Staphylococcus aureus			
	Amoxicillin and clavulanic acid	47	51.1 (37.2-64.7)
	Ampicillin	54	81.5 (69.2-89.6)
	Cefoxitin	35	42.9 (28-59.1)
	Ceftazidime	57	12.3 (6.1-23.2)
	Ceftriaxone	74	41.9 (31.3-53.3)
	Cefuroxime	93	20.4 (13.5-29.7)
	Chloramphenicol	176	56.2 (48.9-63.4)
	Ciprofloxacin	161	41 (33.7-48.7)
	Clindamycin	120	16.7 (11.1-24.3)
	Erythromycin	181	68 (60.8-74.3)
	Gentamicin	158	31 (24.3-38.6)
	Imipenem	101	13.9 (8.4-21.9)
	Levofloxacin	61	0 (0-5.9)
	Moxifloxacin	43	0 (0-8.2)
	Ofloxacin	61	0 (0-5.9)
	Oxacillin	68	30.9 (21.2-42.6)
	Penicillin G	106	86.8 (79-92)
	Tetracycline	162	72.2 (64.9-78.5)
	Trimethoprim-sulfamethoxazole	134	76.9 (69-83.2)
	Vancomycin	97	15.5 (9.6-24)
Enterococcus sp			
	Ampicillin	32	87.5 (71.9-95)
	Chloramphenicol	21	61.9 (40.9-79.2)
	Ciprofloxacin	22	81.8 (61.5-92.7)
	Erythromycin	35	91.4 (77.6-97)
	Gentamicin	14	57.1 (32.6-78.6)
	Tetracycline	15	73.3 (48-89.1)
	Vancomycin	32	50 (33.6-66.4)
	Gentamicin-high	14	64.3 (38.8-83.7)
Streptococcus sp			
	Ceftriaxone	14	64.3 (38.8-83.7)
	Chloramphenicol	45	35.6 (23.2-50.2)
	Clindamycin	49	32.7 (21.2-46.6)
	Erythromycin	52	59.6 (46.1-71.8)
	Penicillin G	15	66.6 (41.7-84.8)
	Tetracycline	29	51.7 (34.4-68.6)
	Trimethoprim-sulfamethoxazole	20	75 (53.1-88.8)
	Vancomycin	24	25 (12-44.9)

[a]R+I: Resistance + Intermediate.

Discussion

Principal Findings

The findings of our surveillance program show the feasibility of setting up a national AMR surveillance program based on the WHO GLASS manual recommendation while building systems for quality assurance, data sharing, linking results to patient care, and building partnerships. AMR is a global health threat, and the establishment of national surveillance systems is necessary to identify the emerging drug-resistant infections [2]. The African region still has suboptimal microbiology laboratory capacity and surveillance systems for AMR [3]. However, in Africa and Uganda in particular, resistance to recommended antibiotics has been reported for the WHO GLASS priority pathogens [12]. This paper presents the processes undertaken to set up a national AMR surveillance system according to WHO GLASS standards in Uganda, which could be benchmarked for other LMICs. The surveillance sites were RRHs and an academic institution. The RRHs represented the majority of the geographical distribution as they received referrals from district hospitals and health centers IVs and IIIs.

The success of establishing the national AMR surveillance program in Uganda highlights the feasibility of implementing the WHO GLASS program in LMICs. AMR surveillance programs are fundamental in Sub-Saharan African countries such as Uganda for generating antibiograms that can inform the development of treatment guidelines and antibiotic procurement plans and contribute toward standardized reporting [25,26]. Clinicians at surveillance sites can also access bacterial ID and AST results to inform patient care because of the availability of strengthened quality microbiology services.

In Uganda, the AMR surveillance system has been established using a systematic capacity-building pyramid model [17] and in alignment with the London School of Hygiene and Tropical Medicine stepwise road map for participating in GLASS [16]. The rolling out of the NAP for AMR [13], AMR national and subnational structures with Terms of Reference, and supporting surveillance plans and protocols has strengthened antimicrobial stewardship. In addition, the establishment of data-sharing platforms, including software programs such as WHONET [18], has supported data collation, analysis, reporting, and electronic archival, supplementing the existing paper-based methods.

The Uganda surveillance program identified selected resistant priority pathogens, including *E coli*, *S aureus*, *K pneumoniae*, and *N gonorrhoeae*, which present a high diversity of pathogens seen in Central Africa, Gabon [27]. *E coli* and *S aureus* isolates were the most prevalent WHO priority pathogens isolated in Uganda. This is fundamental baseline information that could be used for pretesting the novel WHO protocol [28] for estimating mortality attributable to AMR bloodstream infections. Monitoring priority pathogens and analyzing their antimicrobial susceptibilities together with epidemiological information on sex, age, and surveillance site can inform early hospital-level interventions [29].

There was a high rate of resistance of *E coli* to ampicillin and cotrimoxazole, as recently reported [3]. However, proportion of ceftriaxone- and ciprofloxacin-resistant *E coli* was slightly lower than that observed in Equatorial Guinea [30]. More worryingly, there was a significant proportion 18.8% (61/324) of *E coli* resistance to imipenem, which is considerably higher than 3%, recently reported in other parts of the African continent [3]. For *K pneumoniae*, there was notable resistance to ceftriaxone at 79% (63/79) and cotrimoxazole at 82% (55/67) in the surveillance program, similar to findings in Uganda's neighboring country Kenya [31].

To our knowledge, this is the first documentation of the implementation of a national AMR surveillance program on the African continent using the WHO-recommended methodology. Although all components of the WHO GLASS manual are implemented, the approaches were not sequential and were contextualized to Uganda cognizance of existing national policies and programs.

The main limitations included suboptimal recovery of the AMR GLASS priority pathogens and inconsistent setting of the recommended antibiotics against the pathogen in the laboratory. This was attributed to the fact that staff members were still undergoing comprehensive training on microbiology skills, stock-outs, and acquiring extensive knowledge on AMR surveillance [32]. The number of samples sent to the microbiology laboratory was relatively low, coupled with low rates of completion of the microbiology laboratory request forms. This was partially attributed to the lack of a laboratory-clinician interface to bridge these anomalies.

Conclusions

Using the WHO guidance, Uganda has successfully completed key foundational building activities for the successful implementation of a national AMR surveillance program. The emerging antibiotic resistance data can be refined, appraised, and used for further improvement of the current methodological approaches being used to implement AMR programs in Uganda and other LMICs. Uganda successfully enrolled in the WHO GLASS system and has consistently reported annual program progress to the WHO since 2016. There is an extremely high prevalence of AMR to the most commonly used antibiotics, similar to what has been found in other studies conducted in the research context.

Recommendations

The current Uganda Clinical Guidelines need to be reviewed in response to the AMR burden in Uganda. In addition, strengthening the capacity of the microbiology laboratory is fundamental for the successful implementation of surveillance protocols in hospital wards to further profile the emerging global health threat of AMR.

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Authors' Contributions

HM and SN provided strategic national leadership for the surveillance program. FK and RK wrote the first draft of the manuscript. AK, ML, RW, and HK provided technical oversights on the implementation of surveillance activities. RK, JM, and JB developed the surveillance documents. MS and IM coordinated the operational requirements for implementation. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMR: antimicrobial resistance
AST: antimicrobial susceptibility testing
GLASS: Global Laboratory Antimicrobial Resistance Surveillance System
HAI: hospital-acquired infection
LMIC: low- and middle-income country
MoH: Ministry of Health
NAP: National Action Plan
NCC: National Coordinating Center
RRH: regional referral hospital
UNAMRsC: Uganda National Antimicrobial Resistance Sub-Committee
WHO: World Health Organization

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Original Paper

Health Communication About Hospice Care in Chinese Media: Digital Topic Modeling Study

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Abstract

Background: Hospice care, a type of end-of-life care provided for dying patients and their families, has been rooted in China since the 1980s. It can improve receivers' quality of life as well as ease their economic burden. The Chinese mass media have continued to actively dispel misconceptions surrounding hospice care and deliver the latest information to citizens.

Objective: This study aims to retrieve and analyze news reports on hospice care in order to gain insight into whether any differences existed in heath information delivered over time and to evaluate the role of mass media in health communication in recent years.

Methods: We searched the Huike (WiseSearch) news database for relevant news reports from Chinese mass media released between 2014 and 2019. We defined two time periods for this study: (1) January 1, 2014, to December 31, 2016, and (2) January 1, 2017, to December 31, 2019. The data cleaning process was completed using Python. We determined appropriate topic numbers for these two periods based on the coherence score and applied latent Dirichlet allocation topic modeling. Keywords for each topic and corresponding topics' names were then generated. The topics were plotted into different circles, and their distances on the 2D plane was represented by multidimensional scaling.

Results: After removing duplicated and irrelevant news articles, we obtained a total of 2227 articles. We chose 8 as the suitable topic number for both study periods and generated topic names and associated keywords. The top 3 most reported topics in the first period were *patient treatment*, *hospice care stories*, and *development of health care services and health insurance*, accounting for 18.68% (178/953), 16.58% (158/953), and 14.17% (135/953) of the collected reports, respectively. The top 3 most reported topics in the second period were *hospice care stories*, *patient treatment*, and *development of health care services*, accounting for 15.62% (199/953), 15.38% (15.38/953), and 14.27% (182/953), respectively.

Conclusions: Topic modeling of news reports gives us a better understanding of the patterns of health communication about hospice care by mass media. Chinese mass media frequently reported on hospice care in April of every year on account of a traditional Chinese festival. Moreover, an increase in coverage was observed in the second period. The two periods shared 6 similar topics, of which *patient treatment outstrips hospice care stories* was the most reported topic in the second period, implying the humanistic spirit behind the reports. Based on the findings of this study, we suggest stakeholders cooperate with the mass media when planning to update policies.

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KEYWORDS

health communication; hospice care; mass media; China; topic modeling; communication; media; model; hospice; end-of-life; misconception; health information; news

Introduction

Hospice care is the end-of-life care for patients with a terminal illness or critical condition and limited life expectancy, provided usually in their last 6 months of life or less. It also involves support and education about death provided for the patients' families [1]. Hospice care aims to help these patients die peacefully, comfortably, and with dignity by controlling various types of pain and other symptoms [2]. In most situations, hospice care is offered at home, but it can also be offered in private or public health facilities, such as hospitals, specialized hospice facilities, or nursing homes. It is usually provided by a comprehensive unit consisting of nurses, social workers, home health aides, chaplains, volunteers, physicians, and hospice medical management or directors [3]. The first modern hospice was founded by Cicely Saunders, a British nurse, in 1967. Her experience of care for a dying refugee motivated her to build up a caring environment where patients could spend their last days [4]. In mainland China, the establishment of the first mainland China hospice hospital, Songtang Care Hospital, founded in 1987 in Beijing, marks the milestone of hospice care [5]. Since then, many policies have been established to promote hospice care in China. Several other hospice facilities were built, and various research studies on hospice care have also been conducted.

Hospice care is essential as it has been proven to improve the quality of life for patients [6]; ensure lower medical cost [7]; and possibly reduce the risk of death among surviving bereaved spouses, close relatives, or loved ones [8]. There is a huge demand for hospice care in China. Approximately 4.3 million new cancer cases and 2.9 million new cancer deaths were reported in 2018 in China [9]. These patients experience pain, anorexia, fatigue, myalgia, and labored breathing, among other issues [10]. Moreover, the number of patients with chronic diseases is also rising as the proportion of the elderly is increasing. According to the National Bureau of Statistics of China, it is estimated that over 250 million people are aged 60 years and above, accounting for 18.1% of the entire population [11]. Most patients also suffer from ongoing diseases and fear of death, and their families need psychological and spiritual encouragement. However, hospice care lacks adequate public awareness and social acceptance in China. A cross-sectional investigation conducted in two hospitals in Beijing among outpatients and family members revealed that less than 20% of them know or have even heard of hospice care [12]. Not just the patients and their families, but the medical staff alike, have little acquaintance with hospice care. Another cross-sectional study found that only about half of the health care providers know about hospice care, and they consider their overall knowledge of end-of-life care as inadequate [13]. In addition, the society—influenced by the traditional Chinese culture—prioritizes life-prolonging measures rather than improvement of life quality even in cases where the disease is impossible to cure, and death cannot be avoided [5]. Owing to this flawed notion, the family members refuse hospice care because they are afraid of being accused of not being a good son or daughter, as according to the Chinese culture and traditions, they are required to remain devoted to their parents until the end of their lives. Furthermore, many people misunderstand the system and believe that they will be abandoned if they received hospice care [5]. Therefore, the policymakers and health providers have an obligation to break the impediments to providing quality hospice care and further improve the public's knowledge of hospice care.

The Chinese mass media channels have constantly published news reports related to hospice care, which aroused widespread discussion in China. These reports break the taboo of talking about death and dying, and actively engage in public advocacy and education on this topic. However, few studies have focused on the role that mass media plays in communicating the concept of hospice care. Therefore, in this study, we aim to collect the news reports pertaining to hospice care from major Chinese media portals and analyze them to determine the patterns of health communication through mass media. Multimodal data modeling can aggregate numerous information from different resources. To deal with multimodal data, topic modeling, a machine learning method that arranges unstructured data structurally in conformity with latent themes [14], was applied. By this means, we could investigate what health information about hospice care has been conveyed by the mass media to the public and whether it has changed over time.

Methods

Data Collection

"Hospice care" has different references in Chinese, including "gu xi hu li," "an ning hu li," "lin zhong guan huai," and "an ning liao hu." These terminologies are used interchangeably, and their corresponding Chinese characters are shown in Multimedia Appendix 1. We searched the Huike (WiseSearch) new database with these keywords. Founded in 1998, the Huike

database is the leading expert Chinese media content database for integrating a massive number of authentic news reports from the Greater China region. It provides exclusive access to comprehensive Chinese news articles, with an average of over 96 million news items added daily from about 1600 print media sources and more than 50,000 internet media sources [15]. We restricted our collected sample to articles published by newspapers of mainland China. To identify whether any information changed over time, we collected Chinese news articles published in two different periods: (1) January 1, 2014, to December 31, 2016, and (2) January 1, 2017, to December 31, 2019. We specifically set 3-year periods because if we collect reports over long periods, latent Dirichlet allocation (LDA) may extract very broad topics, whereas we may not see the health information change if we check reports published in two adjacent short periods. We started our study in late 2020; therefore, we did not include the reports published in 2020 in our sample.

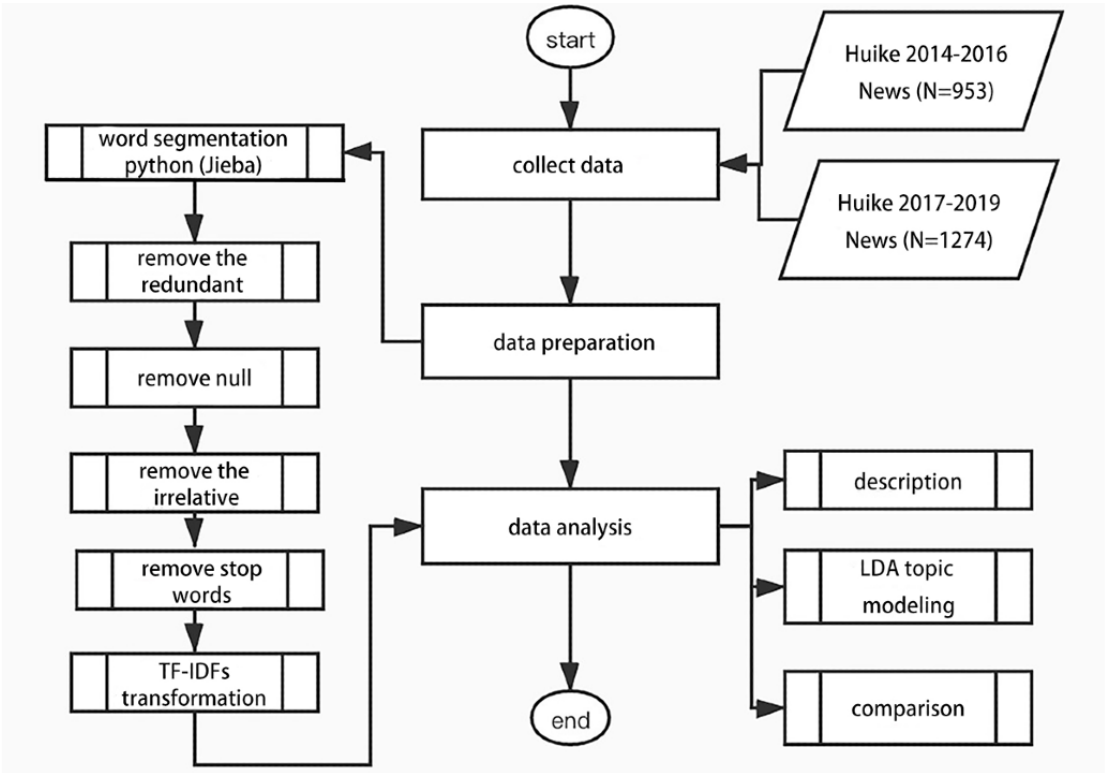
After collecting data, we used topic modeling to obtain useful information from the collected news reports. Topic modeling has been applied in various fields, such as text mining [16], psychology [17], and medicine [18], for data mining. In this study, we used LDA, one of the most well-known topic modeling forms to perform text analysis. LDA is a 3-level hierarchical Bayesian model for modeling text corpora. It assumes that documents, a sequence of random words, can be reflected as random mixtures over latent topics. Each of these topics is also represented by a probabilistic distribution over words [19]. By using Gibbs sampling, a method to estimate the marginal distributions of interested variables, the LDA model can determine the topics among the data pool [20].

Processing

A total of 2227 articles were included, of which 953 articles were published between January 1, 2014, and December 31, 2016. The remaining 1274 reports were published between January 1, 2017, and December 31, 2019.

Data preparation was conducted before we applied the LDA. The process of data preparation is illustrated in Figure 1. Python 3.0 (Python Software Foundation) was used to perform data cleaning, and Python package Jieba was used to conduct word segmentation [21,22]. Redundant and null data were removed, and irrelative data were also excluded from our study. Next, common Chinese stop characters, such as “a,” “of,” and “ten” were removed (see Multimedia Appendix 1). A document-term matrix was established, and term frequency-inverse document frequency, a numerical statistic to show the significance of a word to an article in a corpus, was applied for data processing [23].

Figure 1. Data processing chart. LDA: latent Dirichlet allocation; TF-IDFs: term frequency-inverse document frequencies.



The selection of the LDA topic number is significant. Inclusion of too many topics will cause difficulty in interpretation and subjective validation, whereas too few topics can make the selected topics too broad [14]. To seek the optimum number of topics that LDA needs to extract from the collected news, several evaluation metrics were considered. Topic coherence is a qualitative method to score a topic’s coherence [24]. It measures the degree of semantic similarity between the top words associated with this topic. The generated topic is regarded as coherent if all or most of these keywords support each other, making it easier to interpret the outcomes. In the process of mathematical modeling, each top keyword of a single topic is converted into a context vector using word co-occurrence. The value of topic coherence is computed as the average of cosine

values between every two context vectors [25]. In this study, the coherence model from Gensim (RARE Technologies Ltd)—the Python package for natural language processing—was used to calculate the coherence value [26]. Figures 2 and 3 show that the coherence value reached the highest score when the number of topics reached approximately 8. Thus, we chose 8 as our number of topics and set λ=1 to employ the LDAvis tool [19].

Figure 2. Coherence score for different topic numbers (2014-2016).

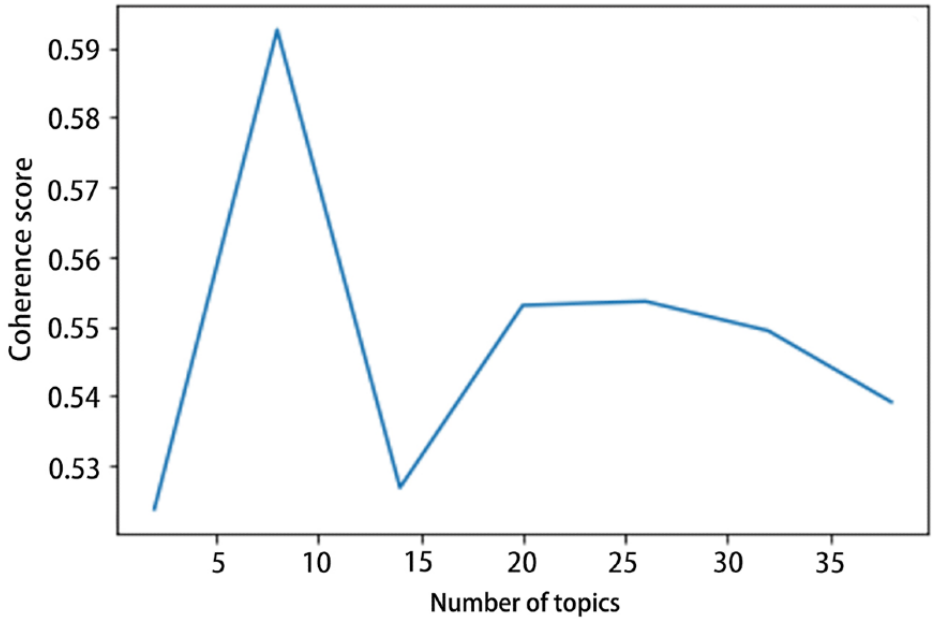
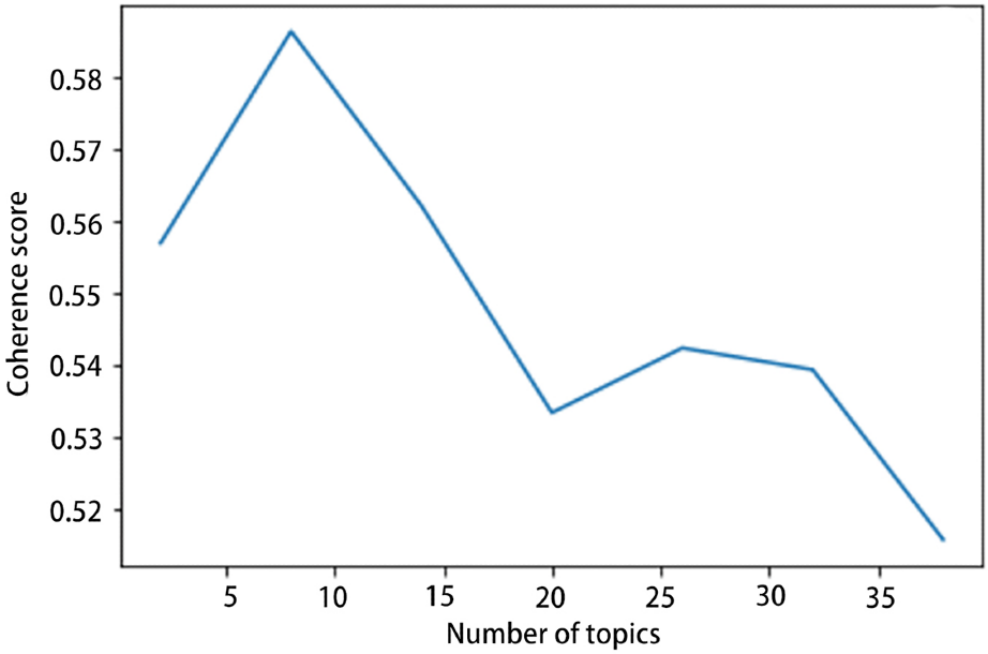


Figure 3. Coherence score for different topic numbers (2017-2019).



Each topic content was generated based on its associated set of keywords. However, no matter how advanced the statistical measures are, the output is not guaranteed to be interpretable because of the complexity of the language [27]. Therefore, we added manual interpretation to analyze the topics. Topics were also named according to the corresponding keywords to illustrate the topics. Tables 1 and 2 show the names of the topics and their keywords across the two periods evaluated.

We also plotted our topics as circles on a 2D plane (Figures 4 and 5) to determine their relationship. The centers of the circles were determined by the calculated distance between topics [19].

Table 1. Topic classification and keywords for 2014-2016.

Topic order	Topic name and keywords	News reports (N=953), n (%)[a]
Topic 1	• Patient treatment • Keywords: hospice care, patient, the sick, hospital, treatment, life, relative, end of life, death, care, in-patient ward, need, pain, medical treatment, mentality, finally, dignity, doctor, cancer, relieve, terminal stage, tumor, accept, nursing, proceed, provide, disease, quality, palliative, at present	178 (18.68)
Topic 2	• Hospice care stories • Keywords: the elderly, one, last, job, life, children, already, hope, mother, doctor, know, people, accompany, at present, think, nurse, everyday, father, always, leave, look after, see, once, time, pass away, inpatient ward, tell, son, face	158 (16.58)
Topic 3	• Development of health care services and health insurance • Keywords: service, development, society, medical care, peaceful, health, medical institution, institution, job, medical, establish, government, carry out, policy, construct, promote, health insurance, hygiene, community health, include, support, system, encourage, correlation, management, medical care and health, service center, improve, perfect, increase	135 (14.17)
Topic 4	• Retirement and nursing home • Keywords: pension, the elderly, service, nursing, institution, the aged, agedness, medical, center, medical treatment and aged care, rehabilitation, combination, hospital, community, provide, household, retirement home, mode, bed, life, journalist, look after, long-term, above, at present, disability, health, demand, profession, construction	129 (13.54)
Topic 5	• Community services and social welfare activities • Keywords: service, hospice care, volunteer, social worker, program, community, activity, carry out, care, social welfare, volunteerism, journalist, organization, profession, spirit, team, mentality, provide, social work, concern, job, family, participate, proceed, compassion, service center, establish, help, China	98 (10.28)
Topic 6	• Huike platform statement • Keywords: content, need, represent, integrity, author, website, in charge of, snapshot, check, only for, statement, connect, search, irrelevant, webpage, click, information, page, original text, instant, linkage, index, free of charge, Huike (WiseSearch), life, offspring, vacation for caring parents, China, society, culture	95 (9.97)
Topic 7	• Hospice ward in the hospital • Keywords: hospital, hospice care, death, journalist, citizen, express, one, enterprise, housing state, education, already, at present, enter, correlation, think, company, America, Hong Kong, around, family, proceed, objection, plan, construction, discover, this year, problem, brilliant, economy, consider	86 (9.02)
Topic 8	• Voluntary service • Keywords: service, volunteer, patient, cancer, terminal stage, hospice care, hospice, hospital, provide, establish, journalist, free of charge, poverty, family, president, life, the, visit, tailor, corpse, nationwide	74 (7.78)

[a]The total percentage is not 100% because of automatic rounding when exporting the results.

Table 2. Topic classification and keywords for 2017-2019.

Topic order	Topic name and keywords	News reports (N=953), n (%)[a]
Topic 9	• Hospice care stories • Keywords: the elderly, life, hospice care, one, death, final, volunteer, job, accompany, inpatient ward, living, hope, relatives, tell, see, leave, face, child, nurse, already, everyday, dying, journalist, livelihood, volunteer, always, know, time, family member	199 (15.62)
Topic 10	• Patient treatment • Keywords: patient, treatment, the sick, relative, cancer, inpatient ward, doctor, terminal stage, suffering, tumor, medical staff, mentality, life, final, nursing, pain, nurse, palliative, dignity, medical, disease, proceed, condition of disease, hospice, relieve, team, look after, provide, admission	196 (15.38)
Topic 11	• Development of health care services • Keywords: health, service, nursing, development, construction, medical, promote, nurse, job, management, establish, society, increase, primary, strengthen, medical institution, complete, implement, carry out, regime, family doctor, industry, encourage, hygiene, push forward, capacity, emphasis, increase, diagnosis and treatment, system	182 (14.27)
Topic 12	• Retirement home • Keywords: pension, service, institution, the elderly, nursing, combination of medical treatment and aged care, the aged, combination, medical, community, rehabilitation, provide, agedness, hospital, household, mode, center, family, disability, look after, bed, life, retirement home, management, above, carry out, journalist, construction, health, countryside	171 (13.42)
Topic 13	• Lin zhong guan huai service (hospice care service in Chinese) • Keywords: hospice care, service, hospital, society, demand, end of life, medical, problem, death, life, China, at present, development, profession, our country, education, suggestion, think, express, some, one, social worker, government, correlation, enterprise, care, need, important, provide, support	164 (12.95)
Topic 14	• An ning liao hu service (hospice care service in Chinese) • Keywords: peaceful, care, service, patient, center, pilot program, hospital, job, carry out, provide, country, nationwide, service center, look after, dignity, life, hygiene, terminal stage, care, community health, impatient ward, mentality, agedness, humanistic, medical institution, pilot work, institution, disease, journalist, establish	136 (10.68)
Topic 15	• Social welfare activities • Keywords: activity, society, volunteer, social welfare, family, compassion, job, community, program, volunteerism, culture, concern and love, China, life, learn, child, help, one, spirit, organization, become, student, charity, participate, Shanghai, team, people, entrepreneurship programs, join, world	113 (8.95)
Topic 16	• Huike platform statement • Keywords: content, represent, in charge of, integrity, author, website, snapshot, statement, check, connection, instant, only for, click, search, free of charge, irrelevant, original text, link, information, page, index, Huike (WiseSearch), webpage, need, profession, journalist, hospital, the newspaper, center, correspondent	111 (8.71)

[a]The total percentage is not 100% because of automatic rounding when exporting the results.

Figure 4. Intertopic distance map (via multidimensional scaling) for 2014-2016. PC: principal component.

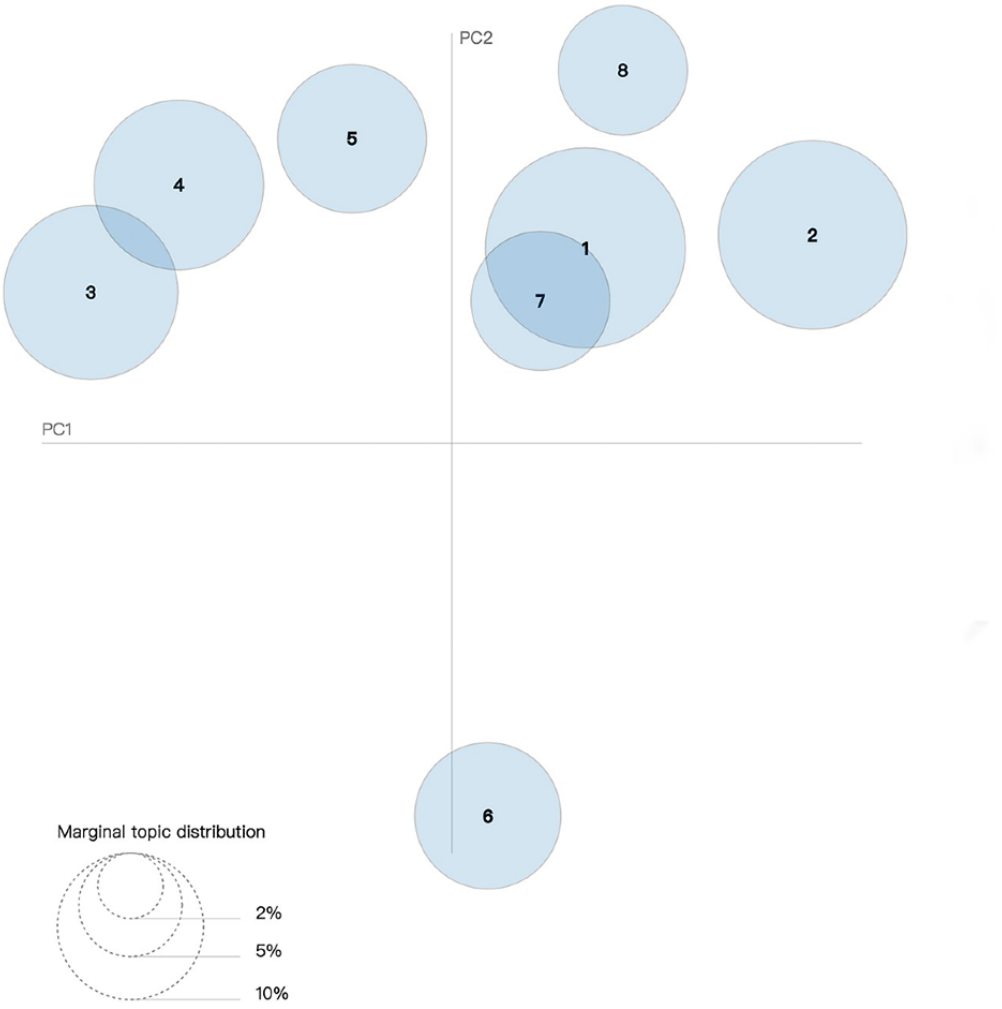


Figure 5. Intertopic distance map (via multidimensional scaling) for 2017-2019. PC: principal component.

Results

We categorized our collected sample of news articles into 8 topics for each period (ie, January 1, 2014, to December 31, 2016, and January 1, 2017, to December 31, 2019) by applying LDA topic modeling (Tables 1 and 2). These two periods share several similar topics, among which *patient treatment* and *hospice care stories* emerged as the two most popular topics. Topic 3 (*development of health care services and health insurance*, n=135) and topic 11 (ie, *development of health care services*, n=182), ranked as the third most popular topic, both accounting for approximately 14%. Topic 4 (*retirement and nursing home*, n=129) and topic 12 (*retirement home*, n=171) accounted for over 13%.

Figures 4 and 5 present the overall view of our topic model. Each figure shows 8 circles that represent various topics. We can calculate the overall prevalence by computing areas of all circles. Intertopic distances are represented by multidimensional scaling on a 2D plane [28]. The principal components PC1 and PC2 represent the transverse axis and longitudinal axis, respectively.

Figures 6 and 7 present the top 30 relevant terms for topics 1 and 9, respectively. These two topics had the highest proportion of news articles in their respective time periods; therefore, we present them as an example for demonstration. The word frequency distribution is relative to the full corpus by the system. The blue bar presents the overall term frequency, and the red bar presents the estimated frequency of a specific topic. With regard to topic 1, Chinese mass media preferred to talk about what treatment the patients can receive at the end of life. Using this approach, as illustrated in the literature, we could interpret the content of a topic [29,30].

Figure 8 shows the number of hospice care news reports published over time. The number of news articles peaks and wanes across different months. In the first period, the total coverage reached 953, and the highest monthly coverage was 85 news reports. In the second period, the number of total relevant news reports was 1274, and the monthly coverage peaked in June 2019. Table 3 shows Chinese laws and policies about hospice care and their release dates.

Figure 6. Top 30 most relevant terms for topic 1 (18.68% of all news reports). Saliency (term w) = frequency (w) * [sum_t p(t | w)/p(t)] for topics t; see [29]. Relevance (term w | topic t) = λ * p(w | t)/p(w); see [30].

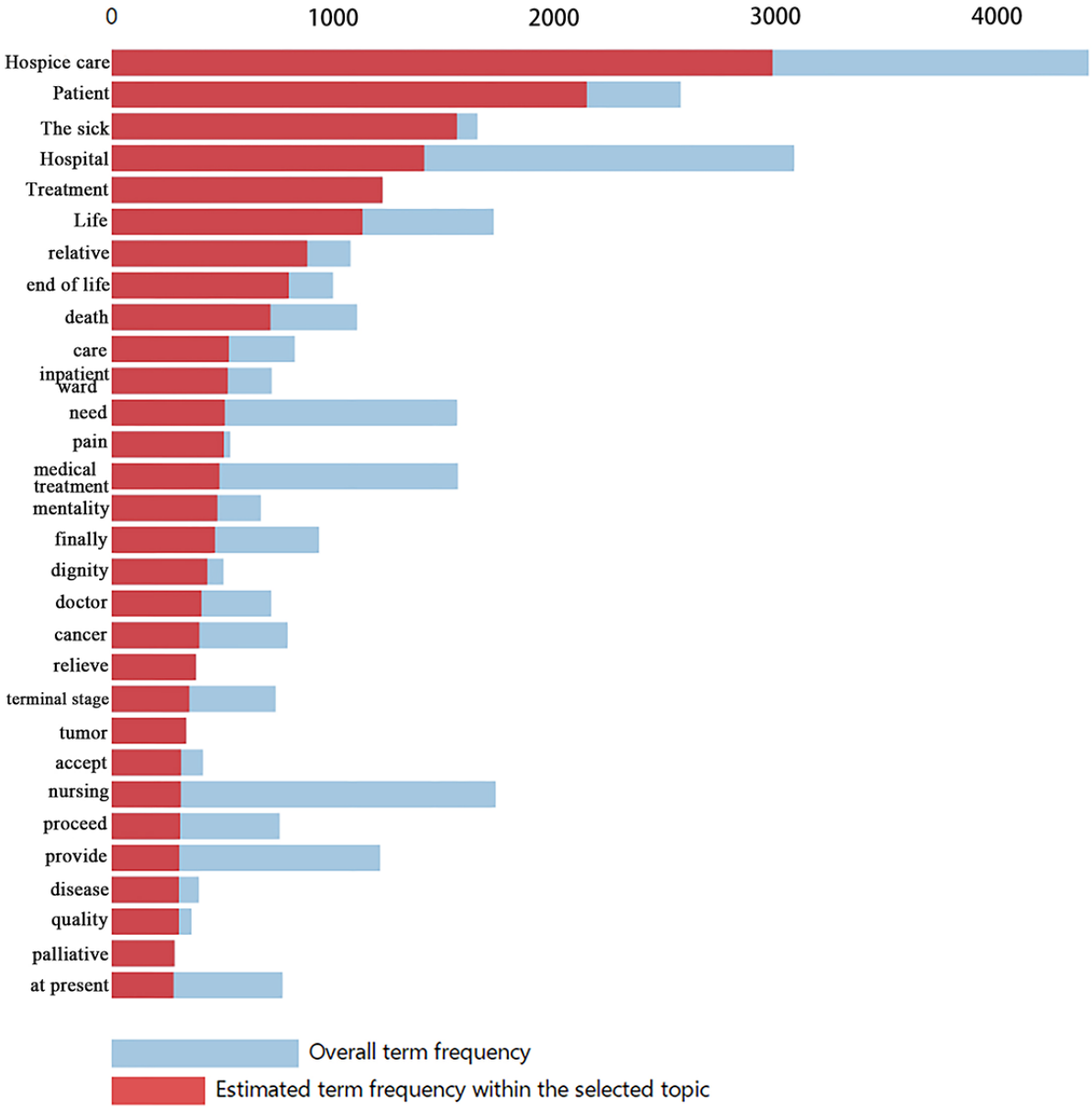


Figure 7. Top 30 most relevant terms for topic 9 (15.62% of all news reports). Saliency (term w) = frequency (w) * [sum_t p(t | w)/p(t)] for topics t; see [29]. Relevance (term w | topic t) = λ * p(w | t)/p(w); see [30].

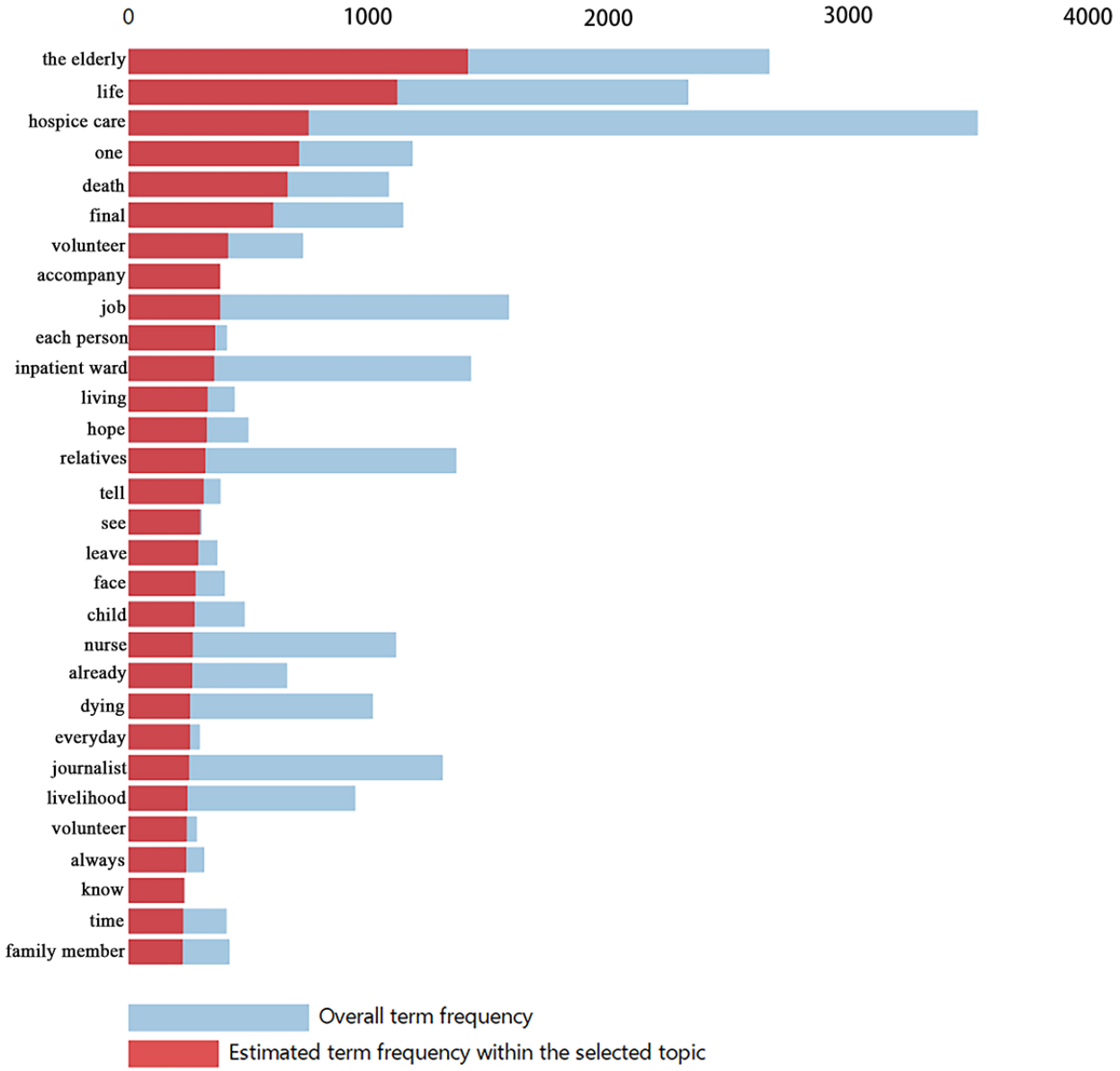


Figure 8. Time series of news streams with corresponding laws and polices during 2014-2019. NHFPC: National Health and Family Planning Commission of the People's Republic of China.

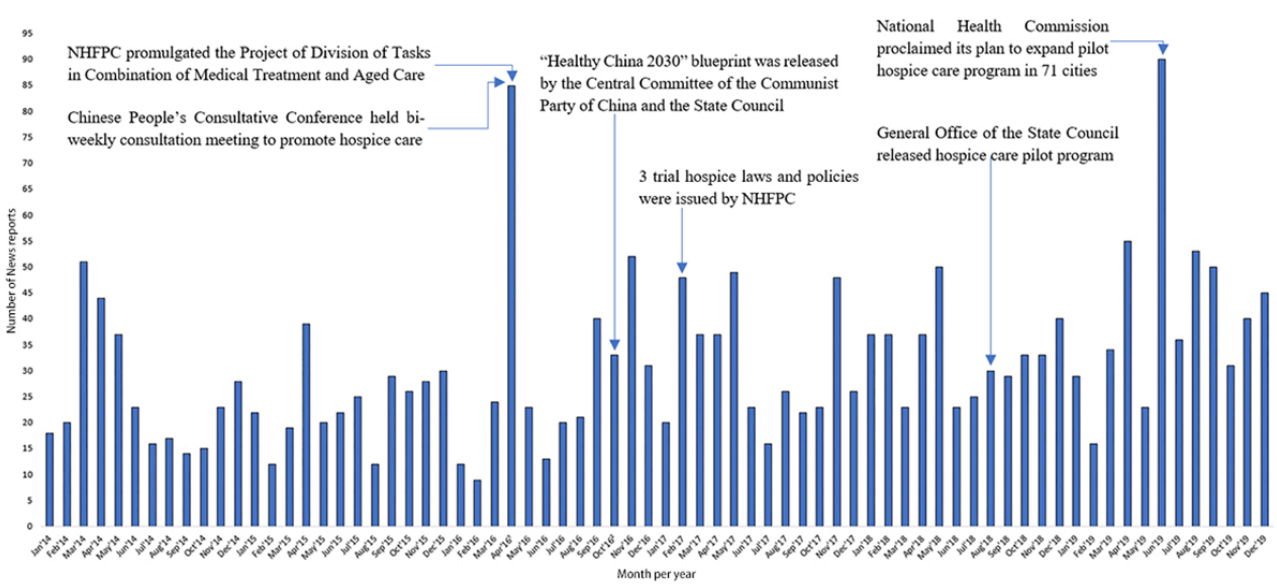


Table 3. Chinese laws and policies about hospice care.

Date	Laws and policies
April 7, 2016	The National Health and Family Planning Commission of the People's Republic of China (NHFPC, the predecessor of National Health Commission) promulgated the Project of Division of Tasks in Combination of Medical Treatment and Aged Care to integrate hospice care into the elderly care system [31].
April 21, 2016	Chinese People's Consultative Conference (a political advisory body of the People's Republic of China and a central part of the Chinese Communist Party's United Front system) held biweekly consultation meeting to promote hospice care [32].
October 25, 2016	"Healthy China 2030" blueprint was released by the Central Committee of the Communist Party of China (a political body that comprises the top leaders of the Chinese Communist Party) and the State Council to strengthen the construction of hospice care institutions [33].
February 9, 2017	Hospice Care Center Basic Standards (trial), Hospice Care Center Management Standardization (trial), and Hospice Care Practice Guideline (trial) were issued by the NHFPC [34,35].
August 28, 2018	General Office of the State Council released Major Projects for Deepening Medical and Health System Reform in the Second Half of 2018, including the hospice care pilot program [36].
June 10, 2019	The National Health Commission proclaimed its plan to expand pilot hospice care program in 71 cities [37].

Tables 4 and 5 show the top 10 productive media sources with regard to publication of news reports on hospice care. Local and national newspapers were all engaged. Table 4 shows that Xin'an Evening News (Digital News) had the highest coverage during 2014-2016, with 21 (11.67%) news reports, followed by Xinmin Evening News and China News service (11/953, 11.11%). As shown in Table 5, the People's Political Consultative Daily (Digital News) was the most active mass media in the second study period, with 39 (23.07%) relevant articles published. It was during the press window of policies and viewpoints of the Chinese People's Political Consultative Conference wherein there was considerable reporting about the biweekly consultation meetings held by the Chinese People's Political Consultative Conference to promote hospice care [32]. In addition, 18 (10.65%) news reports were published in the Middle-Aged Times.

Table 4. The most represented media sources for news reports collected during 2014-2016 (N=953).

Media sources	News reports, n (%)
Xin'an Evening News (Digital News)	21 (11.67)
Xinmin Evening News	20 (11.11)
China News Service	20 (11.11)
Qilu Evening News (Digital News)	19 (10.56)
Shanxi Evening News	18 (10.00)
Sanjin Metropolis Daily	18 (10.00)
Youth Daily	17 (9.44)
Shaanxi Daily	16 (8.89)
Workers' daily	16 (8.89)
Shanxi Daily (Digital News)	15 (8.33)

Table 5. The most represented media sources for news reports collected during 2017-2019 (N=1274).

Media sources	News reports, n (%)
People's Political Consultative Daily (Digital News)	39 (23.07)
Middle-aged Times	18 (10.65)
Yantai Daily	17 (10.06)
Qilu Evening News (Digital News)	17 (10.06)
Shanxi Daily (Digital News)	17 (10.06)
Wuhan Evening News	16 (9.47)
China News Service	12 (7.10)
Xinmin Evening News	12 (7.10)
Zhongshan Commercial Daily	11 (6.51)
Workers' daily	10 (5.92)

Discussion

Principal Findings

Hospice care has received much attention in China in the context of aging of the Chinese population. Topic modeling is a new method that helps to shed light on what health information has been delivered by the mass media. In this study, we observed that the number of reports about hospice care in the second study period slightly increased compared to the first period, indicating Chinese mass media had paid more attention to this topic. We also found that mass media tended to focus on hospice care in April of every year (Figure 8). Of all the monthly news about hospice care published between January 1, 2014, and December 31, 2016, coverage peaked in April (168 reports published). Although the proportion of news reports in April decreased in the second study period, it still accounted for 10.11% of the collected reports, ranking as the second month with the highest number of reports. This is likely because the Tomb-Sweeping Day, a traditional Chinese festival, falls on April 4 to 6 every year. On this day, people in China usually clean up the graves of their ancestors and deceased relatives to show their grief. As a result, mass media channels strategically chose this timeline to focus on hospice care and discuss the contemporary view of life and death, potentially making this concept more acceptable for the general public.

Supportive laws and policies are indispensable for the optimal development of hospice care services [38], and the promulgation of laws and policies often contribute to an increase of coverage. For example, relevant laws and policies were released in February 2017 [34,35] and June 2019 [37], and a considerable increase in articles about hospice care was witnessed in these 2 months (Figure 8). In some cases, however, mass media did not leverage the opportunity to broadcast new policies. For instance, in October 2016, the "Healthy China 2030" blueprint was issued [33], while there were few news reports about hospice care in October. Therefore, if the government wants to ensure the citizens are aware of the latest policies about hospice care, the mass media should be utilized to disseminate these policies.

In the second period, topic 9 (*hospice care stories*) overtook topic 10 (*patient treatment*) as the top news topic. Although both news topics focused on what happened after hospice care was provided to patients, reports pertaining to the topic *patient treatment* tended to follow a well-established pattern of reporting on the care patients received. Mass media channels conveyed health information by elucidating the role of the hospital, hospice, doctor, and family members in the process of treatment.

The news articles addressing hospice care tended toward personal experience. These stories were narrated in a kind and vivid tone, which reflected the humanistic caring spirit in the reports. Mass media should continue to report hospice care with a humanistic caring spirit to make this topic more acceptable and promote health education well.

The development of health care services is also a major concern of the media. In the first period, the mass media linked the development of health care services with the development of health insurance, proclaimed the benefits to patients and medical institutions of the government's promotion, and related system development, which stressed the importance of health insurance. However, most of the hospice care services are still not included in the national health insurance [39]. The high cost of hospice care is a barrier for most patients. In addition to describing the development of health care services, many articles related to topic 11 also introduced the concept of the family doctor, which was a new highlight of the development.

Retirement homes and nursing homes are important places to facilitate hospice care [40]. Coverage of topic 12 focused on the significance of these institutions. Furthermore, topic 4 covered multi-modeled cooperation between hospitals and retirement homes. In April 2016, the NHFPC enacted the Project of Division of Tasks in Combination of Medical Treatment and Aged Care to encourage this multi-modeled cooperation [31]. In the process of cooperation, an integral elderly care system consisting of daily life care, medical treatment, rehabilitation nursing, and hospice care, is expected to be built. It can address the imbalance between the huge need for hospice care and the lack of hospice institutions, as well as maximize the benefits of hospice care in the elderly care system.

In these two defined periods, social welfare activities also received wide coverage in the Chinese mass media. Topic 5 (*community services and social welfare activities*) emphasized that volunteers working in hospice care were significant to society, whereas topic 15 (*social welfare activities*) in the second period also referred to the participation of other social forces, such as student teams and entrepreneurship programs. Since the initial stage, the modern hospice care movement has received sustained support from volunteers who were devoted to eliminating the stigma of hospice care, raising funds, attracting seldom-heard communities, and caring for the patients and their families directly [41]. In China, there are plenty of nonprofit organizations engaged in hospice care promotion, including the Hospice Palliative Care Alliance of China Foundation [42] and the Chinese Association for Life Care [43]. The coverage of welfare activities can help readers get acquainted with the work of volunteers in hospice care and appeal to the public to take part in it, which contributes to the social moral. It is worth mentioning that topic 8 (*voluntary service*) also reported the involvement of volunteers in hospice care.

Two topics from the second period vary from the first period. These are topic 13 (*lin zhong guan huai service*) and topic 14 (*an ning liao hu service*). Although both "lin Zhong guan huai" and "an ning liao hu" both mean hospice care in Chinese, news articles on these two topics attached significance to different contexts. For example, the news reports on topic 13 underlined the role of the hospital and community. The effect of community engagement activities on hospice care development is recognized, and these activities were a priority for most hospices in the United Kingdom [44]. The Chinese government also called on the community to shoulder the responsibility for caring the elderly in its 5-year plan (2016-2020) on care for older adults [45]. Reporting community significance on hospice care can appeal to community members to join in these activities. Topic 14, however, raised the necessity to pay more attention to the psychological problems of patients.

Limitations

Our study is one of the first to reveal the role of Chinese mass media in communicating health information about hospice care. Our study has some limitations. We searched the Huike (WiseSearch) news database for data collection. This database only includes text news articles. Therefore, we might have missed news content in the form of images and short videos through some new media platforms such as WeChat (the most popular instant messaging app in China) and TikTok (a popular video social media platform among the young generation). Moreover, the inherent limitations of LDA restricted some part of our study, as LDA is limited to the analysis of few articles or overly short articles [46]. Sentiment analysis is a helpful method to evaluate positive or negative attitudes in the text [47]; it would be favorable if we could adopt it to help us obtain more information about the Chinese mass media's attitude toward hospice care.

Conclusions

We investigated the information about hospice care disseminated through Chinese mass media during two specific periods by analyzing collected news reports using topic modeling. We conclude that the coverage of hospice care generally increases in April of every year, which is related to a special traditional Chinese festival. We propose that authorities and policymakers in China should cooperate with the mass media to propagate the latest hospice care policies. Two of the most popular topics surrounding hospice care are *patient treatment* and *hospice care stories*, of which hospice care stories have accounted for a greater proportion of reports in recent years, demonstrating the humanistic caring spirit adopted by the mass media while reporting on this public health issue. Development of health care services and retirement homes are also reported, while the emphasis of each topic changes with time.

Acknowledgments

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Authors' Contributions

W-KM, QL, and ZZ conceived the original concept and designed the whole research process. QL, JC, and WT collected and cleaned the data. W-KM, QL, and ZZ performed data analysis and data interpretation, and they wrote the first version of the manuscript. QL and JC created the figures. JS, BA, CZ, and YZ contributed to the administration of the project, data analysis, and data interpretation. ZZ and JC contributed to the final version of the manuscript. W-KM and BA reviewed the manuscript. All authors contributed to the interpretation of the results and reviewed the final manuscript. All authors discussed and agreed on the implications of the study findings and approved the final manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Various references to "hospice care" in the Chinese language and their corresponding Chinese characters.
[DOCX File , 15 KB - publichealth_v7i10e29375_app1.docx]

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Abbreviations

LDA: latent Dirichlet allocation
NHFPC: National Health and Family Planning Commission of the People's Republic of China
PC: principal component

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Original Paper

Readiness for Use of HIV Preexposure Prophylaxis Among Men Who Have Sex With Men in Malawi: Qualitative Focus Group and Interview Study

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Abstract

Background: Men who have sex with men (MSM) are a key group for HIV interventions in Malawi considering their high HIV prevalence (17.5% compared to 8.4% among men in the general population). The use of oral preexposure prophylaxis (PrEP) presents a new opportunity for MSM to be protected. We present the findings from a qualitative assessment designed to assess awareness of and willingness and barriers to using PrEP among MSM in Malawi.

Objective: The 3 main objectives of this assessment were to determine: (1) awareness of PrEP, (2) factors that influence willingness to use PrEP, and (3) potential barriers to PrEP use and adherence among MSM in order to guide the design and implementation of a PrEP program in Malawi.

Methods: Ahead of the introduction of PrEP in Malawi, a qualitative study using in-depth interviews (IDIs) and focus group discussions (FGDs) was conducted in October 2018 in Blantyre, Lilongwe, and rural districts of Mzimba North and Mangochi. With support of members of the population, study participants were purposively recruited from 4 MSM-friendly drop-in centers where MSM receive a range of health services to ensure representativeness across sites and age. Participants were asked what they had heard about PrEP, their willingness to use PrEP, their barriers to PrEP use, and their preferences for service delivery. The data were analyzed using a thematic content analysis framework that was predetermined in line with objectives.

Results: A total of 109 MSM were interviewed—13 through IDIs and 96 through FGDs. Most participants were aware of PrEP as a new HIV intervention but had limited knowledge related to its use. However, the majority were willing to use it and were looking forward to having access to it. IDI participants indicated that they will be more willing to take PrEP if the dosing frequency were appropriate and MSM were involved in information giving and distribution of the drug. FGD participants emphasized that places of distribution and characteristics of the service provider are the key factors that will affect use. Knowing the benefits of PrEP emerged as a key theme in both the IDIs and FGDs. Participants highlighted barriers that would hinder them from taking PrEP such as side effects which were cited in IDIs and FGDs. Key factors from FGDs include cost, fear of being outed, drug stockouts, fear of being known as MSMs by wives, and lack of relevant information. FGDs cited stigma from health care workers, forgetfulness, and community associated factors.

Conclusions: Despite having inadequate knowledge about PrEP, study participants were largely willing to use PrEP if available. Programs should include an effective information, education, and communication component around their preferences and provide PrEP in MSM-friendly sites.

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KEYWORDS

MSM; readiness to use; PrEP; HIV prevention; qualitative assessment; HIV; men who have sex with men; Malawi; prophylaxis

Introduction

Men who have sex with men (MSM) bear a disproportionate burden of the HIV epidemic [1]. In 2019, the Joint United Nations Programme on HIV and AIDS reported that gay men and other MSM accounted for 17% of all new HIV infections globally [2] and that their risk of HIV acquisition was 22 times higher than for heterosexual men. Similarly, in East and Southern Africa, MSM were reported to contribute to 17% of new HIV infections [2]. Data from studies conducted between 2011 and 2014 among MSM in Malawi found HIV prevalence ranging from 18.2% to 21.4% [3,4]. This is more than 3 times the national average of 6.4% among men ages 15 to 49 years in the general population [5].

In September 2015, the World Health Organization (WHO) recommended oral preexposure prophylaxis (PrEP) as part of a combination HIV prevention approach [6] for people at substantial risk of HIV infection. PrEP is the use of antiretroviral medication to prevent HIV-negative individuals from acquiring HIV. PrEP complements condom and lubricant use, behavioral counseling, treatment for sexually transmitted infections, HIV testing and counseling, voluntary male medical circumcision, and antiretroviral therapy (ART) for partners living with HIV [7-9]. A proportion of MSM do not use condoms consistently for various reasons; therefore, using PrEP during periods of higher risk of HIV responds to this reality and strengthens comprehensive HIV prevention [10]. Despite the evidence of its effectiveness in preventing HIV, access to PrEP has been limited in many countries. In Malawi, PrEP was included in the Malawi Guidelines for Clinical Management of HIV in Children and Adults 2016 and National HIV Prevention Strategy 2015-2020; however, at the time of this assessment, PrEP was not yet readily available in the country. This study was conducted ahead of the introduction of PrEP services in Malawi to inform national scale-up of PrEP services, especially for MSM. This assessment was conducted to support the design of the PrEP program in Malawi.

Numerous individual, familial, institutional, and structural factors affect MSM's access to health care in Malawi. These include stigma from community members due to cultural beliefs [3]; hesitancy of MSM to reveal their sexual practices when accessing health care [4], which limits their ability to access appropriate services, information, education, and counseling; inadequate capacity of service providers to provide MSM-friendly health services [1-4]; and unfavorable social and legal environments created by the Malawi penal code that criminalizes same-sex relationships and encourages discrimination against MSM [11]. While MSM have a high turnover of sexual partners, low condom use, and multiple concurrent partnerships, they have reported low levels of individual risk perception [12,13]. However, it is important to note that these studies were conducted several years ago, and there is a need to conduct similar studies to obtain updated data on these risk factors. This discrepancy between actual and perceived risk requires programs to innovate and provide a wide choice of services to MSM to reduce the incidence of HIV among them [1].

Although the legal environment for MSM, transgender people, and other sexual minorities remains constrained in Malawi, significant progress has been made in the provision of health services. For instance, the current national (Ministry of Health) Clinical Guidelines for the Management of Sexually Transmitted Infections [14] and the Malawi National HIV Prevention Strategy 2015-2020 [15] have incorporated MSM-specific interventions. Civil society organizations, legal and advocacy partners, and national and international nongovernmental organizations, such as FHI360's Linkages across the Continuum of HIV Services for Key Populations Affected by HIV (LINKAGES) project, are also providing a mix of human rights, legal, and HIV prevention services. LINKAGES was launched in June 2014 as the US President's Emergency Plan for AIDS Relief (PEPFAR)/US Agency for International Development (USAID)'s largest global HIV project dedicated to providing holistic HIV prevention, care, and treatment programming for key populations. In Malawi, through community outreach services and drop-in centers (DICs), the project has been providing prevention, care, and treatment services to key populations, including MSM and transgender individuals.

The primary aim of this study was to assess MSM's awareness of PrEP, their willingness to use it, and barriers they face to PrEP use in order to guide the design and implementation of a PrEP program in Malawi. Specifically, the study aimed to determine awareness and attitudes about PrEP, factors that will likely facilitate PrEP uptake and adherence, and potential barriers to PrEP uptake and adherence.

Methods

Study Design and Population

A qualitative study consisting of in-depth interviews (IDIs) and focus group discussions (FGDs) was conducted to ascertain MSM knowledge of and perceptions about PrEP uptake and adherence in Lilongwe and Blantyre cities and the two rural districts of Mangochi and Mzimba North. These districts were targeted as the project leveraged on the infrastructure of the LINKAGES project. Study participants were identified in October 2018 from MSM accessing HIV services from peer educators at various sites, including DICs supported by the

LINKAGES project, as well through other projects run by the local civil society organization Center for Development of People (CEDEP). Prior to the study, MSM were engaged through CEDEP to provide input to the design and implementation of the study. Some of the input was on the questionnaire and language, who to include as data collectors, and where to conduct the IDIs and FGDs among others. Subsequently data collectors were picked from the group of MSM who participated in the consultation process. The LINKAGES-supported DICs are key population–friendly service delivery points where MSM access condoms, lubricants, HIV testing, and counseling; services for gender-based violence; and recreational activities. Men were eligible to participate in the study if they were aged 18 years or older, accessed services from LINKAGES-supported DICs or CEDEP projects, self-identified as MSM or were identified as such by peer educators, and tested negative for HIV within the past 3 months.

Sampling

Study participants for FGDs were purposively recruited from men who accessed services at DICs to ensure representation from all sites and different age groups. Lists of eligible study participants were drawn both from LINKAGES DIC records and records of other CEDEP projects and were classified by geographical location, social networks, and age group. Participants were randomly selected within each subgroup. Clinical staff at the DICs were involved in the identification while ensuring that the participants met the eligibility criteria for the study.

A total of 8 FGDs with 12 participants per group were conducted making a total of 96 MSM participating in the FGDs. Two FGDs were conducted per district, including one for younger MSM ages 18 to 34 years and another for older MSM ages 35 years and older. A total of 13 IDIs were conducted, comprising 3 people from each of the 4 districts and one man who has sex with other men who was involved in advocacy. The IDI participants were purposively selected from LINKAGES projects and other social projects to include MSM who are highly hidden from society as well as the MSM community because of their social position. The 3 participants from each district had at least one of the following characteristics: married individuals, educated at a tertiary level or working, and older than 35 years.

Data Collection

Data were collected in October 2018 following study approval. Data were collected by trained study assistants using semistructured interview guides. The study assistants were fluent in both English and Chichewa, a local language, and they conducted IDIs and facilitated FGDs in the language of each participant's choice. Data collected from participants included information about their knowledge, perceptions, and concerns about PrEP; factors that would potentially motivate them to use it; barriers to PrEP use; and service delivery preferences related to infrastructure, knowledge needs, and providers. FGDs were done with 6 to 12 participants per group and conducted at DICs. Each FGD lasted for approximately 70 minutes, and 6 of the 8 FGDs were audiorecorded, as participants of 2 FGDs declined permission for the FGDs to be recorded. IDIs were conducted at a place convenient for the participant. On average, the interviews lasted 50 minutes, and 8 out of 13 interviews were audiorecorded, as 5 people declined to be audiorecorded. IDIs and FGDs used the same questions because the data collected in the IDIs supported the opinions collected in the FGDs from individuals that are highly hidden and could not participate in FGDs.

The 8 IDIs and 6 FGDs that were audiorecorded were transcribed into Chichewa or English by an independent transcriber, and all interviews conducted in Chichewa were then translated to English. Transcripts were proofread and checked for accuracy by listening to the recordings multiple times to ensure that the translation conveyed the participants' answers and descriptions. The aim was to produce the best possible translation and preserve the content and meaning of the original text. For the 5 IDIs and 2 FGDs that were not audiorecorded, study research assistants took notes, including direct quotes.

Data Analysis

Data were analyzed using a thematic content analysis framework, where deductive and inductive approaches were used to code the data. The former was guided by the literature and study objectives in identifying the themes under which data were grouped. Inductive analysis was then conducted by listening to the audiorecording, reading through the transcripts, and identifying emergent themes. The data analysis followed 6 stages [16]: becoming familiar with the data, generating initial codes, searching for themes, refining themes, naming themes, and producing the report [17]. The findings presented include quotes without identifiers to protect confidentiality.

Ethics

The study protocol was reviewed by the University of Malawi, College of Medicine's Research Ethics Committee and FHI360's Protection of Human Subjects Committee. All study staff, including the study assistants, were trained in ethics for conducting research with human subjects, with a focus on ensuring informed consent, privacy, and confidentiality. They were also trained on data collection tools to standardize the information to be collected and the process of data collection. The data collectors were identified from the cohort of peer educators under the LINKAGES project who are part of the MSM community. Potential participants were informed that participation in the FGD and IDI was voluntary and that refusal will not affect continued access to services. Written informed consent was obtained from everyone who agreed to participate. Participants were not compensated for participating in the study but were reimbursed for the cost of travel from their home to the study site. No personal identifying information was collected during the FGD and IDI. Study participants were assigned IDs/unique identifiers, and no names were used. IDIs and FGDs were conducted in places that assured privacy where conversation between interviewer and interviewees and FGD facilitators and participants could not be heard by a third party.

Results

Sociodemographic Characteristics

Table 1 below summarizes the characteristics of the study participants. Most of the study participants were aged 35 to 40 years (30/109, 27.5%) and the least were aged 30 to 34 years (14/109, 12.8%). There was a uniform number of participants from the 4 participating districts.

Table 1. Characteristics of study participants (n=109).

Characteristics	Value, n (%)
Age group (years)	
18-24	21 (19.3)
25-29	17 (15.6)
30-34	14 (12.8)
35-40	30 (27.5)
41+	27 (24.8)
Education	
None	8 (7.3)
Primary	37 (33.9)
Secondary	50 (45.8)
Tertiary	14 (12.8)
Marital status	
Never married	44 (40.3)
Married	44 (40.3)
Separated	18 (16.5)
District	
Lilongwe	28 (25.7)
Blantyre	27 (24.8)
Mangochi	27 (24.8)
Mzuzu	27 (24.8)
On salary	
Yes	30 (27.5)
No	79 (82.5)

Awareness and Attitudes Regarding PrEP

Of the 96 FGD participants, 40 indicated that they heard about PrEP before the study while 20 indicated that they heard about the drug during the survey. Of the IDI participants, 69% (9/13) had heard about PrEP prior the study and 4 learned about it during the study.

> *I hear it a drug you take before having sex to protect yourself from catching HIV.* [FGD participant]
>
> *It is a drug for HIV prevention which you take before you have sex with you partner.* [IDI participant]

When asked what they knew about PrEP, 35% (34/96) of the FGD participants and 67% (6/9) of the IDI participants said they did not know much. Of the FGD participants, 45% (18/40) who heard about PrEP confused PrEP with postexposure prophylaxis (PEP). Awareness was better among younger MSM participants than older MSM participants, as they were able to describe PrEP as prevention before acquiring HIV.

> *I have heard about PrEP of which I can't describe well. I heard that these are drugs to be provided to HIV-negative people to protect them from HIV.* [IDI participant]
>
> *You use it to kill the virus within 72 hours of sleeping with someone without a condom.* [FGD participant]

When asked about the main source of their information on PrEP, the majority reported friends while others reported civil society organizations (CSOs) and social media. Family was not mentioned as one of the sources of information. There were some mixed ideas about the awareness and importance of using condoms while taking PrEP.

> *I heard about it this other day when I was drinking at a bottle store. I heard that when you do not have HIV you can take these drugs to protect yourself from HIV.* [IDI participant]

Participants from both IDIs and FGDs acknowledged the importance of using condoms when one is on PrEP to have

double protection for HIV and prevent sexually transmitted infections. However, others pointed out that using condoms combined with PrEP defeats the purpose of using PrEP for HIV prevention as condoms similarly protect against HIV and other STIs.

> *Why should we use two things? I wish we could be choosing between the two.* [FGD participant]

Some participants were male sex workers and reported that condom use with clients was sometimes challenging due to client preferences. One participant described the appeal of PrEP in cases where he did not know clients' HIV status.

> *I prefer having sex with a partner without using a condom. Sometimes we meet clients and we don't have time to go for HIV test before sex. So if PrEP is available for use, I will be taking PrEP before having sex with someone whose HIV status I don't know. PrEP will help me protect myself from HIV.* [IDI participant]

> *I wish the service could start immediately for us MSM like the female sex workers [FSWs] because PrEP will help me save my life as I don't use condoms all the time because some clients prefer sex without a condom.* [FGD participant]

Attitude

Despite the limited awareness of PrEP, there was overall a positive attitude toward PrEP. Study participants from both IDIs and FGDs noted that since PrEP will reduce their chances of being infected with HIV, the intervention was welcome within the MSM community. Of the FGD study participants, 67% (64/96) also indicated that they would not wait for a long time or for someone they knew to use PrEP before using it themselves, and they said they would use it right away. Some asked for the intervention to come to Malawi soon. From the IDIs, 38% (5/13) indicated that they would not wait to take PrEP but take it immediately as it is rolled out. A total of 62% (8/13) of FGD study participants indicated that they have multiple sexual partners and stated that they were more willing to use PrEP as an additional HIV prevention because sometimes they indulged in unprotected sexual intercourse with their partners.

> *Every time I am worried about getting infected with HIV. I want to have a long life. This initiative will make me healthy.* [IDI participant]

> *Let the drugs come, we are waiting.* [FGD participant]

> *Why would we wait for a year, were you trying us?* [FGD participant]

> *Once the drug is in we will use immediately, we can't wait because the drug has already been tried in other countries.* [IDI participants]

Benefits From PrEP

All 13 IDI participants indicated that if PrEP were available for them to use, they would want to use it to benefit from the protection from HIV. They mentioned preventing acquisition of HIV, enjoying a long life, and avoiding long-term ART if they otherwise get infected as benefits they would get from using PrEP. Another benefit was that PrEP would be able to prevent HIV transmission to sexual partners, including one's wife. Likewise, 61% (52/96) of FGD participants both young and old indicated that HIV prevention will be their primary motivation.

> *I don't know what I can do if I test HIV positive. It means I have to be on [antiretrovirals] daily. With PrEP maybe I would not be taking ART drugs daily.* [IDI participant]

> *If I protect myself from HIV I will not have to take ART for the rest of my life.* [FGD participant]

Formulation and Dosing Preferences

Study participants were asked which of the different frequencies of dosing they were comfortable with and in what formulation (tablet or injection). Study participants were concerned about the dosing frequency and reported that they would be more likely to use PrEP if the dosage is not daily.

> *If we will be using daily tablets, it means we will have to go to the facility to collect medications so often. We do not have that kind of cash to be traveling all the time.* [IDI participant]

> *Weekly is good, because taking drugs brings bad taste in the mouth, so taking the drug daily for a long time is not good.* [FGD participant]

Preferences for oral or injectable PrEP were mixed. Some indicated that they would prefer an injectable form, while others wanted pills because they feared injections. However, some who were married indicated that they would like PrEP use to be disguised so that their spouses or parents would not suspect anything. Specifically, some participants expressed that they would prefer small pills, which would be less noticeable and easier to swallow.

> *I am married also to a woman. She may suspect something if I am using pills every day at home.* [IDI participant]

> *Once a month injection, because a daily pill is too difficult to be taken. And for it to be attractive, it must not have more side effects.* [IDI participant]

MSM Involvement for PREP Demand Creation and Distribution

Participants also indicated the need to involve members of the MSM community to promote awareness of the product, as well as distribution of the drug. They pointed out the need to build the capacity of MSM representatives to share information about PrEP within the MSM community.

> *Choose MSM representatives from the MSM community to be like peer educators.* [IDI and FGD participants]

FGD Participants Spelled Out Where It Is Provided and Who Provides It

Study participants were asked about their health services preferences that would contribute to PrEP uptake and adherence. DICs were the most preferred service delivery point, followed

by outreach services. These settings were most often reported as venues where PrEP could be provided and accessed without concerns about stigma and discrimination. Many (30/96) participants from FGDs said they would prefer PrEP to be available in DICs and outreach sites, where there was minimal to no stigma and discrimination.

> *If you want MSM to take PrEP, then make sure that you provide services in places where we are already comfortable, like drop-in centers.* [FGD participant]

They also proposed changes such as improved attitudes for service providers, reduced waiting time, and provision of clear information about PrEP. Participants felt it was important for facilities to offer the following to accompany PrEP services: condoms and lubricants, HIV testing and counseling, and education on PrEP. Participants also said they would be more likely to adhere to PrEP if it was provided by nonjudgmental MSM-friendly service providers.

> *Use the friendly providers who do not take their personal beliefs to stop us from being MSM, those who understand that we are also human beings.* [FGD participant]

Two participants in IDIs reported a mission (church-affiliated) hospital in northern Malawi as especially well-placed to provide care for the MSM community, and private pharmacies were reported as potential sites by one person in an IDI.

Potential Barriers for MSM to PrEP Uptake and Adherence

Despite the positive attitude and their willingness to take PrEP, the participants had several concerns that would stop them from taking PrEP which need to be considered during implementation of the services.

The potential side effects of PrEP were the most commonly mentioned concern in both IDIs and FGDs. When asked about the factors that will prevent them from accessing PrEP, 54% (7/13) of IDI participants and 23% (22/96) of participants from FGDs mentioned side effects.

> *They are medicines just like any other medicines, and inevitably there will be side effects. What are these side effects? … There could be smell or bad taste that one may have to deal with.* [IDI participant]
>
> *Medicines are medicines. Perhaps one may vomit after taking the medicines. That is why I think injections are better. I do not like the taste of medicines.* [IDI participant]
>
> *I have some fears. For example, what are the side effects of PrEP being a drug?* [FGD participant]

The costs (financial and time), fear of being identified as an MSM, insufficient information, dosage, and stockouts were identified in the IDIs as potential factors that can limit uptake of PrEP. Issues related to cost included transport costs to the point of care that could make it expensive to access PrEP through private community pharmacies. A total of 77% (10/13) of IDI participants indicated that it is important to use MSM peers as PrEP distributors, use male-only facilities, and target all men and not just MSM. Participants from IDIs also recommended the system should ensure that stock is consistently available.

> *The private pharmacies can be a good source of PrEP…. But nothing from these pharmacies is provided for free. We may not afford the cost of PrEP.* [IDI participant]
>
> *In public health facilities, PrEP should be provided to all men and not just MSM. For contraceptives, they give contraceptives to all women and not just female sex workers. In that case, there is no stigmatization.* [IDI participant]
>
> *If I go to facility and am sent back because drugs are out of stock, I will not go again because I am not sick.* [IDI participant]
>
> *You should package the drug in a way that people should not realize that it is a drug otherwise like for me I can't take pills as it is difficult for me to keep them in the house because my wife can wonder and discover that I am an MSM.* [IDI participant]
>
> *The good thing that I see is best to take the pill once a month because it's not easy to take drugs daily as people can be forgetful. ...and if you take once a month life will not be tough because when you take once a month you will take a long time before thinking of taking again which leaves you free.* [IDI participant]
>
> *If I don't know how the drug works, its side effects and all other relevant information to help me make a decision, I wouldn't bother to take it because it is drug I can't be sure whether it will help me or harm me.* [IDI participant]

Common potential barriers that we identified among the FGDs included stigmatization of MSM by health care workers and community perception of persons on PrEP. Over 63% (60/96) of FGD participants reported experiencing stigma from health providers when they accessed sexual and reproductive health services, which could be similar when accessing PrEP services. They observed that when they want to access services in public health facilities, they are sometimes labeled by the providers as individuals who like sex "too much." Three participants from the FGDs pointed out that it defeats the purpose of using PrEP if it cannot offer dual protection for STI and HIV like condoms.

> *If we go to get lubricants and condoms, the health providers think that you like sex too much.* [FGD participant]

Although some of the participants did not seem to care what the community would think, 22% (21/96) of FGDs participants reported concerns about how the drug is being advertised.

> *If the drug is for MSM and FSWs only and people know it, they will know that once you take it you are an MSM.* [FGD participant]
>
> *Why should we use two things? I wish we could be choosing between the two.* [FGD participant]

Discussion

Principal Findings

This study demonstrated that the majority of MSM in Malawi knew about the existence of PrEP and were enthusiastic about being able to access it. However, a significant number did not have many details about PrEP and only learned of it during the study. The overall level of understanding of PrEP seemed to be very limited. Formulation, frequency of dosing, place of distribution, and side effects were identified as key factors that can affect the uptake and continued use of PrEP. Participants of both the FGDs and IDIs indicated that MSM should be involved in the design of any education program promoting the use of PrEP.

A total of 42% (40/96) of persons from the FGDs and 69% (9/13) of participants of the IDIs indicated they had previously heard of PrEP. Common sources of information on PrEP included peers and the CSOs where they accessed services. Participants reported not having heard of PrEP from health care providers in public health facilities. This could be because PrEP was not yet available in public health services in Malawi. In addition, MSM normally access sexual and reproductive health services from MSM-friendly DICs owned by CSOs, whereas they attend public health facilities for services not related to sexual and reproductive health services. A total of 35% (34/96) of FGD participants and 46% (6/13) of IDI participants reported they had a limited knowledge of PrEP. Study participants were not aware that the WHO-approved PrEP regimen was oral dosing, and they questioned how or whether PrEP would work after unprotected sex with an HIV-infected partner. This finding suggests the need for adequate information for the MSM to understand the benefits of the drug and enhance uptake.

The MSM in this study demonstrated a positive attitude toward PrEP from both IDIs and FGDs despite the limited awareness and were enthusiastic about having another option for HIV prevention. A total of 67% (64/96) of FGD participants indicated that they would not wait to take the drug if it becomes available in Malawi. One FGD participant stated the following:

> *Let the drugs come, we are waiting.* [FGD participant]

The study identified factors that would enhance willingness for MSM to take PrEP. All participants from IDIs and 58% (56/96) of the FGD participants expressed that the benefits of PrEP will motivate them to take the drug. One IDI participant stated the following:

> *I don't know what I can do if I test HIV positive. It means I have to be on [antiretrovirals] daily. With PrEP maybe I would not be taking ART drugs daily.* [IDI participant]

A quantitative study from the United States identified that not believing that it helps was one of the barriers that hinder MSM from being willing to take the drug [18]; therefore, this finding emphasizes the need for promoting awareness of the benefits of PrEP.

Other factors that promote willingness to take the drug include formulation and dosing of the medication with mixed expression with some liking the pills and others injection. In terms of dose, some did not care about daily dose while others preferred weekly dose. The responses could have been mixed because the participants were asked leading question between oral and injectable and among daily, weekly, and monthly doses, which could be different to reality where there are not many options. However, proper counseling will be needed to help MSM make the right choices and develop positive attitudes toward available formulation and dosage. MSM involvement in demand creation for the drug was another motivating factor as it will enhance peer motivation. Where the drug is provided and who provides it was another factor to enhance willingness. Considering that the medication is taken by people who are not sick, they may be easily put off if the environment of providing the service is not favorable. This is one of the key areas to address as many MSM face stigma and discrimination within the health care system and from the community [1-4]. Participants also expressed barriers to potential use of PrEP with the highest concern being about potential side effects expressed in both IDIs and FGDs. This may not appear to be a major issue for the program, since a review of the combination antiretroviral PrEP regimen TDF/emtricitabine taken as a single pill once daily showed that only 2 out of 15,678 participants discontinued therapy because of side effects [19]. However, it will be important to educate MSM about the potential side effects and how to manage them, and to address this perception regarding the side effects of the drug. Participants also discussed other barriers to potential use of PrEP: (1) lack of relevant information on PrEP, (2) the need to take PrEP daily, (3) potential stigma from public health facility providers, (4) stigma from the greater community if PrEP is thought to be used by MSM only, (5) forgetfulness, and (6) the costs (time and financial) required to access the drug. Study participants were also concerned that even if they themselves used PrEP, their partners may be exposed through their other partners, therefore there is need for universal partner education about PrEP. However, these concerns are not unique to MSM in Malawi, as these similar issues were noted in a review of 18 randomized controlled trials on PrEP: stigma, an unacceptable dosing regimen, side effects, low risk perception, low decision-making power, and the logistics of daily life [20]. In another PrEP-related study from Kenya, there were concerns around the competency of service providers to understand the multifaceted issues that key populations face [21]. This relates to the finding in our study that it is important to understand the needs of MSM before implementing PrEP services to promote uptake of services. These concerns may result in nondaily use of PrEP [22], thereby providing less-than-optimal protection. PrEP programs will need to develop and implement strong information and education interventions to ensure that high levels of knowledge among PrEP users are achieved.

The new PrEP program in Malawi needs to use a multifaceted approach to educating MSM about PrEP and ensuring access to PrEP. This may include dissemination of information through MSM-friendly service providers who understand their needs, use of MSM peers as educators and distributors of PrEP, and use of DICs to deliver services as well as male-only facilities such as barber shops for information sharing—when using public facilities they should target all men and not just MSM.

There will need to be various modes of delivering the messages such as face to face interaction, printed materials like leaflets, and online platforms among others.

While we expected that MSM would mention the MSM-friendly CSO where some of the participants were recruited as a preferred setting to receive PrEP without stigma and discrimination, outreach settings were also reported as alternatives, especially for the highly hidden populations who do not go to DICs. Nevertheless, distance to the dedicated sites was identified as a bottleneck, suggesting that a combination of DICs and outreach facilities may be ideal. Hidden participants who do not go to DICs were most likely to mention public and private static health services, including community pharmacies, as settings where PrEP could be offered by MSM-friendly staff. However, it is important to note that a mission hospital in one of the districts was mentioned as a preferred site. This observation is somewhat counterintuitive because of the common narrative that religious facilities exhibit homophobic tendencies. This serves as a reminder that while it is possible to broadly categorize potential service providers as supportive or not supportive, individual preferences may also come into play.

Our study pointed out the need to minimize stigma and its effects in the environment where PrEP will be provided as a way of ensuring accessibility. The stigma is usually from other members of the community and MSM themselves. PrEP services will therefore need to be offered in settings that are stigma-free to accommodate this initiative. Community readiness is often defined as the various attributes of a community's context that constitute a prerequisite to the implementation of effective change. Thus, the affected community's knowledge and attitudes and its capacity to implement change strategies before an intervention is implemented should be reviewed [22,23]. It is important to take into consideration the readiness of community members other than MSM to accommodate the provision of PrEP services to avoid the fear of stigma underscored in this assessment.

Limitations

Since the study was qualitative with nonprobability sampling, it was not designed to quantify the proportion of MSM in the study area who find PrEP acceptable. The findings may not be generalizable beyond the study setting and study groups because the study largely included MSM who accessed health services through the LINKAGES project or other projects within the same coverage and did not include MSM who are not obvious and regular health and social service users. However, IDIs included MSM who are more hidden and access health and other social services through other projects within CEDEP. Data were collected through self-report and so may be influenced by social desirability bias (where study participants respond to questions in a manner they believe the researchers want to hear). However, the risk of this bias was mitigated by the research assistants not being health professionals and by the fact that they, too, were members of the MSM community; therefore, there was less likely to be a power differential between the study participants and the study assistants. While a few key quotes may have been missed from the 2 FGDs and 5 IDIs that were not recorded, we do not believe that this significantly affected the overall conclusion from the study.

Conclusion

The study provided insights on areas to pay attention to when designing a PrEP program for MSM in resource-constrained settings where MSM are criminalized like Malawi. It is critical to engage the MSM community to develop MSM-appropriate and relevant educational and informational materials on PrEP to address most of the concerns raised in this study and possibly promote both uptake and adherence. PrEP counseling should include, but not be limited to, information on side effects and how to manage them and the expected duration of side effects. Awareness-raising (information, education, and communication) activities should involve MSM as champions and provide clear information on the importance and value of taking PrEP in relation to the perceived risk of contracting HIV to promote adherence, regardless of PrEP formulation. Making community-based distribution of PrEP more prominent could avoid potential accessibility barriers, but it is critical to also consider how to target PrEP within the general population to reduce stigma and the perception that PrEP is only for MSM and other key populations. Furthermore, implementers should consider development of innovative public-private partnerships and explore how MSM-friendly health workers in the public and private health system may be mobilized and trained for the provision of PrEP in addition to usual safe spaces such as DICs. Other suggested factors necessary to improve access through health facilities should also be addressed (eg, drug stock, waiting time, and key population–friendly services).

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Authors' Contributions

EM and NP designed the study. EM coordinated the study and collected data. DB and CA supervised the study. EM, NP, and DB analyzed the data. EM, NP, CA, and DB developed the first draft of the manuscript. All authors contributed to and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
CEDEP: Center for Development of People
CSO: civil society organization
DIC: drop-in centers
FGD: focus group discussion
FSW: female sex worker
IDI: in-depth interview
LINKAGES: Linkages across the Continuum of HIV Services for Key Populations Affected by HIV
MSM: men who have sex with men
PEP: postexposure prophylaxis
PEPFAR: US President's Emergency Plan for AIDS Relief
PrEP: preexposure prophylaxis
USAID: US Agency for International Development
WHO: World Health Organization

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Original Paper

Associations Between Online Pornography Consumption and Sexual Dysfunction in Young Men: Multivariate Analysis Based on an International Web-Based Survey

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Abstract

Background: Expanding access to the internet has resulted in more and earlier consumption of online pornography. At the same time, a higher prevalence of erectile dysfunction (ED) among young men is seen. Increased pornography consumption has been suggested as a possible explanation for this rise.

Objective: The aim of this study was to better understand associations between problematic pornography consumption (PPC) and ED.

Methods: A 118-item survey was published online, and data collection took place between April 2019 and May 2020. Of the 5770 men who responded, the responses from 3419 men between 18 years old and 35 years old were analyzed. The survey used validated questionnaires such as the Cyber Pornography Addiction Test (CYPAT), International Index of Erectile Function (IIEF-5), and Alcohol Use Disorders Identification Test-Concise (AUDIT-C). The estimated amount of porn watching was calculated. Univariable and multivariable analyses were performed. For the multivariable analysis, a logistic regression model using a directed acyclic graph was used.

Results: According to their IIEF-5 scores, 21.48% (444/2067) of our sexually active participants (ie, those who attempted penetrative sex in the previous 4 weeks) had some degree of ED. Higher CYPAT scores indicating problematic online pornography consumption resulted in a higher probability of ED, while controlling for covariates. Masturbation frequency seemed not to be a significant factor when assessing ED.

Conclusions: This prevalence of ED in young men is alarmingly high, and the results of this study suggest a significant association with PPC.

Trial Registration: Research Registry researchregistry5111; https://tinyurl.com/m45mcaa2

(JMIR Public Health Surveill 2021;7(10):e32542) doi:10.2196/32542

KEYWORDS

erectile dysfunction; ED; pornography; pornography-induced erectile dysfunction; PIED; sexual health; young adults

Introduction

As we cannot ignore the presence of the internet (and therefore also the presence of explicit sexual materials) in the lives of young people, the effects of pornography consumption on mental and sexual well-being are often questioned.

Several reports have underlined positive effects of pornography consumption (more sexual comfort and self-acceptance, lower levels of shame and anxiety towards personal sexual orientation, increased interest in sex and sexual experimentation, relational happiness, more acceptance towards different sexual activities) [1-4]. Others express concern about the negative effects of pornography on sexual desire and sexual functions. However, studies looking into the impact of the frequency of pornography use on sexual functioning have not come up with consistent associations [4,5]. Still, personal and media reports (eg, [6,7]) and even TED talks (eg, [8]) claim that pornography consumption has an important effect on erectile dysfunction (ED). Even a specific term, porn-induced erectile dysfunction (PIED), was introduced [1,9,10]. Given that pornography is often accompanied by masturbation, PIED is questioned and criticized by some sexologists stating that the frequency and duration of masturbation are the key factors contributing to these negative effects and not the pornography consumption itself [11,12].

What cannot be denied is that expanding access to the internet has resulted in more and earlier consumption of online pornography. Between 50% and 70% of adult men use pornography on a regular basis, and for adolescent lifetime use, the numbers are even higher than 80% [13,14]. Simultaneously, the reported prevalence of ED in young men has increased enormously over the last decades, from 2%-5% in 1999 and 2002 to 20%-30% in more recent reports [15-18].

Getting an erection is, of course, a process that requires the neurological, hormonal, and circulatory systems to work together. Inability to get or maintain an erection can be due to penile (vascular or neurological) problems or to more centralized issues (eg, depression, lack of desire, anxiety), but these conventional components cannot entirely explain the higher prevalence of ED in young men [1]. While men aged over 50 years are more prone to have a physical cause for their ED, younger men are more likely to have a psychological cause such as performance anxiety, depression, anxiety, or relational problems [19]. There is no obvious explanation for the high prevalence of ED in younger men these days, and additionally, some patients are resistant to traditional therapy [9]. Some patients actively consult health care professionals convinced they are experiencing sexual difficulties due to their pornography consumption [20].

Certain scholars attribute these self-perceived difficulties to moral incongruence towards pornography consumption, and some link it to addiction, while others are more critical and question whether addiction models are applicable based on findings from neuroscientific studies [21-23]. Furthermore, sex addiction, porn addiction, and porn-induced sexual dysfunctions are not recognized as diagnosable entities in the 5th edition of the Diagnostic and Statistical Manual of Mental disorders (DSM-5). Patients with self-perceived porn-induced sexual problems often find themselves in a vicious circle and may struggle to find appropriate help. Individuals with problematic pornography consumption (PPC) may use pornography frequently but frequency of pornography consumption may not always be problematic [4]. As long as a theoretical framework is missing, diagnosing this entity and developing a treatment algorithm are difficult. The new International Classification of Diseases, 11th Revision (ICD-11) may bring some change for these patients as it has added compulsive sexual behavior disorder (CSBD) as a diagnosable entity. However, including CSBD in the ICD-11 did not happen without controversy [24,25]. There are many potentially dysregulated sexual behaviors that may lead to this diagnosis, but one may argue that online pornography use will be one of the most encountered in clinical settings [26]. Rather than approaching it via an addiction framework, PPC is seen as an impulse control disorder and as such might have an impact on a person's sexual pleasure [4]. Although not completely fitting with the CSBD criteria, several screening instruments for problematic pornography use were developed and validated, making it possible to assess PPC in a more structured way [27].

A better understanding of the associations between PPC and ED might add new insights in the prevention and treatment of ED, especially in young men. These associations are complex and can only be fully understood in a multidisciplinary setting, as they require knowledge from different research fields (eg, psychology, sexology, sociology, urology) [28,29]. The aim of this study was to evaluate the frequency of pornography consumption and PPC in young men and to better understand their connection with ED.

Methods

We organized 4 brainstorming meetings between a urologist and 2 medical practitioners with an interest in sexual health. First, a framework was designed identifying variables (including pornography consumption) that could possibly contribute to ED in young men. After a literature review by the team members, several indicators linked to pornography consumption (eg, frequency of use, age at start of use, problematic use) were listed in another brainstorming meeting. A literature review was performed identifying validated scales to measure our outcome and exposure variables, and based on scientific evidence available at that time, certain questionnaires were chosen. Then, a 118-item questionnaire was developed including questions on demography, medical history, alcohol and drug usage, sexual preferences, ED, masturbation, pornography consumption, and partner satisfaction using validated scales such as the Cyber Pornography Addiction Test (CYPAT), International Index of Erectile Function (IIEF-5), and Alcohol Use Disorders Identification Test-Concise (AUDIT-C) [30-35].

We used the definition of pornography as defined by Kraus et al [30], as "any material designed to cause or enhance sexual arousal or sexual excitement in the viewer. Such materials show clear and explicit sexual acts such as vaginal intercourse, anal intercourse, oral sex, group sex etc. Pornography does not include materials such as underwear catalogs or materials

containing men and women posing naked unless these images portray clear and explicit sexual acts."

CYPAT was included to measure the exposure, PPC. It is composed of 11 items scored on a 5-point Likert scale. Higher sum scores (minimum=11, maximum=55) indicate more problematic behavior [33]. While initially developed to screen for pornography "addiction," it is conceived as a reliable instrument with robust psychometric properties to screen for PPC. Strong correlations with other instruments were documented, providing evidence for criterion-related validity and convergent validity [36]. CYPAT deeply measures conflict parameters and includes a use despite harm component, which is a CBSD criterion.

Outcome (ED) was measured using the IIEF-5 questionnaire, composed of 5 questions scored on a Likert scale focusing on erectile function and intercourse satisfaction. The possible sum scores for the IIEF-5 range from 5 to 25, and ED was classified into 2 categories based on the sum scores: ED (5-21) versus no ED (22-25) [31,37,38]. The IIEF-5 meets psychometric criteria for structural validity, test-retest reliability, construct validity, and criterion validity [39]. It can also be assessed online [40]. Scores on the IIEF-5 in this study were only reported for those who were sexually active in the last 4 weeks.

After a thorough review by the authors, an online, English, web-based survey was created using the Qualtrics platform and tested several times by the team members. One of the drawbacks of a web-based survey is that due to the possible nonrepresentative nature of the internet-based study sample, it can be difficult to draw population-based conclusions [41]. However, our aim was not to study the incidence of (problematic) pornography consumption or erectile dysfunction. We wanted to pilot test if and how pornography consumption correlates with sexual functioning in young men. Due to the personal and sensitive questions, the huge variation in pornography consumption and masturbation frequency in young men, and the possible small percentage of young men experiencing problematic consumption, a large sample of participants was necessary. This motivated our choice for a web-based survey as those surveys are more inclusive than postal or phone surveys allowing us to find a reasonable number of respondents with different pornography consumption habits and willing to answer these sensitive personal questions. Furthermore, once set up, a web-based survey is easy to carry out, is cheap, and creates an easy way to reach many respondents. The data are captured directly in electronic format making analysis faster and easier [42]. In the 18-35-year-old age group, it can be expected that almost everyone has access to the internet, so that the risk of selection bias by having no internet access is insignificant. We further tried to reduce selection bias by announcing the questionnaire as a survey to study current sexual health in young men without specifically mentioning this questionnaire was surveying pornography consumption.

The link to the questionnaire [43] was spread mainly in Belgium and Denmark through (social) media, posters, and flyers. Data were collected between May 2019 and March 2020. No specific sample size was calculated as we tried to reach as many participants as possible. All participants signed informed consent before participating. The Qualtrics settings allowed us to avoid duplicate entries. This research adhered to the latest version of the Declaration of Helsinki and was approved by the ethics committee for the Social Sciences and Humanities of the University of Antwerp. All data were anonymized and nonidentifiable.

To evaluate the association between PPC and ED in those who had penetrative sex in the previous 4 weeks, the initial research group teamed up with a psychologist, a sociologist, and an epidemiologist to participate in multidisciplinary brainstorming sessions to conceptualize the exposure-outcome relationship between PPC and ED. A directed acyclic graph (DAG) was used to visualize the associations between the covariates and CYPAT and ED and to classify the covariates as confounders (common causes of CYPAT and ED), mediators (covariates on the causal pathway from CYPAT to ED), and colliders (CYPAT and ED independently cause a third variable). DAGs have become an established framework for the analysis of causal inference in epidemiology and are used to show how associations translate into causal relations [44,45]. For this study, a DAG was used a posteriori to examine potential causality of PPC on ED and to guide the multivariable data analysis.

Descriptive statistics summarizing and describing the characteristics of the data (eg, demographics, sexual interests, masturbation frequency, PPC) were performed both for those men who had penetrative sex during the preceding 4 weeks and those who had not. The pornography consumption time (PCT) in minutes per week was calculated post hoc based on frequency of masturbation, the number of times pornography was used for masturbation, and the average length of 1 pornography session.

Nonparametric tests (chi-square, Kruskal Wallis, and Mann-Whitney-U) were used for the univariate analyses. A significance level of .05 was used to determine statistical significance.

The minimal sufficient adjustment sets for estimating the direct effect of PPC on ED were identified using the DAGitty v3.0 web application and included in a multivariable regression analysis [45]. The following 12 covariates were identified as potential confounders, mediators, or colliders: masturbation frequency, relationship status, partner satisfaction, substance abuse, somatic causes, libido, depression, use of antidepressants, exercise, sexual identity, real sex vs pornography preference, and performance pressure. Statistical analyses must account for confounding factors, without introducing bias when controlling for variables that are not on the causal path between the exposure and the outcome. DAGgity software was used to identify the minimal sufficient adjustment set. Assuming this DAG is plausible, a minimal sufficient adjustment set for estimating the direct effect of PPC on ED consisted of 8 covariates: identity, libido, masturbation frequency, relationship status, use of antidepressants, arousal (real sex vs pornography), partner satisfaction, and performance pressure. These covariates were included in a logistic regression model.

This multivariable logistic regression model was constructed to estimate the effect of the selected covariates. Odds ratios (OR) and corresponding 95% CIs were calculated to evaluate the strength of the associations. All statistical analyses were performed using R software v4.02, RStudio v 1.3.959, and Jamovi v1.8.

Results

Sample Characteristics

A total of 5770 men responded to our questionnaire spread mainly but not exclusively via newspaper or radio (2423/5770, 41.99%), social media (1789/5770, 31.00%), and student mailing (577/5770, 10.00%); 2351 participants (2351/5770, 40.75%) were excluded because they were over 35 years of age. Median time to complete the questionnaire was 20 minutes. Eventually, the results of 3419 participants were analyzed. As IIEF-5 asks questions specifically about problems during penetrative sexual intercourse, the participants were divided in 2 categories: those who had penetrative sex in the previous 4 weeks and those who did not. See Figure 1 for a flowchart of our participant selection. Demographics based on these 2 categories can be found in Table 1.

Figure 1. Flowchart for participant selection. ED: erectile dysfunction; IIEF-5: International Index of Erectile Function, Short version.

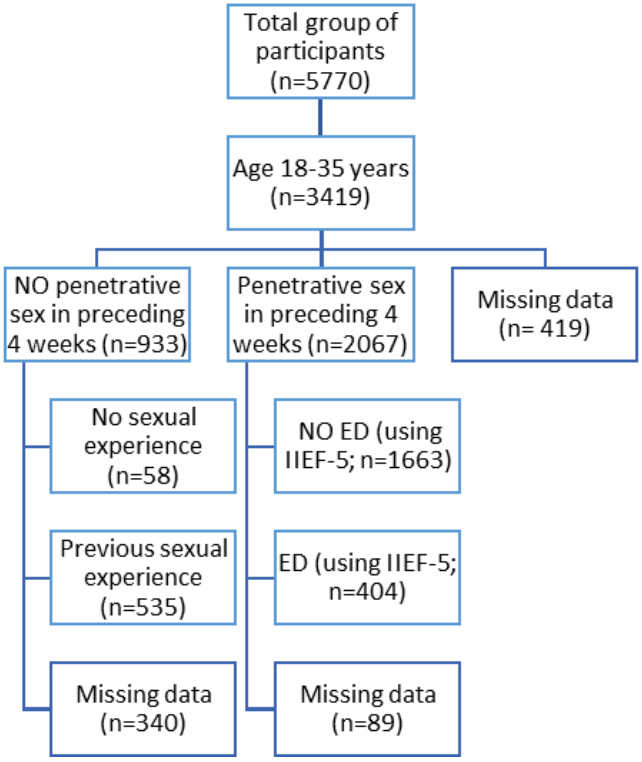


Table 1. Demographics.

Characteristics	Penetration attempt in the past 4 weeks?		Overall (n=3419)
	No (n=933)	Yes (n=2067)	
Age (years), median (minimum-maximum)	22.0 (2.00-35.0)	25.0 (0.340-35.0)	24.0 (0.340-35.0)
Educational level, n (%)			
Less than high school diploma	34.0 (3.6)	57.0 (2.8)	112 (3.3)
High school diploma or equivalent degree	387 (41.5)	545 (26.4)	1093 (32.0)
Bachelor's degree	320 (34.3)	808 (39.1)	1278 (37.4)
Master's degree	183 (19.6)	606 (29.3)	865 (25.3)
Doctorate	9 (1.0)	51 (2.5)	71 (2.1)
Relationship status, n (%)			
Single	814 (87.2)	368 (17.8)	1340 (39.2)
In a "new" relationship (<6 months)	28 (3.0)	201 (9.7)	277 (8.1)
In a longstanding relationship (>6 months)	74 (7.9)	1107 (53.6)	1327 (38.8)
Engaged or married	15 (1.6)	387 (18.7)	435 (12.7)
Divorced or widowed	2 (0.2)	4 (0.2)	9 (0.3)
Missing	0 (0)	0 (0)	31 (0.9)
"**Do you smoke?", n (%)**			
No, I never smoked	644 (69.0)	1162 (56.2)	1981 (57.9)
No, but I did smoke in the past	94 (10.1)	356 (17.2)	502 (14.7)
Yes, but only occasionally	108 (11.6)	321 (15.5)	477 (14.0)
Yes	87 (9.3)	228 (11.0)	349 (10.2)
Missing	0 (0)	0 (0)	110 (3.2)
AUDIT-C[a] score, median (minimum-maximum)	5.00 (1.00-12.0)	5.00 (1.00-12.0)	5.00 (1.00-12.0)
Missing AUDIT-C values, n (%)	133 (14.3)	117 (5.7)	442 (12.9)
"In the past 2 weeks, have you frequently been hindered by depressive feelings or feelings of helplessness?", n (%)			
No	573 (61.4)	1661 (80.4)	2393 (70.0)
Yes	360 (38.6)	406 (19.6)	822 (24.0)
Missing	0 (0)	0 (0)	204 (6.0)
"I identify myself as", n (%)			
Heterosexual only	631 (67.6)	1477 (71.5)	2235 (65.4)
Heterosexual mostly	122 (13.1)	302 (14.6)	446 (13.0)
Heterosexual, somewhat more bisexual	36 (3.9)	83 (4.0)	126 (3.7)
As equally heterosexual as homosexual	16 (1.7)	25 (1.2)	46 (1.3)
Homosexual, somewhat more bisexual	18 (1.9)	14 (0.7)	32 (0.9)
Homosexual mostly	33 (3.5)	47 (2.3)	80 (2.3)
Homosexual only	64 (6.9)	112 (5.4)	184 (5.4)
Asexual	8 (0.9)	2 (0.1)	10 (0.3)
Missing	0 (0)	0 (0)	247 (7.2)
"I am attracted to", n (%)			
Women only	653 (70.0)	1536 (74.3)	2322 (67.9)
Women mostly	112 (12.0)	266 (12.9)	396 (11.6)
Women somewhat more than men	25 (2.7)	51 (2.5)	80 (2.3)
Men and women equally	12 (1.3)	20 (1.0)	37 (1.1)

Characteristics	Penetration attempt in the past 4 weeks?		Overall (n=3419)
	No (n=933)	Yes (n=2067)	
Men somewhat more than women	21 (2.3)	18 (0.9)	40 (1.2)
Men mostly	38 (4.1)	46 (2.2)	85 (2.5)
Men only	70 (7.5)	123 (6.0)	202 (5.9)
Missing	0 (0)	0 (0)	247 (7.2)
"My sexual fantasies are about", n (%)			
Women only	614 (65.8)	1439 (69.6)	2182 (63.8)
Women mostly	118 (12.6)	303 (14.7)	437 (12.8)
Women somewhat more than men	33 (3.5)	67 (3.2)	107 (3.1)
Men and women equally	24 (2.6)	45 (2.2)	70 (2.0)
Men somewhat more than women	23 (2.5)	26 (1.3)	54 (1.6)
Men mostly	40 (4.3)	56 (2.7)	101 (3.0)
Men only	74 (7.9)	119 (5.8)	200 (5.8)
Missing	0 (0)	0 (0)	247 (7.2)
CYPAT[b] score, median (mininum-maximum)	18.0 (11.0-52.0)	16.0 (11.0-55.0)	17.0 (11.0-55.0)
CYPAT categories			
11-13	151 (16.2)	464 (22.4)	617 (18.0)
13-16	134 (14.4)	360 (17.4)	494 (14.4)
16-21	175 (18.8)	390 (18.9)	565 (16.5)
21-55	208 (22.3)	381 (18.4)	589 (17.2)
Missing	265 (28.4)	472 (22.8)	1154 (33.8)
IIEF[c] score, mean (SD)	N/A[d]	22.8 (2.78)	22.7 (2.97)
IIEF score, median (minimum-maximum)	N/A	24.0 (6.00-25.0)	24.0 (5.00-25.0)
IIEF categories			
No ED[e]	N/A	1474 (71.3)	1523 (44.5)
Mild ED	N/A	327 (15.8)	349 (10.2)
Mild-moderate ED	N/A	63 (3.0)	74 (2.2)
Moderate ED	N/A	11 (0.5)	14 (0.4)
Severe ED	N/A	3 (0.1)	6 (0.2)
Missing	N/A	189 (9.1)	1453 (42.5)
"How nervous are you to have any kind of sexual contact?", median (minimum-maximum)	6.20 (0-10.0)	1.10 (0-10.0)	2.00 (0-10.0)
Missing values for "How nervous are you to have any kind of sexual contact?", n (%)	330 (35.4)	295 (14.3)	1043 (30.5)
"Do you sometimes feel enormous pressure to perform in bed or to keep an erection while having sex?", median (minimum-maximum)	6.00 (0-10.0)	2.00 (0-10.0)	3.00 (0-10.0)
Missing values for "Do you sometimes feel enormous pressure to perform in bed or to keep an erection while having sex?", n (%)	443 (47.5)	285 (13.8)	1146 (33.5)
"At which age did you first start masturbating?" (years), n (%)			
<10	38.0 (4.1)	131 (6.3)	169 (4.9)
10-12	323 (34.6)	773 (37.4)	1098 (32.1)
13-14	314 (33.7)	748 (36.2)	1062 (31.1)
15-17	57 (6.1)	137 (6.6)	194 (5.7)

Characteristics	Penetration attempt in the past 4 weeks?		Overall (n=3419)
	No (n=933)	Yes (n=2067)	
≥18	12 (1.3)	9 (0.4)	21 (0.6)
Missing	189 (20.3)	269 (13.0)	875 (25.6)
"At which age did you start masturbating to porn?" (years), n (%)			
<10	7 (0.8)	20 (1.0)	27 (0.8)
10-12	126 (13.5)	303 (14.7)	429 (12.5)
13-14	350 (37.5)	851 (41.2)	1202 (35.2)
15-17	218 (23.4)	536 (25.9)	755 (22.1)
≥18	32 (3.4)	74 (3.6)	106 (3.1)
Missing	200 (21.4)	283 (13.7)	900 (26.3)
"How often do you normally masturbate?", n (%)			
Regularly more than once a day	104 (11.1)	138 (6.7)	242 (7.1)
(Almost) every day	282 (30.2)	516 (25.0)	798 (23.3)
A few times a week, not every day	280 (30.0)	756 (36.6)	1038 (30.4)
A few times a month	26 (2.8)	143 (6.9)	169 (4.9)
Once a week	43 (4.6)	173 (8.4)	216 (6.3)
Once a month	2 (0.2)	32 (1.5)	34 (1.0)
Less than once a month	4 (0.4)	27 (1.3)	31 (0.9)
Never	3 (0.3)	13 (0.6)	16 (0.5)
Missing	189 (20.3)	269 (13.0)	875 (25.6)
PCT[f], median (minimum-maximum)	47.3 (0-1580)	35.0 (0-1560)	39.4 (0-1580)
Missing PCT values, n (%)	220 (23.6)	361 (17.5)	998 (29.2)
PCT categories (minutes), n (%)			
0-12	106 (11.4)	438 (21.2)	545 (15.9)
12-35	148 (15.9)	433 (20.9)	582 (17.0)
35-73	196 (21.0)	408 (19.7)	604 (17.7)
73-1575	263 (28.2)	427 (20.7)	690 (20.2)
Missing	220 (23.6)	361 (17.5)	998 (29.2)

[a]AUDIT-C: Alcohol Use Disorders Identification Test-Concise.

[b]CYPAT: Cyber Pornography Addiction Test.

[c]IIEF: International Index of Erectile Function.

[d]N/A: not applicable.

[e]ED: erectile dysfunction.

[f]PCT: pornography consumption time.

Descriptive and Univariate Analyses

Masturbation

With 84.91% (2160/2544) of the participants starting masturbating between the ages of 10 years and 14 years, masturbation was a common practice in our study population. Most of our participants masturbated multiple times per week, with more than 70% (1836/2544, 72.17%) masturbating between a few times a week to daily and 9.51% (242/2544) masturbating even regularly, at more than once a day. Those who were not sexually active in the past 4 weeks seemed to masturbate more often (P<.001). While 89.5% (666/744) of single men masturbated multiple times a week or more, 78.42% (1410/1798) of single men in the sexually active group masturbated at the same level (P<.001). People in new relationships (<6 months of duration) seemed to masturbate the least (P<.001).

Pornography Consumption

Of our study participants, 98.98% (2518/2544) had consumed pornography during masturbation. Pornography was consumed during a median 8.4 of 10 masturbation sessions. In fact, 17.70% (441/2492) of our study population never masturbated without pornography consumption, and 91.40% (2222/2431) of viewers skipped to the best parts of the videos they watched. Table 2

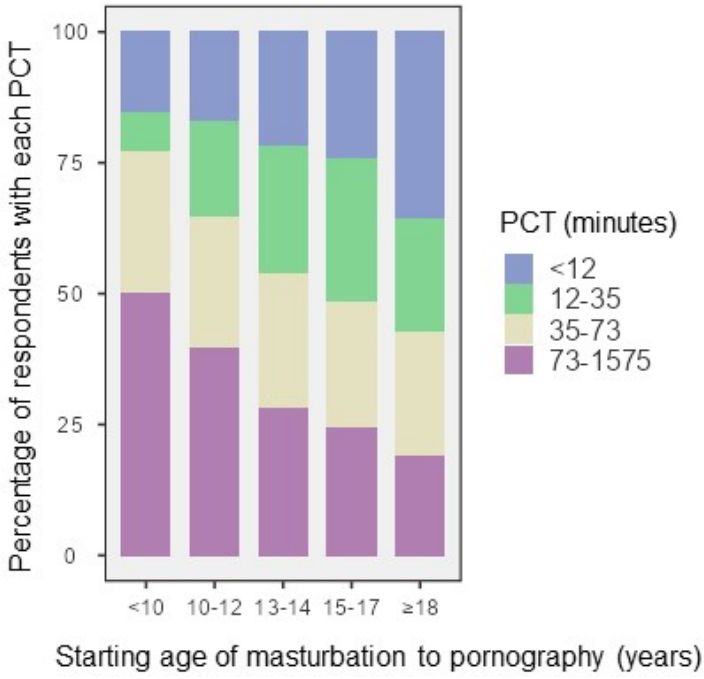
shows the reasons for watching, where they watched, and with whom they watched.

The median age at which the participants started masturbating to porn was 13-14 years in our population. The average porn session lasted between 5 minutes and 30 minutes in 81.50% (1973/2421) of our population. For 11.03% (267/2421), when they masturbated to pornography, it lasted, on average, more than 30 minutes. The median calculated PCT was 39.4 minutes per week. There was a statistically significant difference (P<.001) between those that had penetrative sex in the past 4 weeks (median 35 minutes per week) and those who had not (median 47.3 minutes per week). The starting age correlated with PCT (P<.001; Figure 2).

Table 2. Reasons for watching sexually explicit material, where they watched, and with whom they watched.

Responses	n (%)
Reasons for watching pornography (n=3729)	
Because I'm horny	3145 (84.33)
Stress relieve	1994 (53.47)
To produce arousal for masturbating	1932 (51.81)
Lack of real sexual contact	1597 (42.82)
Out of boredom	1548 (41.51)
Out of habit	1253 (33.60)
To be able to experience fantasies or things not done/forbidden in real life	1229 (32.96)
Sexual development/learning how to...	819 (21.96)
Because masturbating without porn isn't arousing enough	757 (20.30)
To spice things up with sexual partner(s) (watching together)	740 (19.84)
Other	108 (2.90)
With whom they watched pornography (n=3739)	
Alone	3662 (97.94)
With sexual patner(s)	1601 (42.81)
With friend(s)	1022 (27.33)
With stranger, online date, webcam	358 (9.57)
Where they watched pornography (n=3741)	
At home/apartment/bedroom	3726 (99.60)
Public places/toilets	1137 (30.39)
Work	1034 (27.64)
Friend's house/apartment	859 (22.96)
Romantic partner's home	857 (22.91)
Others (eg, stranger's house)	591 (15.80)

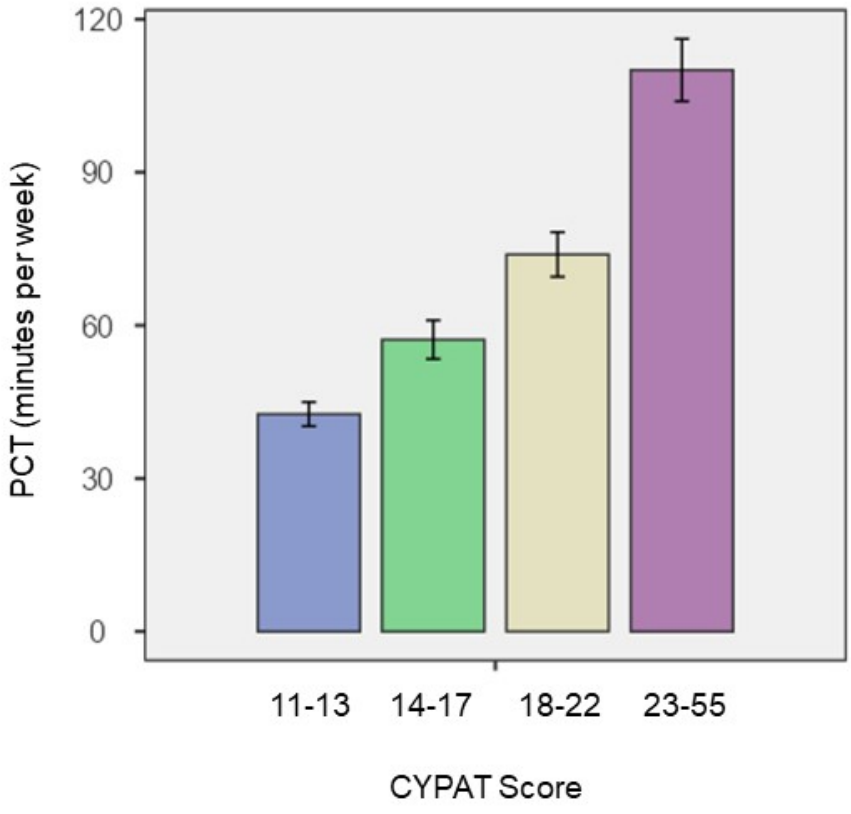
Figure 2. Correlations between pornography consumption time (PCT; minutes/week) and age at which masturbation to pornography started.



Problematic Pornography Consumption (PPC)

As there is no defined cutoff score for CYPAT, we divided the scores of our participants into quartiles, according to the distribution of the CYPAT scores [46]: 27.18% (615/2263) had a CYPAT score in Q1 (11-13 points), 27.31% (618/2263) in Q2 (14-17 points), 23.16% (524/2263) in Q3 (18-22 points), and 22.36% (506/2263) in Q4 (23-55 points). The median CYPAT score in the total sample was 17 points (of a total possible of 55 points). There was a statistically significant (P<.001) difference between the median CYPAT score for those who attempted penetrative sex in the past 4 weeks (median 16) versus those who did not (median 18). Higher CYPAT scores were correlated with higher weekly exposure to pornography (P<.001; Figure 3).

Figure 3. Correlation between Cyber Pornography Addiction Test (CYPAT) scores and pornography consumption time (PCT; minutes).



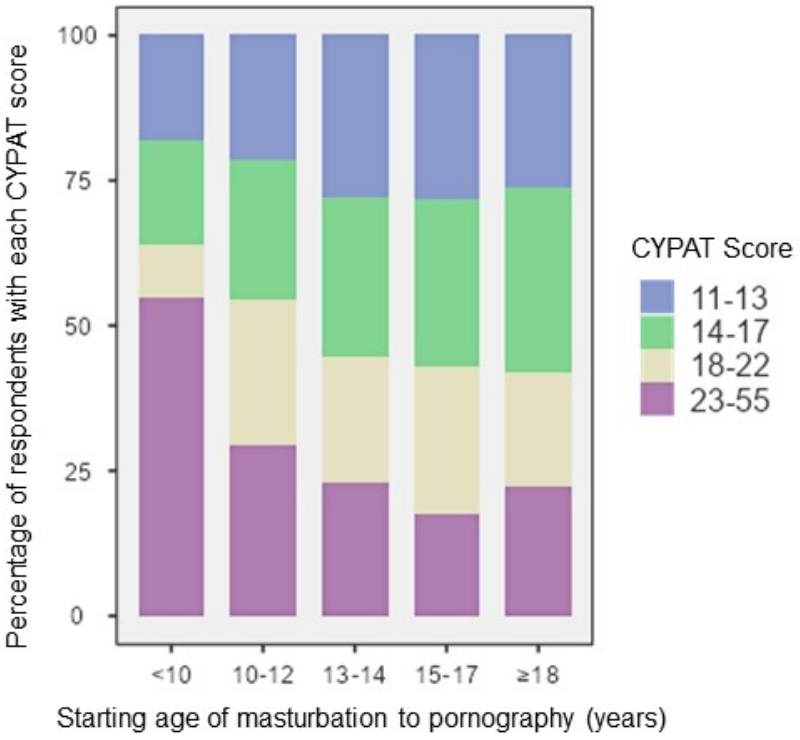
An earlier starting age was correlated with higher CYPAT scores (*P*<.001; Figure 4). In the group that started watching pornography below the age of 10 years old, >50% (12/22, 55%) had a CYPAT score in the 4th percentile of our population scoring range.

Of our participants, 21.61% (525/2429) indicated a need to watch an increasing amount of or increasingly extreme pornography to achieve the same level of arousal, and 10.39% (252/2425) needed to do this to get the same rigidity of their penis.

Of the sexually active participants, 72.74% (1238/1702) said they never had erectile, arousal, or climaxing difficulties in the previous 4 weeks when masturbating with porn, compared with 64.8% (456/704) of the sexually inactive men. Only 43.03% (756/1757) of the sexually active men had never had erectile, arousal, or climaxing difficulties when masturbating without porn, compared with 39.43% (289/733) of the sexually inactive men.

Of the sexually active men who were classified as having ED, 61.4% (213/347) admitted to never having erectile, arousal, or climaxing difficulties when masturbating with porn, versus 32.5% (115/354) when masturbating without porn.

Figure 4. Correlation between Cyber Pornography Addiction Test (CYPAT) score and age at which masturbation to pornography started.



Erectile Dysfunction

The following results are based on the participants who attempted sexual intercourse during the past 4 weeks (2067/3419).

According to their IIEF-5 scores, 21.48% (444/2067) of our sexually active participants (ie, those who attempted penetrative sex in the previous 4 weeks) had some degree of ED (mild: 77/444, 17.4%; mild-moderate: 15/444, 3.4%; moderate: 3/444, 0.6%; severe: 1/444, 0.2%). Most ED was mild (IIEF-5 score: 17-21). However, this mild ED bothered 61.2% (272/444) of affected individuals.

Regarding the correlation between PPC and ED, as shown in Figure 5, there was a statistically significant correlation between ED and CYPAT (*P*<.001). Higher CYPAT categories were associated with a higher prevalence of ED. Categorical analysis between the absence or presence of ED and CYPAT score showed a significantly higher median CYPAT score in the ED group (ED: median 19; no ED: median 16; *P*<.001). In men with the lowest CYPAT scores (Q1), only 12.9% (59/459) suffered from ED, increasing to 34.5% (127/368) in Q4. In the group who was sexually active and had a CYPAT score >28 (9th percentile), 49.6% (58/117) had some form of ED. When looking at the different ED categories based on the IIEF-5 scoring, there was a highly significant difference in CYPAT score (*P*<.001). Post hoc analysis showed a difference in median CYPAT scores between mild to moderate ED (median CYPAT: 24), mild ED (median CYPAT: 19), and no ED (median CYPAT: 16).

Of the participants classified as having ED, 27.7% (123/444) needed to watch more or more extreme pornography to achieve the same level of arousal, compared with 18.9% (84/444) in those participants who did not experience this need.

Of the participants who had started masturbating to porn at a very early age (<10 years), 58% (11/19) had some form of ED (*P*=.01), compared with 20.7% (61/295) in the group who started at 10-12 years old, 20.8% (173/831) in the group who started at 13-14 years old, 18.6% (97/521) in the group who started at 15-17 years old, and 24% (17/70) in the group who started at an age of 18 years or older.

Regarding the correlation between PCT and ED, we could not find a statistically significant correlation between ED and PCT when divided in quartiles (*P*=.17; Figure 6). However, in the group of participants with ED, the median time spent masturbating to porn was 39.81 minutes versus 31.50 minutes in the non-ED group, which was statistically significant (Kruskal Wallis 4.74; *P*=.029).

Figure 5. Correlation between Cyber Pornography Addiction Test (CYPAT) scores and erectile dysfunction (ED). 0=No, 1=Yes.

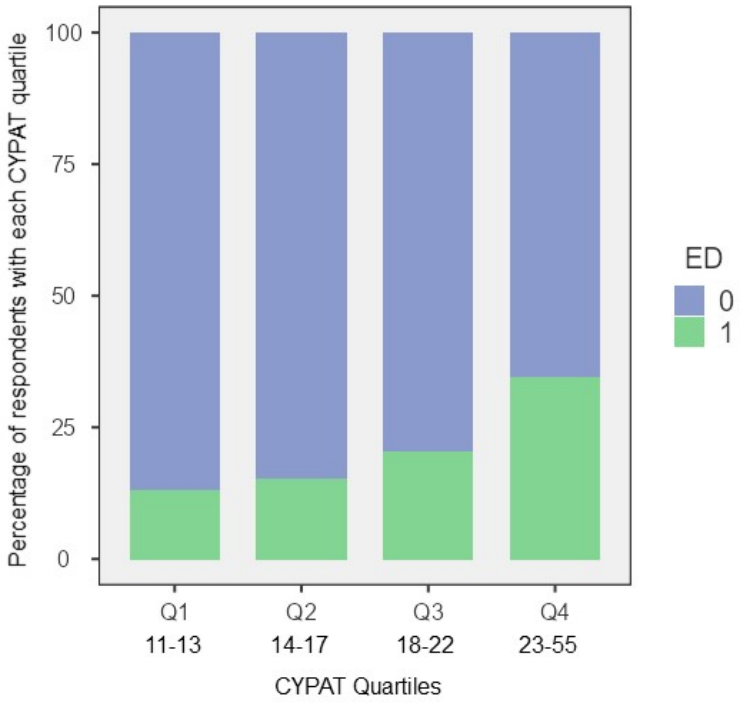
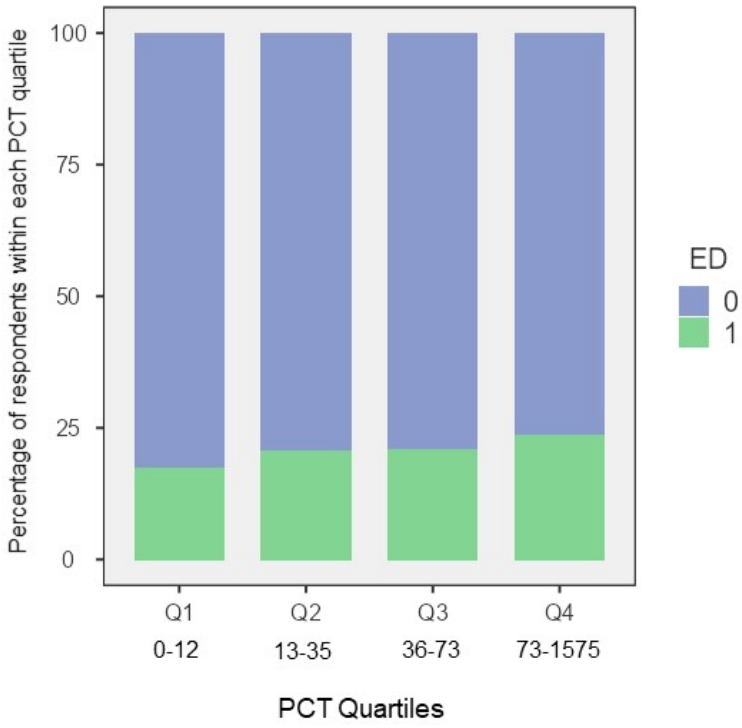


Figure 6. Correlation between pornography consumption time (PCT; minutes) and erectile dysfunction (ED). 0=No, 1=Yes.



There was a statistically significant difference in the percentage of ED between people that frequently watched porn for more than 30 consecutive minutes (84/341, 24.6%) and those who did not (261/1330, 19.62%; *P*=.041). We did not find any correlation between ED and the number of opened videos per session

Regarding the correlation between masturbation frequency and ED, there was no statistically significant difference in masturbation frequency between the ED and no ED groups (*P*=.28; Figure 7), even when 3 categories of self-reported masturbation frequency were defined: low frequency: never to once a week, 388/1798, 21.58%; medium frequency: few times

a week to every day, 1272/1798, 70.75%; and high frequency: regularly more than once a day, 138/1798, 7.68%. ED was found in 16.9% (65/384) of the low-frequency, 21.59% (266/1232) of the medium-frequency, and 23.9% (32/134) of the high-frequency groups. However, this difference was not statistically significant (*P*=.09). The median IIEF-5 scores in the low-frequency, medium-frequency, and high-frequency group were the same (ie, 24).

Regarding other possible confounders and ED, we observed a difference in self-reported presence of morning and spontaneous erections between those affected by ED (spontaneous: 344/404, 85.1%; morning: 375/404, 92.8%) and those not affected by ED (spontaneous: 1321/1474, 89.62%; morning: 1408/1474, 95.52%; *P*=.02).

There was a small but statistically significant (*P*<.001) difference in median self-reported libido score on a scale from 1 to 10 between those affected by ED and those who were not (7.4 vs 7.8).

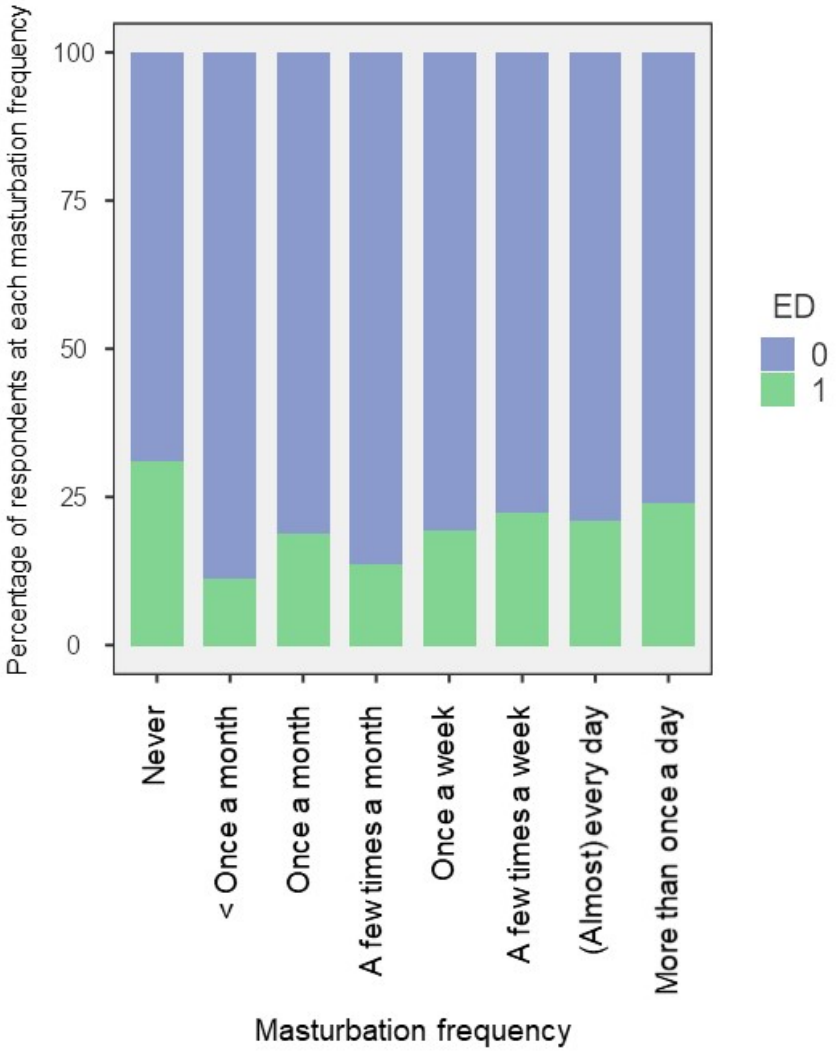
In our study population, we could not find a correlation between AUDIT-C score and ED (median score was 5 in both groups). However, smoking was correlated with worse erectile function (active: 517/1966, 26.3%; occasionally: 497/1966, 25.3%; never: 411/1966, 20.9%; past: 332/1966, 16.9%; *P*=.020).

In the ED group, 17.4% (77/443) and 4.5% (20/443) said that most or a lot of their sexual contact happened under the influence of alcohol or drugs, respectively, versus 6.50% (99/1523) and 1.97% (30/1523) of those without ED (*P*<.001 [alcohol] and *P*=.003 [drugs]). For those who frequently had sex under the influence, >40% (77/176, 43.8%) were classified as having ED.

There was no significant correlation between the use of antidepressants and ED in our study population (*P*=.08).

Relationship satisfaction also seemed to be correlated with ED (*P*<.001): 10.8% (55/508) of people that were extremely satisfied with their relationship had ED versus 33% (10/30) of people that were extremely unsatisfied. However, this correlation did not seem to be linear.

Figure 7. Correlations between masturbation frequency and erectile dysfunction (ED). 0=No, 1=Yes.



Problematic Pornography Consumption and ED in the Multivariate Analysis

A multivariable logistic regression model was built using the presence or absence of ED as a dichotomous outcome variable, taking exposure and other selected variables into account. CYPAT, performance pressure, and libido were considered as continuous variables (not normally distributed). Sexual identity, masturbation frequency, relationship status, real sex versus pornography preference, use of antidepressants, and partner satisfaction were considered as categorical variables. Table 3 contains an overview of the logistic regression model results.

There were 8 factors that were statistically significant (P<.05). The OR for CYPAT was 1.06 (95% CI 1.03-1.08; P<.001), which means that for each unit increase in CYPAT score, the odds of ED increase by 6%. Participants who answered having sexual fantasies about men only resulted in an OR of 2.66 (95% CI 1.52-4.66; P<.001) as compared with men having fantasies about women only. The OR for libido ("How would you rate your libido on a scale from 1 to 10?") was 0.79 (95% CI 0.71-0.89; P<.001), which means that the odds of ED decrease by 21% for every unit increase in libido. Experiencing performance pressure ("Pressure to perform in bed or to maintain an erection while having sex on a scale from 1 to 10") resulted in an OR of 1.30 (95% CI 1.24-1.38; P<.001). Being single or having a new relationship was found to raise the odds of ED (OR 2.12, 95% CI 1.34-3.36; P=.001 and OR 2.27, 95% CI 1.40-3.66, P<.001, respectively) as compared with men in a longstanding (>6 months) relationship. The OR for arousal (real sex vs pornography) was also found to be statistically significant, comparing men who reported that real sex gave them a lower level of arousal than pornography with men reporting the same level of arousal with real sex and pornography (OR 2.34, 95% CI 1.29-4.25; P=.005). There was also a significant difference between men who were extremely satisfied with their overall sexual relationship and men who were moderately satisfied (OR 0.58, 95% CI 0.39-0.86; P=.007). Masturbation frequency and the use of antidepressants were not statistically significant in this model.

Table 3. Logistic regression model coefficients and odds ratios for erectile dysfunction.

Predictor	Estimate[a]	SE	*Z*	*P*	Odds ratio	Lower 95% CI	Upper 95% CI
Intercept	–160.857	0.4993	–322.144	.001	0.200	0.0752	0.533
CYPAT[b] score	0.05586	0.0122	456.757	<.001	1.057	1.0324	1.083
Performance pressure	0.26506	0.0271	977.692	<.001	1.304	1.2361	1.375
Libido (“How would you rate your libido?” [scale 1-10])	–0.23398	0.0579	–403.809	<.001	0.791	0.7064	0.887
Masturbation frequency (Ref=a few times a week, not every day)							
Never	134.592	0.8864	151.842	.13	3.842	0.6761	21.829
Less than once a month	–0.88466	0.9204	–0.96113	0.34	0.413	0.0680	2.508
Once a month	–0.14011	0.6079	–0.23046	0.82	0.869	0.2640	2.862
A few times a month	–0.41440	0.3257	–127.235	0.20	0.661	0.3490	1.251
Once a week	0.13267	0.2592	0.51177	0.61	1.142	0.6870	1.898
(Almost) every day	–0.22186	0.1846	–120.164	0.23	0.801	0.5578	1.150
Regularly more than once a day	–0.06230	0.2866	–0.21741	0.83	0.940	0.5358	1.648
Use of antidepressants (Ref=No)							
Yes	0.71061	0.4453	159.573	0.11	2.035	0.8503	4.872
Partner satisfaction (“How satisfied are you with the overall sexual relationship you have with your main partner?”; Ref=moderately satisfied)							
Extremely satisfied	–0.55291	0.2038	–271.344	0.007	0.575	0.3859	0.858
Extremely unsatisfied	0.00388	0.5325	0.00729	0.99	1.004	0.3536	2.850
Moderately unsatisfied	–0.24571	0.2816	–0.87252	0.38	0.782	0.4504	1.358
Neither satisfied nor unsatisfied	–0.30223	0.2834	–106.627	0.29	0.739	0.4241	1.288
Sexual orientation (Ref=women only)							
Men and women equally	–0.85470	0.5628	–151.873	0.13	0.425	0.1412	1.282
Men mostly	0.58608	0.4662	125.715	0.21	1.797	0.7206	4.481
Men only	0.97824	0.2858	342.253	<.001	2.660	1.5190	4.657
Men somewhat more than women	0.29131	0.6834	0.42628	0.67	1.338	0.3506	5.107
Women mostly	–0.18640	0.2140	–0.87090	0.38	0.830	0.5456	1.262
Women somewhat more than men	0.57143	0.4021	142.123	0.16	1.771	0.8052	3.894
Relationship status (Ref=in a longstanding relationship [>6 months])							
Divorced/widowed	159.908	13.664	117.029	0.24	4.949	0.3399	72.036
Engaged/married	–0.13043	0.2211	–0.58989	0.56	0.878	0.5690	1.354
In a “new” relationship (<6 months)	0.81798	0.2448	334.148	<.001	2.266	1.4024	3.661
Single	0.75201	0.2346	320.566	.001	2.121*	1.3394	3.360
Arousal (Ref=real sex gives me the same level of arousal as pornography)							
Real sex gives me a higher level of arousal than pornography	–0.18049	0.1902	–0.94916	0.34	0.835	0.5751	1.212
Real sex gives me a lower level of arousal than pornography	0.84936	0.3043	279.130	0.005	2.338	1.2878	4.245

[a]Estimates represent the log odds of “ED” vs “No ED.”

[b]CYPAT: Cyber Pornography Addiction Test.

Discussion

Principal Findings

Since 2006, with the rise of so-called "porn tube sites," pornography has become widely available and easily accessed on the internet. With just a click, the consumer can indulge his fantasies in ways that would never be possible in real life. Although our study was not intended to examine pornography consumption habits in the general population, the high pornography consumption rates in our study were similar to those in several population studies [47,48] and in line with Pornhubs' 2019 statistics [49]. While pornography-assisted masturbation is more frequent nowadays, this is not necessarily a sign of pathology [50]. Masturbation with pornography is even a source of sexual health for many young men.

However, since many men start using pornography at a very early age and masturbate more with the help of pornography than without, it is important to study its possible consequences on erectile function.

Frequency of pornography use did not seem to have an important impact on the occurrence of ED. Only when consuming pornography for more than 30 minutes in a row was the frequency of ED slightly higher, but most participants (89%) do not consume pornography for more than 30 minutes.

For the multivariate analysis, a DAG was used to guide the multivariable data analysis to avoid inappropriate adjustment for variables on a causal path between exposure and outcome. Our DAG might be biased since the associations between the covariates are not well known. We hypothesize that the DAG is in proximity of the truth since it was based on the best available evidence and multidisciplinary subject matter expertise when evidence was not available. Age, a well-known covariate for ED, was not included in the DAG because the effect of age was not considered important in our target population (≤35 years of age). Alternative logistic regression models including other variables such as "duration of one pornography session," "masturbation ratio with and without pornography," and "whether pornography is needed to climax" were examined but had lower performance and resulted in a poor model fit compared with the model based on the DAG. Among the model's covariates, there was little multicollinearity, and no extreme influential observations were detected, thus meeting the assumptions for logistic regression.

More PPC, as measured by CYPAT in our study, resulted in a higher probability of ED, while controlling for covariates. While an OR of 1.06 seems low, it is important to remember that for each increase in CYPAT score, the chance of ED increased by 6%. As the CYPAT consists of 11 questions and for each question, a score of 1-5 is given, it means that when 3 questions are scored 1 point higher, the odds for ED increase by 18%, which is high. While a longitudinal study will be necessary to draw conclusions, it is striking how many young men who are not having sexual intercourse (yet) have high CYPAT scores.

There was a wide variety of PCT for different CYPAT categories, meaning that the time of pornography consumption is not necessarily predicting CYPAT scores and vice versa.

Two other instruments are recommended to assess PPC [36]: the Problematic Pornography Use Scale and Problematic Pornography Consumption Scale (PPCS). However, they were published after we developed our survey. The PPCS should be considered in future studies as it has a clear cut-off for problematic versus nonproblematic use and furthermore assesses tolerance. However, CYPAT includes a use despite harm component, which is a relevant CBSD criterium. A correlation study between both scores would be relevant.

Masturbation frequency is often seen as a confounding factor when examining pornography consumption and relational happiness [3], as pornography consumption is mostly accompanied by masturbation. However, in our study, we found no evidence to support that masturbation frequency has an effect on ED. Masturbation frequency was not statistically significantly different between the ED versus no ED groups. Although men with ED watch more pornography per week, when examining the effect of CYPAT on ED, there was no significant effect of masturbation frequency.

ED was reported more frequently by men identifying themselves as homosexual and by men who had sexual fantasies about other men, but not necessarily identifying themselves as homo- or bisexual. Janssen and Bancroft [10] also documented a higher prevalence of ED among homosexual men in 2007. Sexual orientation, identity, and sexual fantasies towards other men seem to be important covariates when assessing the effect of PPC on ED. We also noticed that there are discrepancies between how men identify themselves and who their fantasies are about. Men who are sexually oriented to other men watch more pornography, have higher CYPAT scores, and report more ED. A follow-up study is being planned to understand the role of sexual identity, sexual orientation, and sexual fantasies on PPC and ED and how these covariates relate with each other.

Single men and men in a new relationship reported more ED than men in a longstanding relationship. Performance pressure, anxiety, and insecurity are important factors to assess when a young man consults for ED. Finding pornography more arousing than real sex also contributes to this situational ED (56% ED in our study sample versus 17% for those who found real sex more arousing). This was also seen in a study by Berger et al [51]. In his study, 79% of participants who preferred pornography over partnered sex were classified as having ED. Whether this is due to the incongruence between the participants who preferred pornography category or sexual preference and the partnered performance or if certain pornography categories are more prone to be more arousing needs to be studied further. However, it seems interesting to question pornography watching habits, including which pornography categories men find more arousing and how these relate to their own sexual practices.

One of the strengths of our study is that we assessed ED with a validated and broadly used scale with well-defined cut-off values to evaluate ED in a clinical urological context. However, many participants who did not have intercourse in the preceding 4 weeks were excluded from the analysis, as the IIEF questions were related to sexual intercourse during this period. In that sense, a questionnaire evaluating (situational) ED in young men based on questions not relating to sexual intercourse would be

of great value. The ED part of the Male Sexual Health Questionnaire seems promising; however, no cut-off values are available as of yet. Also, the newly developed Masturbation Erection Index could be of great value [52].

On the other hand, it is clear that the ED seen in our study is situational, as many participants experiencing some ED during partnered sex did not experience ED nor climaxing difficulties while masturbating with pornography. In a clinical setting, while questioning a young patient presenting with ED, it can be interesting to question erectile function while masturbating with and without pornography consumption separately.

It should be said that our results are based on a survey sample. As is seen with the association between frequency of pornography use and problematic pornography use, it is possible that the association between PPC and ED could even be stronger in a clinical sample of treatment-seeking individuals [4].

Therefore, we should not wait to assess PPC in young males consulting for ED. Earlier studies showed only 3%-4.4% of men will consider themselves addicted to pornography [48].

However, most men experiencing ED possibly due to PPC cannot be considered as "addicted." The prevalence of ED already significantly increases with moderate CYPAT scores. Is it possible this situational ED is an early warning signal for the impact pornography has on their sexual functioning?

As pornography consumption is common nowadays (and is even growing, with 11% increased global traffic during the COVID-19 pandemic [53]), most young men will not bring up the topic themselves, and if health care professionals treating ED do not assess pornography consumption in a structured way, the impact in the clinical setting will not be known. As long as this impact is not known, even if it is only self-perceived, it will be impossible to agree on diagnostic criteria and possible treatment algorithms, keeping many individuals in a vicious circle affecting quality of life, possibly having an adverse effect on a man's psychosocial well-being, and placing a burden on relationships [15].

While the existence of "porn addiction" is disputed, there seems a strong correlation between CYPAT and ED. We found an OR of 1.06 for every point increase in CYPAT scores and ED. Indeed, to this day, "PIED," "porn addiction," and "sex addiction" do not exist as diagnosable entities in the DSM-5. On the other hand, very recently, the World Health Organization included a new related diagnosis to their ICD-11, CSBD, under which compulsive use of pornography could be classified. It was categorized as an impulse control disorder and not as a behavioral addiction because there is insufficient evidence to do so [36].

Of course, further neuroscientific and psychophysiological studies will be necessary to explain why PPC can have an effect on ED. To achieve tumescence, a man needs sexual arousal, and this may come from visual stimulation. With sufficient arousal, nitric oxide is released in the penile cavernous tissue and the GTP-cGMP-5'GMP cascade is started. This is the physiological target for PDE-5 inhibitors that are commonly used to treat ED. In the absence of arousal, there will be no erection. A hypothesis is that pornography may give such an extreme visual stimulus that it overactivates the reward system in our brains [21,22]. As with other addictions, the brain rewires itself and accommodates this overstimulation; thus, more and more extreme porn is required to achieve the same level of arousal (tolerance), to the point where normal sex with a partner is no longer sufficient for arousal. Although not validated, this hypothesis will implicate that PDE-5 inhibitors commonly used to treat ED will be less effective in patients suffering from PIED.

As our study shows a higher ED rate in those who started consuming pornography at an earlier age, we need to learn more about adolescents' pornography use in a larger social and cultural development context [54] and consider media effects [55]. Also, we need to focus on longitudinal studies to examine the effects of early exposure, as a Croatian study already found that higher baseline levels of pornography use as well as higher levels of negative emotions and impulsivity predicted higher levels of PPC 3 years later [56]. This should also trigger more interdisciplinary work on this topic with medical specialists, sexologists, (developmental) psychologists, sociologists, and specialists in media literacy. Next, we should focus on porn literacy programs. A recently developed digital prototype seems promising to address the pornography literacy needs of young people [57].

Strengths and Limitations

We consider the large number of observations, the use of validated scales, the multidisciplinary approach, and the multivariable analyses based on a DAG as the major strengths of this study. Although the study was conducted with great care, possible biases might have been introduced. The study sample might not be fully representative of the population intended to be analyzed. Men with sexual health problems might have been more prone to participate in the study, resulting in a higher prevalence of ED in the study sample. Measurement bias due to using CYPAT as a (initially unintended) measure for PPC may also be present. It is also possible that recall bias was present caused by differences in the accuracy of the recollections retrieved by study participants regarding past behavior, especially when estimating the PCT per week. Also, one of the big problems in this field of research is that there is basically no control group, since nearly all young men seem to watch pornography during masturbation.

The association we found between PPC and ED does not necessarily mean that PPC causes ED. It is perfectly possible that ED leads to higher levels of pornography consumption. However, our multivariable analysis was based on a DAG model that included ED as outcome parameter, not the other way around. This suggests a possible causal association, although more research is needed to investigate causality in depth. Also, DAGs are usually used to encode a priori assumptions about relationships between variables to express causal assumptions and to guide the data collection and analysis [58]. Here, a DAG was used a posteriori.

Conclusions

The prevalence of ED in young men is alarmingly high, and the results of this study suggest a significant association with PPC. Higher CYPAT scores result in a higher probability of ED,

when controlling for covariates. Masturbation frequency is not a significant factor when assessing ED. Multivariable analysis identified sexual orientation, experiencing performance pressure, and relationship status as important factors when evaluating the effect of PPC on ED in young men.

Authors' Contributions

TJ, KFP, and GDW conceptualized the study. TJ curated the data, performed the investigation, and administered the project. TJ, BG, and GDW designed the methodology and performed the formal analysis. GDW provided the resources, and BG provided the software. GVH, IG, and GDW supervised the study, and TJ and BG created the visualizations. TJ, BG, GVH, IG, and GDW wrote the original manuscript draft, and all authors reviewed and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AUDIT-C: Alcohol Use Disorders Identification Test-Concise
CSBD: compulsive sexual behavior disorder
CYPAT: Cyber Pornography Addiction Test
DAG: directed acyclic graph
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ED: erectile dysfunction
ICD-11: International Classification of Diseases, 11th Revision
IIEF-5: International Index of Erectile Function, Short version
OR: odds ratio
PCT: pornography consumption time
PIED: porn-induced erectile dysfunction
PPC: problematic pornography consumption
PPCS: Problematic Pornography Consumption Scale

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Original Paper

High Work-Related Stress and Anxiety as a Response to COVID-19 Among Health Care Workers in South Korea: Cross-sectional Online Survey Study

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Abstract

Background: The COVID-19 outbreak had a severe impact on health care workers' psychological health. It is important to establish a process for psychological assessment and intervention for health care workers during epidemics.

Objective: We investigated risk factors associated with psychological impacts for each health care worker group, to help optimize psychological interventions for health care workers in countries affected by the COVID-19 pandemic.

Methods: Respondents (n=1787) from 2 hospitals in Korea completed a web-based survey during the period from April 14 to 30, 2020. The web-based survey collected demographic information, psychiatric history, and responses to the 9-item Stress and Anxiety to Viral Epidemics (SAVE-9), 9-item Patient Health Questionnaire (PHQ-9), and 7-item Generalized Anxiety Disorder-7 (GAD-7) scales. We performed logistic regression to assess contributing factors as predictor variables, using health care workers' depression as outcome variables.

Results: Among 1783 health care workers, nursing professionals had significantly higher levels of depression (PHQ-9 score: meannurse 5.5, SD 4.6; meanother 3.8, SD 4.2; P<.001), general anxiety (GAD-7 score: meannurse 4.0, SD 4.1; meanother 2.7, SD 3.6; P<.001), and virus-related anxiety symptoms (SAVE-9 score: meannurse 21.6, SD 5.9; meanother 18.6, SD 6.3; P<.001). Among nursing professionals, single workers reported more severe depressive symptoms than married workers (PHQ-9 score ≥10; meannurse 20.3%; meanother 14.1%; P=.02), and junior (<40 years) workers reported more anxiety about the viral epidemic (SAVE-9 anxiety score; meannurse 15.6, SD 4.1; meanother 14.7, SD 4.4; P=.002). Logistic regression revealed that hospital (adjusted odds ratio [OR] 1.45, 95% CI 1.06-1.99), nursing professionals (adjusted OR 1.37, 95% CI 1.02-1.98), single workers (adjusted OR 1.51, 95% CI 1.05-2.16), higher stress and anxiety to the viral infection (high SAVE-9 score, adjusted OR 1.20, 95% CI 1.17-1.24), and past psychiatric history (adjusted OR 3.26, 95% CI 2.15-4.96) were positively associated with depression.

Conclusions: Psychological support and interventions should be considered for health care workers, especially nursing professionals, those who are single, and those with high SAVE-9 scores.

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KEYWORDS

COVID-19; health personnel; occupational stress; anxiety; depression; stress; mental health; South Korea; health care worker; assessment; intervention

Introduction

COVID-19 is a highly contagious respiratory disease first reported in December 2019 in Wuhan, Hubei Province, China [1]. In Korea, the first patient was diagnosed on January 20, 2020, and the number of infections increased rapidly, exceeding 5000 infections within 6 weeks as people who participated in religious events were infected [2]. The Korean government raised the country's infectious disease alert level to the highest level on February 23, 2020 [3], set up and operated 638 screening clinics to quickly examine individuals with fever or respiratory symptoms, expanded specialized infectious disease hospitals nationwide to treat patients with severe symptoms, and allocated 10,000 beds for the treatment of patients with mild symptoms. People were obligated to follow strong social distancing measures, such as voluntarily refraining from going out and restricting movement set by the Korean government for at least 2 weeks. Two months after the government raised the alert to the highest level, the average daily number of new infections gradually decreased and remained under 20 from April 18, 2020, until July 2021, when the number of confirmed infections increased again, exceeding 1000 per day. As of July 9, 2021, Korea reported a total of 165,344 individuals with confirmed infections, of whom 15,462 were quarantined (152,498 completed quarantine; 10,810 quarantined) and 2036 were deceased [3].

Health care workers on the frontlines play a major role in preventing the spread of COVID-19 by implementing the government's strong countermeasures. Despite their heroic efforts during the early phase of the pandemic, their mental health faces a considerable threat. In other disasters, health care workers take care of patients who have been hurt, but they are not themselves affected directly by the disaster. In contrast, health care workers can be directly affected during epidemics. For health care workers who are in close contact with patients with confirmed or suspected COVID-19, lack of personal protective equipment, work overload, poor infection control, and pre-existing medical conditions were identified as risk factors for the disease [4]. Previous studies conducted during severe acute respiratory syndrome (SARS), influenza A/H1N1, and the Middle East Respiratory Syndrome (MERS) outbreaks showed that health care workers face the fear of infecting family, friends, and colleagues [5-7]; had increased workloads and reluctance to work; perceived stigmatization, coping by avoiding crowds and colleagues; and felt scrutinized [7-9]. Many experienced severe emotional stress, such as anxiety, worrying, burnout, insomnia, and depressive symptoms, and were diagnosed with acute stress disorder or posttraumatic stress disorder [6,7,10-13]. The rate of distress among health care workers is higher than that in the general population [14]. Similarly, recent studies have shown that a significant proportion of health care workers experienced psychological impacts during the COVID-19 outbreak, such as depression, anxiety, and stress [15-21]. These studies reported that the psychological impact of COVID-19 on health care workers was highly associated with their sociodemographic characteristics and was related to stress vulnerability or social support. Occupation and workplace differences are also important factors. Female health care workers, nurses, and frontline workers directly engaged in the diagnosis, treatment, and care of patients with COVID-19 are particularly vulnerable to mental health symptoms [15,20].

As of July 2021, the COVID-19 pandemic has been ongoing for more than a year and a half. Psychological problems and exhaustion are not only a burden on health care workers but could also affect society as a whole, by threatening essential health care services or resulting in severe staff shortages. It is, therefore, important to establish a process for psychological assessment and intervention for health care workers affected by epidemics. Studies have assessed psychological symptoms using well-known scales such as the 7-item Generalized Anxiety Disorder scale (GAD-7), 9-item Patient Health Questionnaire (PHQ-9) [15,16,18], 6-item version of State-Trait Anxiety Inventory, and Center for Epidemiologic Studies Depression Scale [19]. However, these scales are not specific to viral epidemics but apply to general situations. Few have used specialized rating scales for health care workers in epidemics. One such study [13], in which 150 health care workers participated, developed a questionnaire for health care workers during the MERS outbreak and the 6-month period after the outbreak ended. However, the questionnaire lacks qualitative validity and comparison with other scales, rendering it impractical for use. Therefore, a rating scale that is brief, specific to a viral epidemic, and tailored to health care workers is necessary to assess their work-related stress in response to a viral epidemic.

In this study, we aimed to assess the stress and anxiety response of health care workers specific to the COVID-19 pandemic, by using the Stress and Anxiety to Viral Epidemics-9 (SAVE-9) scale [22], which we developed to measure specific anxiety responses of health care workers to the viral epidemic, along with other well-known scales to assess general anxiety and depression. In addition, we investigated which demographic risk factors, such as type of health care job, age, sex, and marital status, affected stress, anxiety, and depression symptoms during the pandemic, and we screened health care workers who were having an anxiety response to the viral epidemic but who had been identified by preexisting rating scales (not specific to the viral epidemic) as not having general anxiety, in order to highlight the need for establishing psychosocial support services for evidence-based rapid evaluations and psychological crisis interventions for vulnerable health care workers during any future infectious disease outbreak.

Methods

Study Site

This study was conducted among health care workers at the Asan Medical Center, a tertiary hospital (2705 beds; 7970 health

care workers) in Seoul, and the Uijeongbu St. Mary's Hospital, a secondary hospital (716 beds; 1800 health care workers) in Uijeongbu, Gyeonggi province, South Korea. During the outbreak, due to the rapid increase in the number of confirmed COVID-19 cases in Uijeongbu St. Mary's Hospital, the entire hospital was placed in isolation for 3 weeks starting from March 1, 2020. During cohort isolation, outpatient departments were closed, and the discharge of in-patients was withheld. Wards exposed to patients with confirmed COVID-19 were quarantined and only essential medical staff were allowed to enter the wards. Quarantined individuals were regularly tested for COVID-19, and those who tested negative remained in quarantine, whereas those who tested positive were transferred to a designated COVID-19 treatment institution. On May 11, 2020, the hospital was restored to full functionality.

A patient who had visited Uijeongbu St. Mary's Hospital on March 25, 2020, was admitted to the emergency room of Asan Medical Center on March 26, 2020, and was confirmed to have COVID-19 on March 31, 2020. Afterward, 4 wards were placed in cohort isolation and 57 health care workers were quarantined. Cohort isolation in the wards was lifted on April 15, 2020, and Asan Medical Center the COVID-19 intensive care medical institution status was removed on April 19, 2020.

Participants and Procedure

The survey was conducted from April 14 to 18, 2020, at Uijeongbu St. Mary's Hospital and from April 20 to 30, 2020, at Asan Medical Center. We used a cross-sectional, anonymous survey design to assess the psychological impact on health care workers. We advertised this study through notice boards at the 2 hospitals, and 1787 health care workers responded voluntarily. To avoid face-to-face contact, respondents completed the questionnaires through a web-based survey platform. Respondents were not compensated for their participation. This study was approved by the Asan Medical Center institutional review board (2020-0580, UC20RADI0090). Written informed consent was waived, as the respondents could declare, while answering the web-based survey, whether or not they agreed to the use of their information for the study.

Health care workers were classified into 5 groups based on the International Standard Classification of Occupations 2008 revision (ISCO) [23]: medical doctors (ISCO codes: 2211 and 2212); nursing professionals (ISCO code: 2221); health associate professionals (ISCO codes: 2240, 2261, 2262, 2264, 2265, 2266, 2267, 3211, 3212, 3213, 3214, 3221, 3252, and 3253); health management and support personnel (ISCO codes: 1342, 2131, 2133, 3141, and 3344); and clerical support workers, service and sales workers, trade workers, and plant and machine operators; and health service provided not classified elsewhere.

Assessment Measures

SAVE-9 scale

The SAVE-9 scale was developed to assess work-related stress and anxiety response of health care workers to the COVID-19 pandemic [22]. Respondents rated agreement with each item on a 5-point scale from 0 (never) to 4 (always). In the previous validation study [22], satisfactory internal consistency (Cronbach α=.795) was observed, and a 2-factor structure was adopted: (1) anxiety about viral epidemics and (2) work-related stress associated with viral epidemics. A SAVE-9 score of ≥22 (or total anxiety subcategory score ≥15) was comparable to at least a mild degree with GAD-7 total score. We used the Korean version of the SAVE-9 scale, since it was originally developed in the Korean language.

PHQ-9

PHQ-9 is a self-administered, 9-item questionnaire used to assess depression. Each item is scored on a 3-point scale from 0 (not at all) to 3 (nearly every day). Scores can range from 0 to 27, with higher scores reflecting greater symptom severity. A PHQ-9 score >10 indicates depression [24]. In this study, we used the Korean version of the PHQ-9 scale [25].

GAD-7

GAD-7 is a self-administered, 7-item questionnaire specific to general anxiety. Each item is scored on a 3-point scale from 0 (not at all) to 3 (nearly every day). Scores can range from 0 to 21, with higher scores reflecting greater symptom severity. In this study, a score ≥5 was used for mild anxiety [26], as we wished to screen health care workers with at least mild degrees of anxiety. In this study, we used the Korean version of the GAD-7 scale [25].

Sociodemographic data

Sex, age, marital status, type of health care job, and years of employment were collected. Additionally, respondents were asked whether they had a current or previous diagnosis of depression, anxiety, or insomnia.

Analysis

Statistical analyses were performed using SPSS software (version 21.0 for Windows; IBM Corp). The clinical characteristics were summarized as mean (SD) values. To calculate frequency, the number of each sample was divided by the total number of samples in each health care worker group. The student *t* test (2-tailed) was used for continuous variables, and the chi-square test (2-tailed) was used for categorical variables for between-group analyses. The level of significance for all analyses was P<.01. Logistic regression analysis was conducted to explore risk factors for health care worker depression. Finally, the additional value (ie, detection of those who were not screened through GAD-7) of the SAVE-9 was estimated using the McNemar test. To obtain robust odds ratios (OR), considering previously (or clinically) important factors, variables with P<.10 in univariate analysis were included.

Results

A total of 1023 Asan Medical Center health care workers and 764 Uijeongbu St. Mary's Hospital health care workers participated in the web-based survey. We analyzed data from 1783 health care workers (Table 1) after excluding 4 responses of health care workers who did not agree to the use of their responses in this study. Of 1783 respondents, 76.1% (1356) were female, 52.7% (939) were single. The proportion of participants was high among those in their 20s and 30s. Asan Medical Center had more nursing professionals as respondents, more health care workers with psychiatric histories, and higher

PHQ-9, GAD-7, and SAVE-9 work-related stress subcategory scores than Uijeongbu St. Mary's Hospital.

Among the 5 categories of health care workers, nursing professionals were younger (75.1% of juniors in nursing professionals, 60.2% in all workers excluding nursing professionals, *P*<.001), more depressed (PHQ-9 score: 5.5, SD 4.7, vs 3.8, SD 4.2; *P*<.001), and more anxious (GAD-7 score: 4.0, SD 4.1, vs 2.7, SD 3.6; *P*<.001) than workers in all other groups (Tables 2 and 3). The SAVE-9 scale score was significantly correlated with PHQ-9 score for all health care worker groups (all *P*<.001). In nursing professionals, single workers reported more depressive symptoms (higher proportion of workers whose PHQ-9 score ≥10) compared with married workers (*P*=.008). Excluding nursing professionals, other groups' PHQ-9 scores did not differ significantly with respect to sex, age, or marital status; however, female health care workers reported higher anxiety (higher proportions of GAD-7 score ≥5) than male health care workers (*P*<.001), and married health care workers reported more anxiety than single health care workers (*P*=.010). Especially among all married health care workers, nursing professionals had significantly higher SAVE-9 (21.3, SD 5.7, vs 19.3, SD 6.1; *P*<.001), GAD-7 (3.9, SD 3.8, vs 2.9, SD 3.5; *P*<.001), and PHQ-9 scores (4.9, SD 4.5, vs 3.9, SD 4.1; *P*<.001) than those of other health care workers. In nursing professionals, junior workers (<40 years) were more anxious about the viral epidemic situation (*P*=.002); junior (*P*<.001) and single workers (*P*=.001) were more stressed about their work. Female workers among all workers, excluding nursing professionals, were more anxious about the viral epidemic (*P*<.001) and felt more stressed (*P*<.001).

Table 1. Demographic characteristics of the respondents.

Variables	ASAN medical center (n=1019), n (%)	Uijeongbu St. Mary's Hospital (n=764), n (%)	*P* value	All (n=1783), n (%)
Gender			<.001	
Male	211 (20.7)	216 (28.3)		427 (23.9)
Female	808 (79.3)	548 (71.7)		1356 (76.1)
Age			<.001	
20-29 years	309 (30.3)	287 (38.5)		596 (33.4)
30-39 years	387 (38.0)	222 (29.8)		609 (34.2)
40-49 years	253 (24.8)	161 (21.6)		414 (23.2)
50-59 years	70 (6.9)	74 (9.9)		144 (8.1)
60-65 years	0 (0.0)	1 (0.1)		1 (0.1)
Marital status			.304	
Single	529 (52.3)	410 (53.7)		939 (52.7)
Married	482 (47.7)	354 (46.3)		836 (46.9)
Categories of health care workers			<.001	
Medical doctors	192 (18.8)	100 (13.1)		292 (16.4)
Nursing professionals	596 (58.7)	369 (48.3)		967 (54.2)
Health associate professionals	126 (12.4)	120 (15.7)		246 (13.8)
Health management and support personnel	83 (8.1)	85 (11.1)		168 (9.4)
Health service provided not elsewhere classified	20 (2.0)	90 (11.8)		110 (6.2)
Past psychiatric history (yes)	129 (12.7)	49 (6.4)	<.001	178 (10.0)
Years of employment (year)	9.9 (9.0)	9.5 (9.3)	.369	9.7 (9.1)
Assessment measures				
Patient Health Questionnaire–9	4.9 (4.6)	4.4 (4.4)	.006	4.7 (4.5)
Generalized Anxiety Disorder–7	3.7 (4.0)	3.0 (3.7)	<.001	3.4 (3.9)
SAVE-9[a]	20.3 (5.7)	20.2 (7.0)	.642	20.3 (6.3)
Anxiety subcategory of SAVE-9	14.2 (4.2)	14.7 (4.9)	.046	14.4 (4.5)
Work-related stress subcategory of SAVE-9	6.1 (2.3)	5.5 (2.7)	<.001	5.8 (2.5)

[a]SAVE-9: Stress and Anxiety to Viral Epidemics-9.

Table 2. Clinical characteristics of respondents by health care worker category.

Variables	Nursing professionals (n=967)	Medical doctors (n=292)	Health associate professionals (n=246)	Health management and support personnel (n=168)	Health service provided not elsewhere classified (n=110)	All workers excluding nursing professionals (n=816)
Age						
Junior	718 (75.1)	215 (73.9)	152 (62.3)	77 (46.7)	43 (39.8)	487 (60.2)
Senior	238 (24.9)	76 (26.1)	92 (37.7)[a]	88 (53.4)[a]	65 (60.2)[a]	321 (31.8)[a]
Sex (female)	933 (96.5)	122 (41.8)[a]	114 (46.3)[a]	103 (61.3)[a]	84 (76.4)[a]	423 (51.8)[a]
Past psychiatric history	90 (9.3)	33 (11.3)	18 (7.3)	27 (16.2)[b]	10 (9.2)	88 (10.8)
Marital status (married)	396 (41.1)	140 (48.1)[c]	143 (58.6)[a]	94 (56.3)[a]	63 (57.3)[d]	440 (54.2)[a]
Years of employment	10.1 (8.6)	6.6 (7.4)[a]	10.3 (11.0)	11.5 (10.4)	10.4 (9.4)	9.2 (9.7)

[a]*P*<.001 compared to the nursing professionals group.

[b]*P*=.007 compared to the nursing professionals group.

[c]*P*=.035 compared to the nursing professionals group.

[d]*P*=.001 compared to the nursing professionals group.

Table 3. Clinical symptom assessment of the participants by category of health care worker (n=1783)

	Nursing professionals (n=967)	Medical doctors (n=292)	Health associate professionals (n=246)	Health management and support personnel (n=168)	Health service provided not elsewhere classified (n=110)	All workers excluding nursing professionals (n=816)
PHQ-9[a] score	5.5 (4.6)	2.9 (3.4)[b]	3.8 (4.2)[b]	4.6 (4.7)	4.4 (4.5)	3.8 (4.2)[b]
Score ≥10, n (%)						
Junior	138 (19.2)	11 (5.1)	15 (9.8)	11 (14.3)	5 (11.6)	42 (8.6)
Senior	33 (13.9)	4 (5.3)	10 (10.9)	8 (9.1)	9 (13.8)	31 (9.7)
Score ≥10, n (%)						
Male	4 (11.8)	9 (5.3)	9 (6.8)	9 (13.8)	0 (0.0)	27 (6.9)
Female	168 (18.0)	6 (4.9)	16 (14.0)	10 (9.7)	14 (16.7)[c]	46 (10.9)
Score ≥10, n (%)						
Married	56 (14.1)	7 (5.0)	14 (9.8)	9 (9.6)	9 (14.3)	39 (8.9)
Single	115 (20.3)[d]	8 (5.3)	10 (9.9)	10 (13.7)	5 (10.6)	33 (8.9)
GAD-7[e] score	4.0 (4.1)	2.0 (3.0)[b]	3.0 (3.9)[f]	3.4 (4.0)	2.7 (3.1)[g]	2.7 (3.6)[b]
Score ≥5, n (%)						
Junior	257 (35.8)	34 (16.3)	37 (24.3)	30 (39.0)	8 (18.6)	109 (22.7)
Senior	85 (35.7)	11 (14.5)	23 (25.0)	26 (30.2)	18 (27.7)	78 (24.5)
Score ≥5, n (%)						
Male	12 (35.3)	23 (14.1)	25 (18.9)	18 (27.7)	1 (3.8)	67 (17.4)
Female	333 (35.7)	22 (18.0)	36 (31.6)	39 (38.6)	25 (29.8)[h]	122 (29.0)[h]
Score ≥5, n (%)						
Married	142 (35.9)	27 (19.3)	39 (27.3)	33 (35.1)	17 (27.0)	116 (26.4)
Single	202 (35.6)	18 (12.5)	22 (21.8)	24 (33.8)	9 (19.1)	73 (20.1)[h]
SAVE-9[i] score	21.6 (5.9)	17.2 (6.1)[b]	20.2 (5.9)[b]	18.9 (6.3)[b]	18.2 (6.8)[b]	18.6 (6.3)[b]
SAVE-9 anxiety score	15.4 (4.2)	12.0 (4.6)[b]	14.7 (4.3)	13.4 (4.5)[b]	13.3 (4.8)[b]	13.3 (4.6)[b]
Age						
Junior	15.6 (4.1)	11.6 (4.7)	14.8 (4.1)	13.8 (4.9)	13.6 (5.2)	13.1 (4.8)
Senior	14.7 (4.4)[j]	13.0 (4.3)	14.5 (4.7)	13.1 (4.0)	12.9 (4.6)	13.5 (4.5)
Gender						
Male	14.1 (5.8)	11.3 (4.6)	14.2 (4.4)	12.8 (4.8)	11.1 (3.9)	12.5 (4.7)
Female	15.4 (4.1)	12.9 (4.4)[k]	15.3 (4.1)	13.7 (4.2)	13.9 (4.9)[l]	13.9 (4.5)[h]
Marital status						
Married	15.4 (4.0)	12.8 (4.4)	14.6 (4.6)	13.7 (4.2)	13.9 (4.5)	13.7 (4.5)
Single	15.4 (4.3)	11.3 (4.6)	14.9 (3.9)	13.0 (4.7)	12.3 (5.2)	12.7 (4.7)[h]
SAVE-9 work-related stress score	6.3 (2.5)	5.3 (2.2)[b]	5.5 (2.4)[b]	5.5 (2.4)[m]	5.0 (2.6)[b]	5.4 (2.4)[b]
Age						
Junior	6.4 (2.5)	5.4 (2.2)	5.5 (2.4)	5.7 (2.6)	5.0 (2.7)	5.4 (2.4)
Senior	5.7 (2.4)[h]	5.0 (2.3)	5.5 (2.5)	5.4 (2.3)	4.9 (2.6)	5.2 (2.4)
Gender						
Male	5.8 (3.0)	4.9 (2.4)	5.2 (2.3)	5.1 (2.7)	3.5 (2.0)	4.9 (2.4)

	Nursing professionals (n=967)	Medical doctors (n=292)	Health associate professionals (n=246)	Health management and support personnel (n=168)	Health service provided not elsewhere classified (n=110)	All workers excluding nursing professionals (n=816)
Female	6.3 (2.5)	5.8 (1.9)[h]	5.9 (2.5)	5.8 (2.2)	5.4 (2.7) [h]	5.8 (2.3)[h]
Marital status						
Married	5.9 (2.4)	5.3 (2.2)	5.8 (2.4)	5.5 (2.7)	5.4 (2.7)	5.5 (2.4)
Single	6.5 (2.6)[h]	5.3 (2.3)	5.2 (2.4)	4.3 (2.4)	4.2 (2.4)	5.2 (2.4)

[a]PHQ-9: Patient Health Questionnaire–9.
[b]*P*<.001 compared to nursing professionals group.
[c]*P*=.026 among each health care worker group.
[d]*P*=.014 among each health care worker group.
[e]GAD-7: Generalized Anxiety Disorder-7.
[f]*P*=.017 compared to nursing professionals group.
[g]*P*=.031 compared to nursing professionals group.
[h]*P*<.001 among each health care worker group.
[i]SAVE-9: Stress and Anxiety to Viral Epidemics-9.
[j]*P*=.002 among each health care worker group.
[k]*P*=.00 among each health care worker group3.
[l]*P*=.008 among each health care worker group.
[m]*P*=.030 compared to nursing professionals group.

Compared with those of medical doctors and other groups, nursing professionals SAVE-9 scores were higher (Figure 1).

Hospital (Asan Medical Center: adjusted OR 1.45, 95% CI 1.06-1.99), nursing professionals (adjusted OR 1.37, 95% CI 1.02-1.98), single workers (adjusted OR 1.51, 95% CI 1.05-2.16), higher stress and anxiety to the viral infection (high SAVE-9 score: adjusted OR 1.20, 95% CI 1.17-1.24), and past psychiatric history (adjusted OR 3.26, 95% CI 2.15-4.96) were positively associated with depression (Table 4).

Among respondents, 534 (29.9%) health care workers were classified as having high anxiety using the GAD-7 total score (GAD-7 score >5). Among health care workers who were classified as not having high anxiety (n=1240), 400 (22.4%) health care workers were newly screened as having stress and anxiety due to the viral epidemic based on SAVE-9 scores (κ=0.351, *P*<.001).

Figure 1. Stress and Anxiety to Viral Epidemics–9 score distributions for health care worker groups.

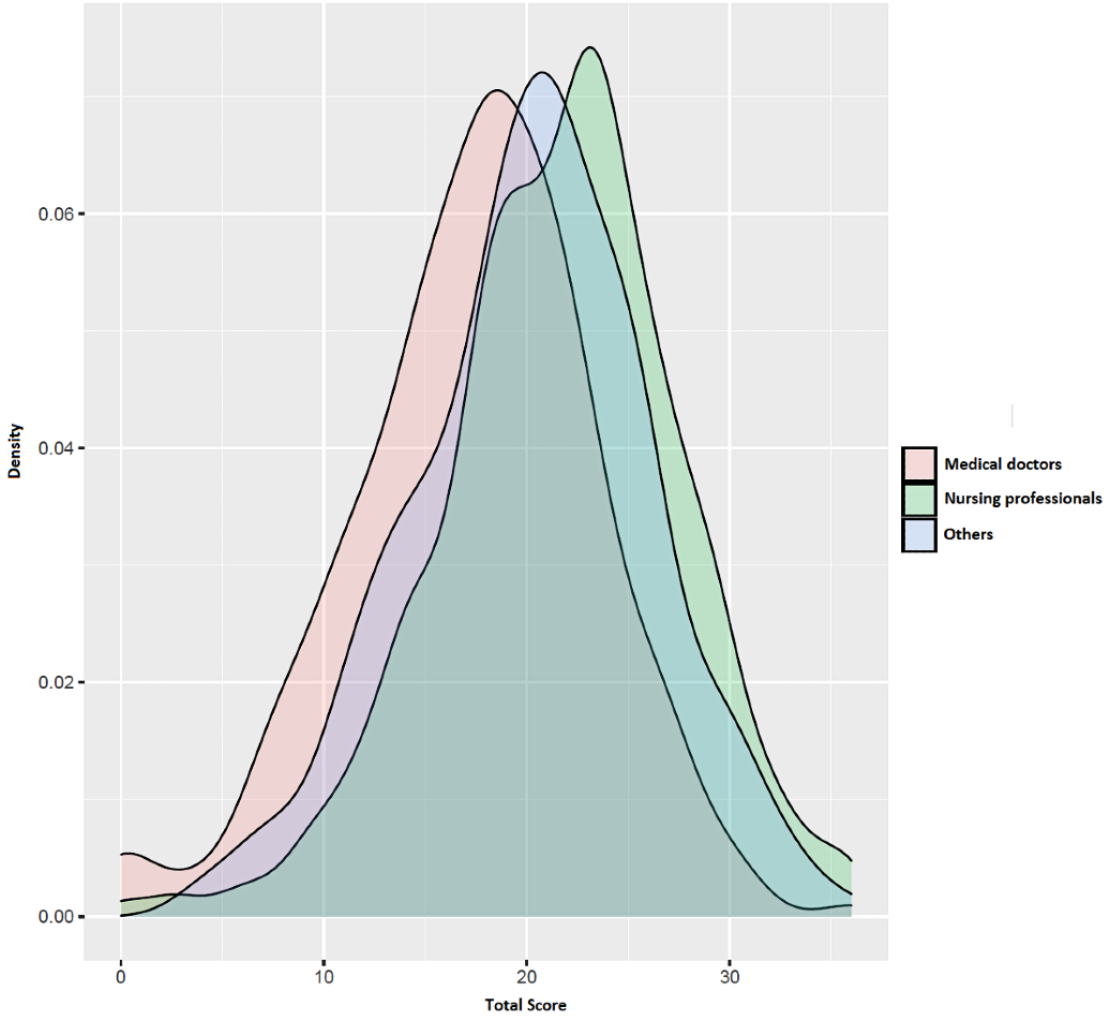

Table 4. Logistic regression analysis to explore predictor variables for depression.

Explanatory variables	Crude OR[a] (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Asan Medical Center (vs Uijeongbu St. Mary's Hospital)	1.43 (1.08-1.89)	.013	1.45 (1.06-1.99)	.021
Junior (vs senior)	1.36 (1.01-1.84)	.049	1.20 (0.81-1.79)	.363
Female (vs male)	2.39 (1.62-3.55)	<.001	1.11 (0.68-1.80)	.684
Single (vs married)	1.46 (1.11-1.92)	.007	1.51 (1.05-2.16)	.025
Nursing professionals (vs others)	2.20 (1.65-2.95)	<.001	1.37 (1.02-1.98)	.041
SAVE-9[b] score	1.19 (1.16-1.23)	<.001	1.20 (1.17-1.24)	<.001
Past psychiatric history	2.47 (1.71-3.56)	<.001	3.26 (2.15-4.96)	<.001

[a]OR: odds ratio.

[b]SAVE-9: Stress and Anxiety to Viral Epidemics–9.

Discussion

The results demonstrated that nursing professionals were more depressed, anxious, and stressed by the viral epidemic than other health care workers during the first phase of the COVID-19 pandemic. Marital status (being single) as well as anxiety and work-related stress associated with the viral epidemic were risk factors for depression among health care workers. The mean SAVE-9 score among health care workers was 20.3 (SD 6.3). Given that our previous study [22] defined mild degree symptoms of virus-related stress and anxiety as a SAVE-9 score greater than 22, this study showed similar results to those of previous studies [15,20,27,28] that showed that a high proportion of health care workers experience psychological impacts during the COVID-19 pandemic. To better fight the COVID-19 outbreak, all health care workers are being employed in activities related to epidemiological investigations and contact isolation.

Along with existing health care workers at the infectious diseases departments, all workers have been recruited at screening clinics [3]. Nursing professionals directly provide care to patients with confirmed or suspected infections and their caregivers. The other health care workers in occupations that do not directly face the patients measure the temperature and sanitize the hands of all incoming people at the hospital entrance, explaining that hospital access and medical treatment are restricted to the contacts identified through epidemiological correlation. All health care workers must wear personal protective equipment at screening clinics and cohort isolation wards.

Consistent with the findings of previous studies, we found that nursing professionals were more likely to feel stress or anxiety than other health care workers [15,16,20,29,30]. Nursing professionals are in crisis as they care for patients with infections, experience fear of infectious diseases, insufficient isolation-patient-care-systems, and ethical dilemmas [31]. In addition, nurses may experience risk in situations where it is difficult to remove and re-wear a gown in-between treatments due to lack of time. Furthermore, they may face distressing situations where uncooperative patients may be exposed to direct infection [32]. As nurses interact most closely with patients and face long durations of infection risk exposure, they reported experiencing physical and emotional difficulties [32]. Feeling burdened by work changes and reacting sensitively to lack of resources may have influenced the high level of stress that nurses report experiencing. Therefore, it has been suggested that mental health and stress management programs are needed for nurses who take care of infected patients [32,33]. Through continuous infection prevention training and protective equipment training, nurses' abilities to cope with crises and ethical dilemmas must be improved [34].

Compared with health care workers who were single, all married workers, excluding nursing professionals, scored higher on GAD-7. Owing to high medical knowledge regarding the high infectivity of the virus and the relatively insufficient medical supplies at the beginning, health care workers had high safety concerns. Married workers may worry not only about their own protection but also about the safety of their family members, including children. This finding is consistent with those of previous studies that noted that the concern for the health of oneself and one's family was significantly higher among married workers [6,35].

However, among nursing professionals, there was no difference in GAD-7 scores of ≥5 according to marital status (single: 35.6%, married: 35.9%), compared to 26.4% of married workers and 20.1% of single workers in all other health care worker groups. Nursing professionals had higher overall depression, anxiety, and virus-related stress and anxiety than other health care workers. The Korean government's emphasis on social distancing made it necessary for participants to submit daily results of viral symptoms monitoring and to be only at home or the hospital. Living as health care workers may have exerted a lot of pressure on them socially to improve the COVID-19 situation. Among single workers, this semicompulsory sequestration was compelled, and they experienced a greater change in life than married workers. As they could not perform daily activities to reduce their stress, their perceived negative emotions increased, and positive emotions remained relatively low [13]. In such unforeseen situations, family support is important to motivate people to continue working [13,36]. Married workers can connect more closely with their families, share things beyond work, and vent emotions better [37]. This finding indicates that single nursing professionals may need more psychological support. We also found that the hospital factor was significantly associated with depression. Asan Medical Center is one of the biggest hospitals in Korea, and there are many more patients with severe illnesses compared with those at other hospitals [38]. Compared to Uijeongbu St. Mary's Hospital, Asan Medical Center had a higher proportion of nursing professionals, more health care workers with psychiatric histories, and higher SAVE-9 scores; these factors may have influenced the association of hospital factors with depression.

In this study, we measured anxiety symptoms among health care workers by using the SAVE-9 scale, which is used for assessing anxiety measures specific to the viral epidemic, and GAD-7 scale, which is used for measuring nonspecific anxiety. In previous SARS and MERS outbreaks, health care workers were exposed to protracted epidemics, and the unfavorable conditions resulted in a high prevalence rate of burnout and depression [39]. The COVID-19 pandemic has been ongoing for more than a year; thus, its impact on the long-term mental health of health care workers should be considered carefully. Studies [15,40] have reported the severe psychological impacts on health care workers during various phases of COVID-19; however, the rating scales used were not specific to the viral epidemic, and therefore, results did not reflect psychological stress specifically in relation to the viral epidemic. We developed SAVE-9 [22] to assess anxiety and stress of health care workers specifically in response to the COVID-19. During a pandemic, a larger number of health care workers need attention and care for maintaining essential care services. We expect that the SAVE-9 scale can be a useful tool for measuring work-related stress and anxiety response of health care workers specifically to the viral epidemic. We could identified an additional 400 (400/1783, 22.4%) health care workers as having significant stress and anxiety response to the viral epidemic to the 534 (29.9%) workers who were classified as having high anxiety using the GAD-7 scale. The GAD-7 is widely used to assess participants' generalized anxiety, but it does not reflect the psychological stress specifically in response to viral epidemics. The viral epidemic-specific rating scale can assess the psychological state of health care workers that is specific to a situation such as the COVID-19 pandemic.

This study has some limitations. First, this was a cross-sectional study; therefore, we can suggest only associations between mental problems and COVID-19 in health care workers but not causal relationships or underlying mechanisms. Second, the survey was conducted only in 1 hospital in Seoul and 1 in Uijeongbu. Thus, the sample may have been biased. In addition, the responses might be biased, as this study utilized a self-report web-based questionnaire. Nevertheless, as the job type distribution of the sample mirrored that of the health care workers at study sites, it can be considered as substantially

representative in these hospitals. Third, the questionnaire was conducted in mid-April 2020, immediately after the end of the cohort isolation. The psychological status of health care workers at the onset or peak of Korea's COVID-19 crisis was, therefore, not assessed. Future research should focus on specific groups, incorporating according to the stage of the epidemics. We will have to collect more comprehensive data on the psychological status of health care workers in other infectious disease outbreaks. Fourth, we were unable to classify workers as parent-facing, contact, frontline health care workers, or those with a history of COVID-19 positivity or quarantine. Lai et al [15] revealed that being directly engaged in clinical activities was an independent risk factor of psychiatric symptoms. Workers with COVID-19 exposure or positivity had a 2 to 4-fold increased risk of being anxious and depressed compared with controls [41]. Moreover, quarantine activity has been shown to adversely affect mental health both during and after quarantine. Finally, the coarse categorization of health care roles may lead to biased findings. Since one of the objectives in this study was to explore which types of workers suffered the severest stress in this pandemic, we categorized them into 2 (nursing professionals vs other health care workers) groups in some of the analyses.

Despite these limitations, our study indicates that all health care workers were at psychological risk of COVID-19 and that they worried about health problems for themselves, their family, and their colleagues. Especially nursing professionals, who are the major health care workers in the medical system and work at the frontline of patient care, can easily be depressed and frustrated. In addition, their marital status (being single), past psychiatric history, and higher level of anxiety specifically in response to the viral epidemic also influence their depressive symptoms. We were able to measure anxiety response and work-related stress among health care workers during this pandemic using SAVE-9, which focuses on viral epidemic–related stress and anxiety.

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Conflicts of Interest

None declared.

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Abbreviations

GAD-7: Generalized Anxiety Disorder-7
ISCO: International Standard Classification of Occupations
MER: Middle East respiratory syndrome
PHQ-9: Patient Health Questionnaire-9
SAVE-9: Stress and Anxiety to Viral Epidemics-9
SARS: severe acute respiratory syndrome

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Original Paper

Smoking Protective and Risk Factors Among Transgender and Gender-Expansive Individuals (Project SPRING): Qualitative Study Using Digital Photovoice

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Abstract

Background: Transgender and gender-expansive (TGE) adults are twice as likely to smoke cigarettes than cisgender individuals. There is a critical gap in research on effective and culturally sensitive approaches to reduce smoking prevalence among TGE adults.

Objective: This study aims to qualitatively examine the risk and protective factors of cigarette smoking among TGE adults through real-world exemplars.

Methods: We conducted a digital photovoice study among a purposeful sample of 47 TGE adults aged ≥18 years and currently smoking in the United States (March 2019-April 2020). Participants uploaded photos daily that depicted smoking risk and protective factors they experienced over 21 days on either private Facebook or Instagram groups. Next, we conducted separate focus group discussions to explore the experiences of these factors among a subset of participants from each group. We analyzed participants' photos, captions, and focus group transcripts and generated themes associated with smoking risk and protective factors.

Results: We identified 6 major themes of risk and protective factors of smoking among TGE individuals: experience of stress, gender affirmation, health consciousness, social influences, routine behaviors, and environmental cues. We describe and illustrate each theme using exemplar photos and quotes.

Conclusions: The findings of this study will inform future community-engaged research to develop culturally tailored interventions to reduce smoking prevalence among TGE individuals.

(JMIR Public Health Surveill 2021;7(10):e27417) doi:10.2196/27417

KEYWORDS

transgender and gender expansive populations; tobacco-related health disparities; United States

Introduction

Background

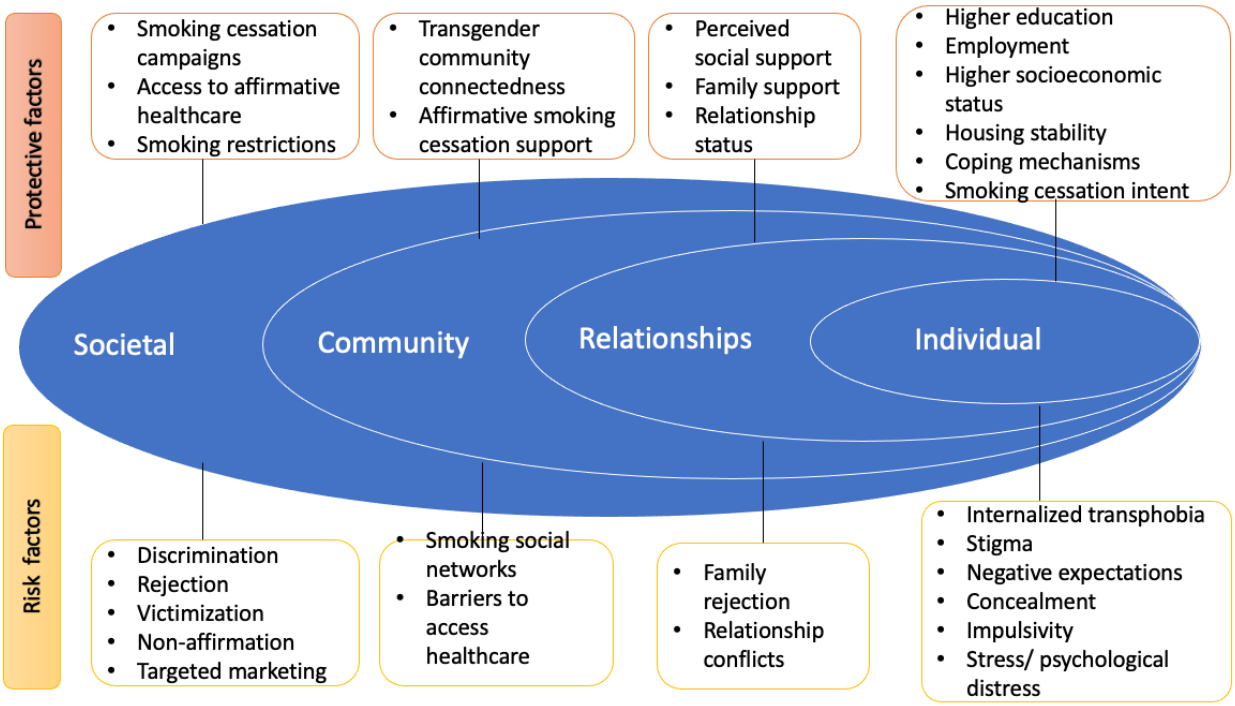
Cigarette smoking is the leading cause of preventable cancer, cardiovascular, respiratory, and other smoking-related illnesses and deaths in the United States [1]. Despite the decline in overall smoking rates in the US population over the past 50 years, there are persistent disparities in the prevalence of smoking among vulnerable populations [2]. Transgender and gender-expansive (TGE) adults—individuals who have a gender identity, behavior, or self-expression that is different from their sex assigned at birth—are twice as likely to smoke cigarettes than cisgender individuals [3]. Approximately 36% of TGE adults smoke cigarettes compared with 21% of heterosexual cisgender adults [3]. An estimated 1 million TGE adults live in the United States [4], which means that approximately 350,000 TGE individuals are at increased risk of developing smoking-related cancers.

The factors associated with increased smoking prevalence among TGE persons are complex and include TGE-specific minority stressors, including everyday discrimination (eg, experiencing denial of equal service, harassment, and physical assault due to TGE status) [5,6], structural discrimination (eg, housing, education, and work discrimination due to TGE status) [6], social determinants (eg, lower socioeconomic position and lack of health insurance in part due to employment discrimination), and alcohol and other substance use [6]. In addition, the tobacco industry targets its product marketing and advertising among lesbian, gay, bisexual, transgender, and queer (LGBTQ+) communities [7,8]. Compounding these risk factors, TGE individuals lack equitable access to health care and, therefore, face barriers in receiving smoking cessation interventions [9]. Research suggests that given the appropriate resources and opportunities, TGE adult smokers are just as likely as cisgender smokers to want to quit [9-11]. Despite experiencing multiple risk factors of smoking, receiving gender-affirming care earlier on recognition of TGE status and social support systems may be protective against smoking among TGE persons [12]. There is a critical gap in research on effective and culturally sensitive approaches to reduce smoking prevalence among TGE adults. Of 384 National Institutes of Health–funded sexual and gender minority research studies in 2018, 20% focused on TGE health and only 1% focused on tobacco use and health [13]. Furthermore, although there is increasing evidence of the effectiveness of using social media for HIV interventions among LGBTQ+ populations [14], there is limited research on the use of web-based social media platforms for tobacco-related research and smoking cessation interventions among TGE populations [15-17].

Objectives

The objective of Project SPRING is to examine TGE individuals' experiences of smoking risk and protective factors in close-to-real time by using a photovoice approach whereby participants "identify, represent, and enhance their community through a specific photographic technique" [18,19]. Photovoice has been used in prior research to examine the social experiences of TGE individuals [20]. The rationale for using photovoice instead of existing approaches such as qualitative interviews or quantitative surveys are threefold. First, we aimed to obtain participants' documentation of their experiences of risks and protective factors in close to real time to minimize recall bias associated with interviews and surveys. Second, photovoice enables the exploration of new or emergent risk or protective factors that are not limited by close-ended survey questions. Third, the photovoice approach involves multiple interactions with participants over time and enables the collection of multiple types of data from the same participants. Focus groups at one time point and cross-sectional surveys are limited in this regard. Our approach was guided by a community-based participatory research approach [21], where TGE persons were included as cocreators of knowledge in several aspects of the study, including data collection, analysis, and interpretation, to inform future research and interventions. This study approach empowers TGE persons to work collaboratively with the study team to understand factors influencing their smoking habits and generate evidence to inform future TGE-tailored smoking cessation interventions. This research is informed by an integrated framework of key concepts from the minority stress model, resilience framework, and socioecological model [22,23]. We conceptualized smoking behaviors among TGE persons to be influenced by both risk and protective factors across individuals, relationships, community, and societal levels (Figure 1). Findings from the real-world exemplars, phrases, meanings of smoking-related triggers, and protective factors from this research will serve as the foundation for designing culturally sensitive narrative messages to promote smoking cessation through social media among the TGE community.

Figure 1. Conceptual framework.



Methods

Research Design

We used a qualitative research design using digital photovoice data collection, focus group discussions, and member checking among participants. The study was approved by the institutional review board of Harvard TH Chan School.

Participant Eligibility and Enrollment

We enrolled a purposeful sample of participants who identify as TGE, live in the United States, have smoked at least 100 cigarettes in their lifetime, currently smoke cigarettes on one or more days in the past 30 days, use either Facebook or Instagram at least once daily, and were able to participate in English. Individuals who were currently quitting smoking, only used e-cigarettes or cannabis, did not smoke cigarettes, and were not able to participate using the English language were ineligible. We used Facebook and Instagram because of the high prevalence of use of these 2 platforms and increased exposure to tobacco-related messages on social media among LGBTQ+ populations [24,25]. The study enrollment was conducted between March 2019 and April 2020. Our initial recruitment was in a northeast metropolitan city, and we expanded the recruitment nationally in October 2019. We recruited most participants through paid Facebook and Instagram advertisements based on the best practices of engaging TGE populations on the web for research studies [26,27]. We also used Craigslist advertisements, snowball sampling, posting flyers at LGBTQ+ events and venues, and outreach through LGBTQ+ community organizations. Two study research assistants screened interested participants over the phone and consented participants who were eligible and agreed to participate in the study. Approximately half of the participants joined separate Facebook groups and half joined separate Instagram groups. The recruitment proceeded on a rolling basis, and participants within each group completed the photovoice collection within the same period of 21 days in their respective groups. There were between 2 and 9 participants per group (average of 5 per group). All participants in each group were given the same start date. Participants received gift cards as incentives for completing each phase of the study procedures (US $10-75 per phase; up to US $300 for completing all phases). We received messages from over 330 interested individuals and were able to contact 110 for screening over the phone or through Facebook messaging. Of the 110 individuals, 47 were eligible and enrolled in the first phase of the study. Of the 47 individuals, 44 completed photovoice data collection. Of the 44 individuals, 29 participated in the focus group discussion. Among these, 9 individuals participated in the member checking discussion.

Study Procedures

Digital Photovoice Data Collection

We used the photovoice technique [18] to obtain participants' close-to-real time personal experiences of risk or protective factors of smoking. Participants were asked to upload pictures and a brief caption of either risk or protective factors in relation to their smoking they experienced to a private study-specific Facebook group or on an Instagram group chat daily for 21 consecutive days. Participants' information on the Facebook or Instagram groups could only be viewed by the participants within their group and the study team. Participants were encouraged to post at least 1 picture per day for at least 5 days per week to ensure a minimum level of participation in the study. They could provide comments on each other's posts. To ensure their privacy and confidentiality, 2 study research assistants conducted training with each study participant to describe the study protocol and examples of the types of appropriate pictures, phrases, and comments that can be shared within their respective

Facebook groups or Instagram group chats. Each participant was assigned a unique study ID code number not connected to any personally identifiable information.

Focus Group Discussion

After each group completed the photovoice data collection, we invited all participants to a focus group discussion with their respective group members. A PhD-prepared nurse researcher with extensive experience and training in qualitative research led the focus groups to research assistants. We conducted in-person focus groups among participants from a northeast metropolitan city and conducted web-based focus groups using the Zoom web conferencing platform (Zoom Video Communications) among participants who were recruited nationally. The number of participants across the focus groups ranged between 2 and 7. The duration of the focus groups ranged from 70 to 170 minutes. During each focus group, participants were first shown photos that they contributed within their Facebook closed private group or Instagram group chat. They were asked to work as a group to complete an image sorting task where they first categorized the images as either risk (things that make them want to smoke) or protective factors for smoking (things that help them resist smoking). Following sorting into risk and protective factors, we asked participants to describe each photo categorized as a risk factor in their own words. This was then repeated for each photo, which was categorized as a protective factor. The moderator provided guidance to the group and probed for the rationale for certain categorization decisions using the SHOWED questions as needed (What do you **S**ee here? What is really Happening? How does this relate to Our lives? Why does this condition Exist? What can we Do about it?). Participants' final categories and names of each category as decided by the group's consensus were recorded. The in-person focus groups were audio recorded, and for the web-based focus groups, we obtained an audiovisual recording and immediately deleted the video component. Following transcription by a professional transcriber, the recordings were deleted per institutional review board requirement for participant confidentiality and privacy.

Member Checking

Following the study team's preliminary analysis of the photos, captions, and focus group transcripts, we invited participants from all the Facebook and Instagram groups to attend a web-based member checking discussion to obtain insights on their interpretation of the risk and protective factors of smoking behaviors, identify the most important factors to address in future interventions, and discuss potential approaches for culturally tailored interventions to reduce smoking among TGE persons. A total of 9 participants were able to attend the member checking focus group. The member checking participants were not all from the same initial Facebook or Instagram group but were members of 5 different groups. This member checking discussion was conducted over 67 minutes over Zoom web conferencing, and we obtained an audio recording. Following transcription by a professional transcriber, the audio recording was deleted.

Analysis

Photos, captions, and focus group transcripts were uploaded to NVivo 12 (QSR International) by the study team for coding. Analyses of photos and captions were conducted in conjunction with the participants during the focus groups (photo sorting and labeling of risk and protective factors using participants' own words). After completing the focus groups, the study team synthesized the data into related categories (eg, weather, climate, and physical environment were combined into the same category). Furthermore, 2 research assistants coded the transcripts from the 2 focus groups to ensure agreement in an initial coding guide. Each research assistant then coded the remaining focus group transcripts individually. Emerging codes or questions were resolved by discussion with the study team, and the codebook was updated following the discussion. The final codebook is available as Multimedia Appendix 1. We categorized factors as being risk or protective factors; occurring at individual, relationship, or community levels; and specific factors (eg, taste of cigarettes, minority stress, and coping mechanisms). We then organized the individual codes into major themes of risk and protective factors. This study followed the Consolidated Criteria for Reporting Qualitative Health Research. On the basis of recommendations from the literature [28], we estimated that 3-6 focus groups would be sufficient for theme saturation.

Results

Participant Characteristics

Saturation of themes was achieved after conducting 7 focus groups between March 2019 and April 2020 with a total of 47 participants. The mean age of the participants was 26 (SD 8.4) years. Approximately half of the participants (25/47, 53%) were identified as nonbinary or gender nonconforming, 15% (7/47) were identified as male, trans male, or trans men, 17% (8/47) as female, trans female, or trans women, and 15% (7/47) identified with other gender identities. Most of the participants identified as nonheterosexual; half of the participants (22/47, 47%) identified with multiple sexual orientations, 17% (8/47) as bisexual, 13% (6/47) as queer, 11% (5/47) as pansexual, and 9% (4/47) as gay or lesbian. Most (40/47, 85%) of the participants were non-Hispanic, with 55% (26/47) identified as White, 13% (6/47) Black, and 32% (15/47) other racial or ethnic identities. Approximately half of the participants (26/47, 55%) were daily smokers, and half were occasional smokers in the past 30 days. Additional details of participant characteristics are summarized in Table 1. We compared the characteristics (eg, age, sex assigned at birth, gender identity, and sexual orientation) between participants in the northeast city and those recruited nationally, and there was no significant difference.

Table 1. Participant characteristics (n=47).

Characteristics	Values
Age (years), mean (SD)	26.0 (8.4)
Sex assigned at birth, n (%)	
Male	17 (36.2)
Gender identity, n (%)	
Male, trans male, or trans man	7 (14.9)
Female, trans female, or trans woman	8 (17)
Nonbinary or gender nonconforming	25 (53.2)
Other	7 (14.9)
Sexual orientation, n (%)	
Heterosexual	2 (4.3)
Gay or lesbian	4 (8.5)
Bisexual	8 (17)
Pansexual	5 (10.6)
Queer	6 (12.8)
Multiple identities	22 (46.8)
Race, n (%)	
White only	26 (55.3)
Black only	6 (12.8)
Other	15 (31.9)
Ethnicity, n (%)	
Hispanic	7 (14.9)
Smoking status, n (%)	
Occasionally smoke	21 (44.7)
Smoke daily	26 (55.3)
Other tobacco product use in past 30 days, n (%)	
Electronic cigarettes	16 (34)
Cigars	10 (21.3)
Pipe	4 (8.5)
Hookah	8 (17)
Snus	1 (2.1)
Kreteks	6 (12.8)
Education, n (%)	
High school or below	12 (25.5)
Some college or associates degree	25 (53.2)
Bachelor’s degree or higher	10 (21.5)
Employment, n (%)	
Employed	25 (53.2)
Unemployed	7 (14.9)
Homemaker	1 (2.1)
Student	8 (17)
Disabled	4 (8.5)
Other	2 (4.3)

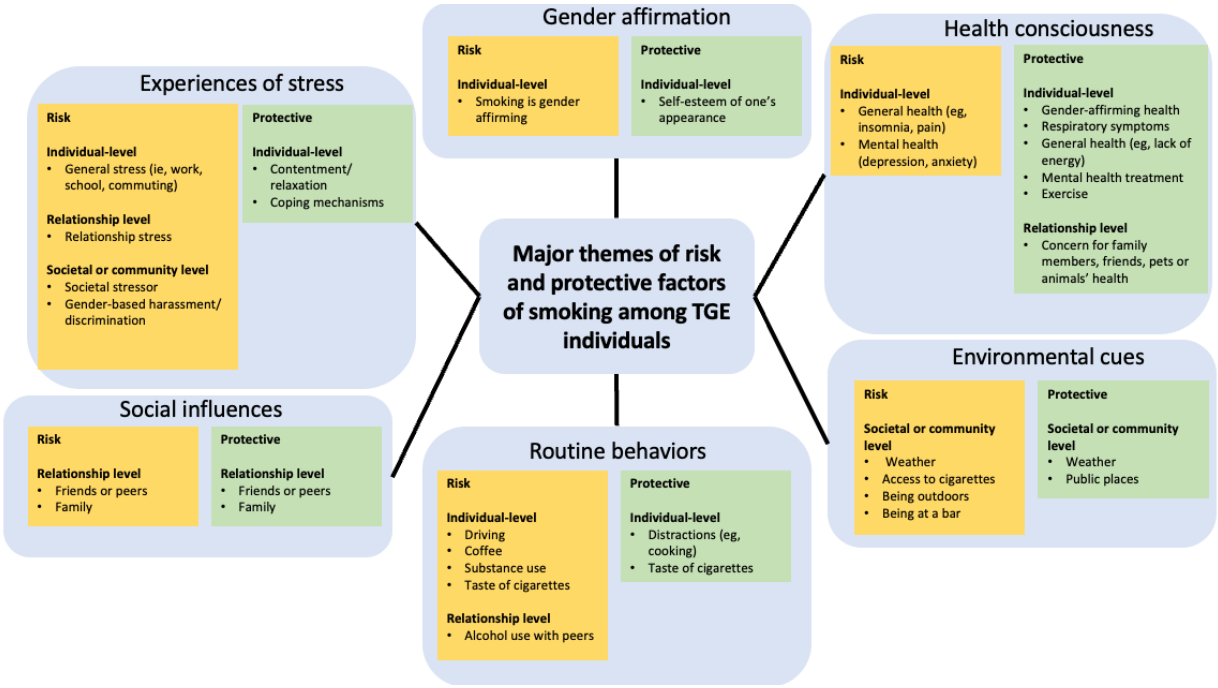
Characteristics	Values
Income (US $), n (%)	
<10,000	17 (36.2)
10,000-19,999	14 (29.8)
20,000-39,999	4 (8.5)
40,000-59,999	6 (12.8)
60,000-79,999	2 (4.3)
80,000-99,999	0 (0)
≥100,000	4 (8.5)
Health insurance, n (%)	
Plan purchased through employer	12 (25.5)
Plan purchased on their own	10 (21.3)
Medicare	4 (8.5)
Medicaid or another state program	12 (25.5)
Tricare	1 (2.1)
Some other source	2 (4.3)
None	6 (12.8)

Risk and Protective Factors

Overview

We identified 6 major themes of smoking risk and protective factors: (1) experiences of stress, (2) gender affirmation, (3) health consciousness, (4) social influences, (5) routine behaviors, and (6) environmental cues. Risk factors were described more frequently than the protective factors. In addition, participants experienced certain factors as risk factors in some circumstances and as protective factors in other circumstances (eg, friends or peers [social influence] were described as risks by some participants, whereas others described having friends or peers who encouraged them to quit smoking). Stress was a cross-cutting factor that occurs at the individual, relationship, and community levels. We describe and illustrate each theme, specific codes within each theme, organized into risk versus protective factors, and indicated which levels the factors were coded in Figure 2. We used they/them/their pronouns in the following section, although individual participants may use other preferred pronouns to present the results. We reviewed the data to compare the risk and protective factors from participants in the northeast city versus national participants, and there was no discernible pattern to distinguish between the 2 sets of participants, with the exception that 2 groups from the national sample had discussed experiences related to the COVID-19 pandemic that were not present in the northeast city participants (because they were recruited before the pandemic).

Figure 2. Smoking risk and protective factors among transgender and gender-expansive individuals.



Experiences of Stress

Participants described a variety of stressors linked to smoking behavior. Some participants highlighted their experiences of minority stress related specifically to their gender identity (eg, stigma associated with their gender identity and concealment) that were associated with their smoking. For instance, one participant recounted a fellow colleague who identified as TGE being harassed by a customer:

> *One of my fellow trans coworkers was harassed, screamed at, and intentionally misgendered as well as received a torrent of slurs from a woman that came in today and that definitely made us all want to smoke.*

Another participant shared a photo of being in an office with their colleagues and having to conceal their identity from them and the following caption:

> *I work in an office with all men and most of them are trans/homophobic but almost none of them know that I'm gay or trans and f* do they test my patience every day and that's what makes me want to smoke.*

Work, school, commuting, transportation, financial situation, housing, and relationship conflicts were factors that triggered increased smoking for some participants. For instance, one participant shared a stock photo of 2 people quarreling to reflect on a conflict with their partner and this accompanying caption:

> *We don't fight much, but I'm a very confrontational person so not getting to finish the argument right away stressed me out to the point of wanting to smoke.*

Participants described societal stressors such as homelessness, the economy, and lack of access to affordable mental health care as risk factors for smoking. For example, one participant posted a drawing depicting homelessness as a source of their stress and smoking with the following caption:

> *This pic represents all the economic issues, personal and larger, that stresses me out. I know there are lots of healthier ways to deal with my financial anxieties...BUT Cigarettes are cheaper than therapy.*

Regarding coping behaviors to reduce feelings of stress, participants described using various strategies including achieving relaxation or contentment, using humor, or exercising. For example, one participant shared about using humor to help avoid smoking:

> *Anything that makes me laugh that's like kind of making fun of anything is like, helpful and not smoking actually, so it feels protective to me because humor helps me get through all the horrors of the world that we're living in.*

Gender Affirmation

Participants described smoking as one way to affirm their gender identity and experience gender euphoria. For instance, one participant shared a photo where they were smoking in their car while driving and a caption:

> *I'm a very good driver I believe, which is a stereotypically "masculine" thing, and smoking is seen by some people as masculine, as well. It's affirming in a weird way.*

Conversely, feelings of self-esteem of one's appearance were associated with not wanting to smoke. One participant shared an occasion of dressing up and not wanting to ruin their appearance because of smoking:

> *I sometimes dress up, put on the whole makeup, wear some nice type of deal. And it kind of ruins that effect when you smell predominantly like smoke and not nice new perfume...*

Health Consciousness

Participants viewed receiving gender affirmation–related health care and health care provider advice to stop smoking as a motivating factor to not smoke. For instance, one participant shared a picture of having completed top surgery and a caption stating that they wanted to quit smoking so that the scars would heal better. Another participant described being receptive to their doctor's advice:

> *If my doctor told me that I had to stop taking estrogen, this happened and this happened and I didn't stop smoking, you know I'd stop smoking.*

General health was a factor that participants experienced as risks for smoking in some situations and as protective in other situations. General physical health issues, such as insomnia and pain, or mental health issues, such as anxiety and mood, were identified as potential risk factors for smoking. Having respiratory symptoms, seeking mental health therapy, and practicing self-care were also described as protective against smoking. One participant shared a photo of a cup of tea and stated in the caption that having a sore throat made them want to drink tea and avoid smoking. Another participant described insomnia and anxiety as triggers of smoking:

> *I feel like sleep and/or lack of sleep and anxiety are pretty close together. I feel like people tend to feel more anxious when they've maybe not slept very well. And cigarettes are one way of like coping with that and sort of addressing that.*

Participants were concerned about the health of family members, pets, or animals around them if they smoked, which motivated some participants to avoid smoking. One participant posted a photo of being with young children and wrote:

> *Being with my kids makes me not want to smoke. Their health and my own makes me always reconsider my choices.*

Another participant shared how they would not smoke near their pet to avoid harming their pet because of secondhand smoke:

> *I remember reading a bunch of articles about how secondhand smoke affects pets. And I really love my cat and I don't want him to get any ill effects from me smoking. So, whenever I do, I try to do it on the porch and I try to lock him out, which he hates...*

Social Influences

Social influences were described as risks in some circumstances and protective factors in others. Being in the company of friends and peers in social situations where smoking and other substance use were present were risk factors for smoking. One participant explained the following in the focus group:

> *...there are things that make me want to smoke, and seeing anyone else with a cigarette or hearing anybody else talk about having a cigarette is one of those things.*

Positive family pressure and friends or peer norms to not smoke were associated with avoiding smoking. One participant posted a photo outdoors with their partner and described their partner's disapproval of their smoking in the caption:

> *My best friend/life partner HATES when I smoke, so thinking of her makes me want to quit.*

Routine Behaviors

Routine behaviors such as driving or drinking coffee were viewed as risk factors for smoking. For instance, one participant shared a photo of sitting in their car and a caption of being triggered to smoke whenever they drive.

The taste of cigarettes was another factor within the theme of habit that increased smoking (risks) for some participants but deterred others from smoking (protective). One participant shared that the taste of finishing one cigarette prompted lighting up another cigarette. Another commented on cigarettes being *nasty* and that made them not want to smoke.

Substance use, including alcohol and cannabis, was also discussed as a risk factor for smoking cigarettes. For example, one participant shared a picture of a can of beer while playing a drinking game that led to their desire to smoke a cigarette:

> *Playing a drinking game tonight. Alcohol always makes me want a cig. Especially since one of my roommates smokes too and I know he'll go out for one at some point.*

Conversely, having distractions was helpful in keeping participants' hands and minds occupied and avoiding smoking. These distractions included cooking a healthy meal, working on a school assignment, occupying their hands by playing a musical instrument, viewing positive images, and watching entertainment shows.

Environmental Cues

Participants described environmental cues that prompted their smoking, including being outdoors, experiencing either good or bad weather, easy access to cigarettes, images related to smoking, or being in a bar. One participant shared a photo of a rainy day outside their home and a caption:

> *Cold, wet, boring, and grey day. Nice time for a cigarette.*

Conversely, some participants described environments or situations that discouraged them from smoking, including places where they were not able to smoke, such as at a transit stop and bad weather, which prevented them from going outdoors to smoke. One participant posted a picture of being at a picnic in a public park and captioned it as follows:

> *I love to have a smoke while walking around. but it was a public park, so I waited until I got home.*

Discussion

Principal Findings

This study described a comprehensive set of risk and protective factors occurring at multiple levels among a sample of TGE smokers based on their real-world experiences and through an analysis of a combination of photos, captions, and focus group discussions. Participants in this study reported more risk factors

for smoking than the protective factors. This was understandable because they were current smokers and did not attempt to quit smoking at the time of the study. This information is unique and essential for understanding the circumstances and reasons for smoking and for avoiding smoking among TGE individuals. Most themes of risk and protective factors described by the participants were consistent with prior literature on the determinants of smoking among LGBTQ+ populations [5,6]. However, to our knowledge, this is one of the first few studies to identify unique factors associated with smoking among TGE individuals, including gender affirmation and gender affirmation–related health care.

These study findings help us understand the important factors that underlie smoking habits among TGE individuals, which can serve as the foundation for future research and smoking cessation intervention design. First, there is a need for future research on the underlying factors linked to smoking or not smoking that either occur more frequently or are unique among TGE populations. Although prior literature reported correlations between receipt of treatment for gender affirmation and smoking behavior or smoking cessation [29,30], this study adds to earlier research by documenting participants explaining in their own words how gender affirmation and gender euphoria were related to their smoking behaviors. This study identifies factors that focus on preventing smoking initiation and promoting cessation among TGE populations that have not been previously described, such as gender affirmation and receiving gender affirmation–related health care. Future work to pretest the relevance and acceptability of health messages that also address the theme of gender affirmation to promote smoking cessation among TGE populations will be needed. Second, the images, phrases, and stories from TGE participants' lived experiences may inform the design of antismoking messages drawn from authentic testimonials that are salient and culturally responsive to TGE individuals. For instance, participants described real-life situations of avoiding smoking by practicing self-care in various ways, which could be adapted as tips for TGE individuals in future antismoking messages. Third, participants described factors that were both risk and protective factors depending on the circumstances and revealed that certain factors occurred across individuals, relationships, and societal or community levels. The findings support the use of a multilevel framework and systems change approach to examine and address smoking holistically among TGE populations. Fourth, some participants affirmed the value of the collaborative research approach and provided feedback and enthusiasm for contributing to the research and future intervention design as community advisors. We will use a community-based participatory research approach by meaningfully engaging with TGE individuals as coequal partners and advisors during the next phase of this research and in future intervention design.

These findings are corroborated by several factors in the conceptual framework (Figure 1). However, some of the factors that we anticipated would be important drivers of smoking were absent in the data obtained from this research. These include the tobacco industry's marketing [7,8] and smoking cessation campaigns, which we hypothesized as potential influences but were not mentioned by participants as risk or protective factors of their smoking behaviors, respectively. A few themes that emerged in the study were not accounted for in the framework. These included health consciousness for others, such as family members and pets, routine behaviors, and environmental cues.

A few themes reported among TGE individuals resemble, at the surface, factors that have been previously described in the general population, including stress, social influences, routines, and environmental cues. Although these factors are not unique to TGE individuals, the *contexts* and *frequency* of experiencing these factors may differ meaningfully between the TGE and non-TGE populations. For instance, the underlying structural discrimination of TGE populations may mean that they experience greater economic stress and financial difficulties [6] than non-TGE populations, which, in turn, widens the disparity in smoking behavior among TGE populations. The issue of the social determinants impacting TGE populations and their linkage with their experience of stress was highlighted by some participants in our study. Future research exploring the similarities or differences in risk and protective factors between TGE and non-TGE populations will help to address questions about the contexts of experiencing these factors.

There were several lessons learned from the use of the digital photovoice approach within closed social media groups. A few participants reported during the member checking discussion that being in the study provided peer support and they appreciated being in a group that understood their experiences as TGE persons. Some participants described how the action of uploading a photo daily related to their smoking behavior helped them to keep track of their smoking use, and they became more aware of the motivations to smoke. Participants reported that the groups provided a safe space that allowed them to connect and communicate with other participants who had similar experiences. For instance, one participant commented that "with these people I can do anything, including try to quit smoking." The study procedures were generally viewed as acceptable and not overly burdensome. We note that this study was not designed as a smoking cessation intervention, and participants did not intend to quit smoking at the outset of the study. However, feedback from the participants suggested that the use of social media peer groups may be a promising component of group-based support and interventions to reduce smoking among TGE populations. Compared with previous research that used different approaches (eg, close-ended cross-sectional surveys [3,5,6,11,30], focus groups among participants in a single geographic location [9], and electronic health record data [12,29]), the photovoice approach in this study has the advantage of obtaining rich and contextual visual data of experiences of smoking risks and protective factors in close to real time (vs recall from the past), detailed exploration of a broad range of factors impacting smoking behaviors using the participants' own words (vs close-ended survey instruments), and the ability to combine multiple sources of data collected from the same participants over time and geographic areas (vs one-time focus groups from one geographic location).

Limitations

This study has a few limitations. Owing to the limited sample size of participants from racial and ethnic minority backgrounds,

we were unable to fully explore whether experiences of multiple axes of discrimination by gender identity, race, and ethnicity intersect in experiences of risk and protective factors among TGE individuals from multiple minority backgrounds. Efforts to increase enrollment of TGE individuals from multiple minority backgrounds in future work will yield data to critically address research questions related to intersectionality among these individuals. Although this study yielded a comprehensive set of risk and protective factors, the study data were not representative of the experiences of the broader TGE population who smoke. However, this work will inform the design of future survey research among a larger national sample of TGE participants to assess the frequency of encountering these smoking risk and protective factors and appropriate strategies to address these factors in reducing smoking among TGE individuals. This study relied on participants who were motivated and comfortable with documenting and sharing their experiences of smoking risk and protective situations in the form of photos to their group. Although we did not receive feedback from participants that this deterred their sharing of certain experiences, we acknowledge that this limitation may mean that certain sensitive topics related to smoking specifically may have been omitted. Future research may include an approach in which participants can submit photos individually instead of within a group.

Conclusions

To summarize, this study identified real-world risk and protective factors among TGE individuals who smoke and collect rich visual representations and participants' own words in labeling risk and protective factors. The long-term goal of this research is to reduce disparities in tobacco use and related health disparities among the TGE populations. The lessons learned from this study approach and rich data will inform future community-engaged research for designing a culturally responsive intervention to address these factors with TGE community members as coequal partners.

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Authors' Contributions

ASLT, SB, PKG, and JP obtained the funding for the study. EH, SB, BCF, FAKC, and PKG contributed to the data collection and analysis. ASLT and PKG wrote the initial draft, and all authors contributed to the revisions and approved the final manuscript. ASLT is responsible for the overall content of the guarantor.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Smoking risk and protective factors.
[DOCX File , 16361 KB - publichealth_v7i10e27417_app1.docx]

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Abbreviations

LGBTQ+: lesbian, gay, bisexual, transgender, and queer
TGE: transgender and gender-expansive

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Original Paper

Self–Training With Quantile Errors for Multivariate Missing Data Imputation for Regression Problems in Electronic Medical Records: Algorithm Development Study

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Abstract

Background: When using machine learning in the real world, the missing value problem is the first problem encountered. Methods to impute this missing value include statistical methods such as mean, expectation-maximization, and multiple imputations by chained equations (MICE) as well as machine learning methods such as multilayer perceptron, k-nearest neighbor, and decision tree.

Objective: The objective of this study was to impute numeric medical data such as physical data and laboratory data. We aimed to effectively impute data using a progressive method called self-training in the medical field where training data are scarce.

Methods: In this paper, we propose a self-training method that gradually increases the available data. Models trained with complete data predict the missing values in incomplete data. Among the incomplete data, the data in which the missing value is validly predicted are incorporated into the complete data. Using the predicted value as the actual value is called pseudolabeling. This process is repeated until the condition is satisfied. The most important part of this process is how to evaluate the accuracy of pseudolabels. They can be evaluated by observing the effect of the pseudolabeled data on the performance of the model.

Results: In self-training using random forest (RF), mean squared error was up to 12% lower than pure RF, and the Pearson correlation coefficient was 0.1% higher. This difference was confirmed statistically. In the Friedman test performed on MICE and RF, self-training showed a *P* value between .003 and .02. A Wilcoxon signed-rank test performed on the mean imputation showed the lowest possible *P* value, 3.05e-5, in all situations.

Conclusions: Self-training showed significant results in comparing the predicted values and actual values, but it needs to be verified in an actual machine learning system. And self-training has the potential to improve performance according to the pseudolabel evaluation method, which will be the main subject of our future research.

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KEYWORDS

self-training; artificial intelligence; electronic medical records; imputation

Introduction

Background

When trying to use data in machine learning or statistical analysis, the missing value problem is one of the most common challenges. A missing value is caused by situations such as a malfunction of the inspection machine, incorrect inspection, or human error. It can also happen when converting data for analysis purposes. Missing values reduce the number of data points available and adversely affect the analysis results. In the medical field, inaccurate analysis is fatal as it can lead to a misdiagnosis. The best way to deal with this problem is to fill in missing values with the actual values. However, filling up medical data with the real values may require expensive retesting or assistance from a professional medical practitioner, which is extremely cumbersome and costly. Also, it may be impossible to fill in missing values due to patient privacy issues. For this reason, many studies on the imputation of missing values have been conducted.

The most naive way to fill in the missing value is to fill it with an appropriate value such as zero or the average. Mean imputation is one of the most frequently used methods because it is simple. In other cases, the median and mode can be used as substitutes instead of using the mean. These methods have the disadvantages of increasing errors and introducing bias in datasets with a high number of missing data points. In addition to these simple methods, attempts have been made to resolve the missing value problem statistically, represented by expectation-maximization (EM) [1] and multiple imputations by chained equations (MICE) [2]. EM finds the local minimum and does not guarantee that the value found is the global maximum. Additionally, since it is a single imputation replacing only one value, the accuracy may be degraded when the missing rate of the data is large. The multiple imputation (MI) [3] method compensates for this shortcoming of single imputation. In MI, several imputed values are statistically analyzed and used. MI works under missing at random (MAR) [4] conditions. MICE is one of the MI algorithms. MICE performs statistical modeling by creating several imputation sets of missing values through simulation and derives values by averaging the generated imputation sets. Like any other MI algorithm, MICE operates under the assumption of MAR, and execution under the assumption that it is not MAR can lead to biased results.

As research on machine learning becomes more active, machine learning algorithms such as multilayer perceptron (MLP) [5,6], k-nearest neighbor (KNN) [7,8], and decision tree (DT) [9-11] have been used for imputation as alternatives to statistical methods. Recently, generative models such as generative adversarial networks [12,13] have been applied to missing value problems as they have shown significant performance in several fields. Jerez et al [14] compared statistical programs and machine learning methods to replace missing values in breast cancer datasets. In their study, mean, hot deck [15,16], SAS [17], Amelia [18], and MICE were used as the statistical methods, and MLP, KNN, and self-organizing map [19] were used as the machine learning methods.

Objective

The objective of this study was to impute numeric data such as physical data and laboratory data. Laboratory data and physiological data are valuable data that directly represent the patient's health condition, and these continuous values are usually harder to predict than discrete ones, making them worth studying. On the other hand, discrete data, such as the diagnosis reached by the physician, may not be appropriate to impute as an external factor. Since the patient does not undergo all of the tests, just the necessary tests, there is always a missing value in the electronic medical record (EMR) data. Unlike the universal tests performed on many patients, some tests are performed on only some patients. Features corresponding to these special tests are suitable for imputation because there are many missing parts and they have a high potential advantage.

EMR data have characteristics that distinguish it from other data, and our objectives are subdivided according to these characteristics [20-23]. The most distinctive feature of EMR is that there is a difference in the missing rate between features, and this difference in missing rates is an important consideration for imputation. Therefore, our first detailed objective was to impute rare features using general features.

Another characteristic of EMR is that there are far more incomplete (or unlabeled) data than complete (or labeled) data. In fact, although most of the data have this property, medical data are much more lethal because the process of obtaining labels is expensive and cumbersome. Existing methods can be vulnerable in these circumstances, and the second aim of our progressive method was to ameliorate these vulnerabilities.

To overcome this vulnerability, we adopted self-training, a progressive method, in which self-training performs 2 processes repeatedly: self-learning and pseudolabeling. Self-training repeats the 2 processes using a complete dataset called a teacher and an incomplete dataset called a student. First, the teacher model learns the teacher dataset, and then the teacher model predicts the missing values of the student data. This step is called pseudolabeling. Second, the valid pseudolabeled student data are converted to teacher data. In the next iteration, the same process is repeated with this new teacher, which is called self-learning.

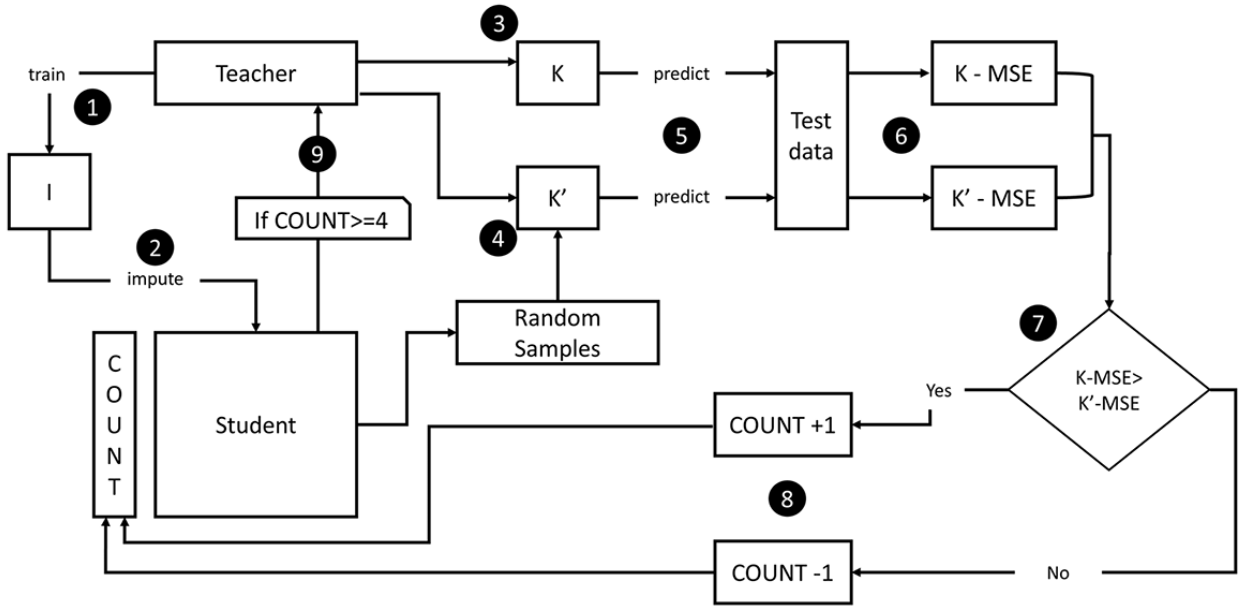
The most important part of the self-training process is how to evaluate the validity of the pseudolabel. However, the actual value is unknown, which is why we cannot directly evaluate its validity; thus, a new evaluation method is necessary. In the classification problem, probability is used as an indicator, and a simple example can be found through binary classification. Suppose that a model trained with labeled data predicts that the test set has a 96% probability of being negative and a 4% probability of being positive. This result can be interpreted as meaning the model is confident that the predicted class is negative. Conversely, if the model predicted the test set has a 55% probability of being negative and a 45% probability of being positive, the interpretation is unclear. In the former case, it can be said that the test set belongs to the negative class, but in the latter case, it is difficult to determine whether it is positive or negative. In the case of self-training, the test set in the first case is labeled as a negative class and transferred to the teacher.

Unfortunately, there is no such intuitive judgment factor in the regression problem. Therefore, most studies related to self-training are conducted mainly using classifications like image net challenges [24]. Our final objective was to apply this self-training to the regression problem.

Methods

In this section, we present an approach to semisupervised learning for continuous EMR imputation. Our approach is based on a self-training paradigm, and we named it SQMI-R. Figure 1 shows a full overview of the proposed method. The numbers in Figure 1 represent the sequence of the process, and each sequence is explained in the following subsections. The Self-Training Regression Imputation section describes number 1 to number 6 of the process, and the Sampling Strategy section considers number 4 in more detail. The Evaluation Metrics section analyzes step number 6 in more detail, and the Multiple Imputation section describes steps 6 through 9.

Figure 1. Architecture of the self-training process. MSE: mean squared error.



Self-Training Regression Imputation

SQMI-R uses 3 models to impute continuous values: I, K, and K'. First, we pseudolabel the missing values of the student dataset with the imputation model I trained with the teacher dataset. Then, 2 test models K and K', called the tester, train 2 nearly similar datasets. K learns only from the teacher, and K' learns data from both the teacher and samples of the pseudolabeled student. In general, in the case of adding data to an existing machine learning system, it can be said that if the added data are valid, the performance of the model improves; otherwise, the performance decreases. We used the properties shown in Figure 2 to validate the imputed samples.

This process is based on the assumption that valid data improve the performance of the model. Based on these assumptions, the imputed samples are added to the existing data and verified based on performance improvements. The added amount of data is too small compared to the existing data and has a minimal performance impact. Both test models should be able to detect even these small effects, and we used KNN as a tester to satisfy this requirement. KNN is useful for detecting small differences in the data as it always produces the same results for the same data. The special behavior of the KNN algorithm makes it possible to always derive the same value. KNN estimates labels from the average of the surrounding k data without a learning process, which always produces the same results for the same data. Algorithms such as MLP and RF require a learning process, and randomness intervenes, resulting in different results for the same data. In this case, it is difficult to define whether the difference in results is due to differences in the data or randomness of the learning. Although KNN is not performing as well as these machine learning models, the purpose of the test model is to compare and verify the data, not accurately predict it. Moreover, KNN has few parameters to process and is intuitive to use. The loss function also has to be chosen carefully for each purpose. Since there was no specific purpose in this study, mean squared errors (MSEs) that could be used for all continuous value problems were adopted. If the purpose is to learn a classifier, the process can be performed by using cross-entropy as a loss function or by maximizing metrics such as area under the curve or F1 scores.

Figure 2. Validation of the imputed samples.

Require: Complete data $\{(x_1, y_1), \cdots, (x_t, y_t), \cdots, (x_n, y_n)\}$ and uncomplete data $\{(\dot{x}_1, \dot{y}_1), \cdots, (\dot{x}_m, \dot{y}_m)\}$. Data $\{(x_1, y_1), \cdots, (x_t, y_t)\}$ is the training set and $\{(x_{t+1}, y_{t+1}), \cdots, (x_n, y_n)\}$ is the validation set, and these two datasets are shuffled at every iteration.

1. Learn impute model *I* with training set of labeled data. The impute model *I* learns in a way that minimizes loss function $\mathcal{L}$.

$$\textbf{minimize} \sum_{i=1}^{t} \mathcal{L}(y_i, f(x_i, I))$$

2. Use impute model to impute unlabeled data. $\dot{y}_i$ is the target values with missing values and $\ddot{y}_i$ is the state in which the missing values of $\dot{y}_i$ are replaced. $\dot{y}_i'$ is the predicted value corresponding to $\dot{y}_i$, replacing missing values in $\dot{y}_i$ with values in $\dot{y}_i'$ to create $\ddot{y}_i$.

$$\dot{y}_i' = f(\dot{x}_i, I)$$

$$\ddot{y}_i = \dot{y}_i \, OR \, \dot{y}_i'$$

$$\forall i = 1, \cdots, m$$

3. Data $\{(\hat{x}_1, \hat{y}_1), \cdots, (\hat{x}_o, \hat{y}_o)\}$ is randomly sampled from pseudo labeled data $\{(\dot{x}_1, \ddot{y}_1), \cdots, (\dot{x}_m, \ddot{y}_m)\}$, and two testers are learned using sampled data and training set.

$$\{(\hat{x}_1, \hat{y}_1), \cdots, (\hat{x}_o, \hat{y}_o)\} \in \{(\dot{x}_1, \ddot{y}_1), \cdots, (\dot{x}_m, \ddot{y}_m)\} \qquad (o < m)$$

$$\textbf{minimize} \sum_{i=1}^{t} \mathcal{L}(y_i, f(x_i, K))$$

$$\textbf{minimize} \left(\sum_{i=1}^{t} \mathcal{L}(y_i, f(x_i, K')) + \sum_{i=1}^{o} \mathcal{L}(\hat{y}_i, f(\hat{x}_i, K'))\right)$$

4. The imputed values of the sample are indirectly verified by comparing the performance of K and K'. The validly imputed values are integrated into the train-set on the next iteration. **Step 3** and **step 4** are performed m/o times during one iteration.

$$IF \sum_{i=t+1}^{n} \mathcal{L}(y_i, f(x_i, K)) > \sum_{i=t+1}^{n} \mathcal{L}(y_i, f(x_i, K')) :$$

$$\{(\hat{x}_1, \hat{y}_1), \cdots, (\hat{x}_o, \hat{y}_o)\} \; is \; valid$$

5. Back to **step 1**, learn impute model *I* with bigger training set.

Sampling Strategy

The most reliable way to examine pseudolabeled data is to examine them one by one. Nevertheless, the reason for testing multiple samples instead of testing them one by one is related to the characteristics of the KNN. KNN is calculated based on the k-nearest data. Consider the case of testing only one sample x. There may be cases where this x is far from all of the test data. In this case, adding x to K' does not affect the test result. When these cases increase, useless calculations increase, and self-training does not work smoothly. If enough samples are used at once, the validity of the pseudolabel will affect the performance of the model, and accordingly, the validity of the sample can be verified. In this experiment, we adopted 50 samples. After several tests, we selected the 50 that seemed to be the most appropriate in terms of the trade-off between the performance and time. The number of samples is an important parameter. In general, as the number of samples increases, the

speed will increase, whereas the performance decreases. Contrarily, if the number of samples decreases while the performance improves, the time efficiency gets worse. Thus, the number of samples should be chosen appropriately in the trade-off of the relationship between the time and the performance.

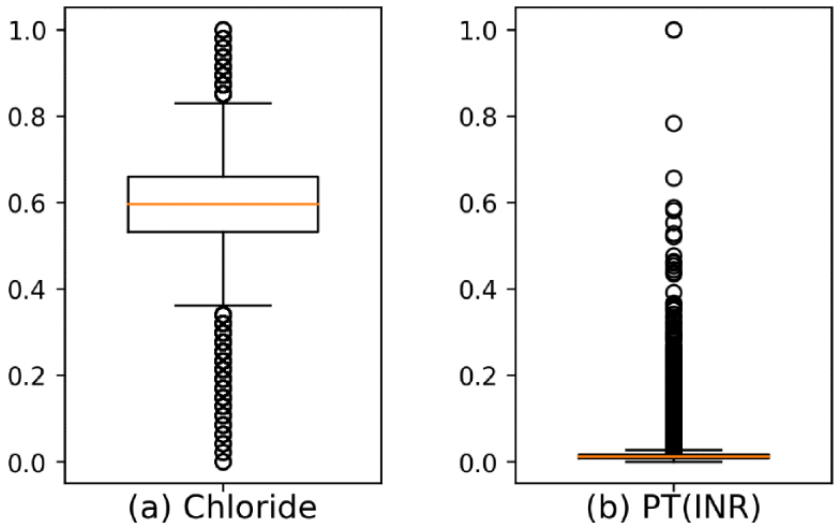
If the number of samples obtained from a single sampling has been determined, how many samplings should be performed during one iteration should be determined. In our strategy, if the number of students is S and the number of samples drawn at one time is N, sampling is done S/N times during one iteration. Such a sampling strategy can, on average, examine all data once during one iteration.

Evaluation Metrics

It is necessary to think about the evaluation metrics when testing the sample. We imputed multiple features, and the effectiveness of the pseudolabel was evaluated by the MSE of the actual and predicted values. This MSE is affected by the distribution of the features. A feature with low density (ie, a wide distribution of data) has a structurally higher MSE in prediction than a feature with a high density and a narrow distribution. Models K and K' test samples using the average MSE of all features. If the density of the data determines the MSE, self-training will work differently than we expected. In other words, self-training will only work around features with widely distributed data to reduce the overall error. This is because reducing errors from data with a low density is more advantageous in reducing the total errors than reducing the errors from data with a high density. Due to the high data density, neglected features may be less improved or worsened during the self-training process.

We can confirm this with practical medical records. The collection of data and data preparation received Asan Medical Center and Ulsan University Hospital institutional review board approval with waived informed consent (AMCCV 2016-26 ver2.1) [25]. Figure 3 shows a boxplot of 2 features — chloride and PT(INR). Note that all features are min-max scaled in Figure 3. The data from PT(INR) are distributed over a small area. Consider the case of predicting a value in the box of PT(INR). Since the box itself is small, the prediction error is small, and the result looks accurate. On the contrary, chloride is distributed over a large area, and even if the predicted value is in the box, the error will be relatively large. In this case, chloride has a greater impact on the overall error. As a result, the self-training process works toward improving chloride even further, even if it worsens PT(INR).

Figure 3. (A) Chloride has a low density, and (B) PT(INR) has a high density. PT(INR): prothrombin time(international normalized ratio).



Medical data have large differences in the data distributions between features, and self-training is vulnerable to such characteristics. The evaluation of the effectiveness of the pseudolabel is based on the average MSE of the features. However, evenly reducing the MSE of all features is a way to make a better dataset. Therefore, it is necessary to correct the effect of the distribution. In this study, we presented a correction method using quantiles. The distribution of the data is estimated using the interquartile range (IQR). IQR is the difference between the third and first quartiles. If the data density is high, the difference between the third and first quartiles will be small. If the density is small, the difference between the third and first quartiles will be large. Let the third quartile of i-th feature be q_i^3 and the first quartile be q_i^3, then the IQR of the i-th feature can be defined as follows:

IQRi is divided by MSE, which is inversely proportional to the distribution of the data. We named it Q-MSE, and the definition is as follows:

In the case of using Q-MSE, if the Q-MSE of K' is smaller than the Q-MSE of K, it is assumed that the imputed value is valid.

Multiple Imputation

The method of evaluating multiple samples at once has a vulnerability. Assume that data X1 are effectively pseudolabeled. However, if X1 was sampled with invalid data, it will degrade the performance of K' in the test. If this happens, even though X1 should be a teacher, it will remain in the student

due to bad luck. This time, we can think of a case in which invalid data X2 are sampled with valid data. X2 and valid samples will improve the performance of the model. In this case, X2 is not valid, but it becomes a teacher. Since X2 is invalid data, if it becomes a teacher, the performance of the algorithm degrades. We present ways to prevent this irrationality.

In the proposed method, students get a new imputed value at each iteration, and if the test passes, this imputed value is stored. In the next iteration, it gets a new value and is tested again. If the test passes again, the stored value is updated by averaging the current value and the stored value. To manage this stored value, we count the number of passes. If the test passes, we add 1 to the count of the data. If it fails the test, the count decreases by 1. Data that count as greater than the threshold become teachers by replacing the missing value with this stored value. Data with a zero count return the stored value to zero. Groups containing X1 already have valid data, which is likely to improve the performance of the model. Thus, X1 has a relatively high probability of passing the test while it belongs to several samples, and it will go to the teacher by filling the count with a threshold with a relatively high probability. Invalid data have a high probability of dropping from the test, deducting 1 point from the counter. In this way, it is possible to avoid making choices by chance. In addition, the values verified from various test data are integrated to make the performance stable. According to this strategy, step 4 from the Self-Training Regression Imputation section is divided into the detailed steps seen in Figure 4.

Figure 4. Detailed steps within step 4.

Require: 2D-array V and 1D-array C and threshold. In V, the validated imputed values are stored by averaging, and in C, the number of times the validation is passed is recorded. Arrays V and C are initialized to zero, and V[$\hat{x}$] represents the average value of verified $\hat{y}$ corresponding to $\hat{x}$.

4.1 Validate and update the values.

IF $\sum_{i=t+1}^{n} \mathcal{L}(y_i, f(x_i, K)) > \sum_{i=t+1}^{n} \mathcal{L}(y_i, f(x_i, K'))$:

$V[\hat{x}] \leftarrow (V[\hat{x}]C[\hat{x}]+\hat{y}) / (C[\hat{x}]+1)$

$C[\hat{x}] \leftarrow C[\hat{x}] + 1$

ELSE:

$C[\hat{x}] \leftarrow C[\hat{x}] - 1$

4.2 If C[x] is bigger than threshold, data (x, V[x]) are converted to complete data. (Subsequent iterations do not use (x, V[x]) for validation sets.)

Setting the threshold of counts is a trade-off between performance and the time required. If you set the threshold higher, you will have to perform more tests and filter more verified data. However, this requires too many iterations to make it into the labeled data. In some cases, the performance can become worse by reducing the number of incorporated data. On the other hand, lowering the threshold shortens the time and increases the amount of data transferred to the labeled set, but it does not guarantee the quality of the data. The lower the threshold, the greater the influence of luck. As a result of conducting several tests, we found that approximately 4 counts could obtain appropriately verified pseudolabeled data with optimized periods of time. Thus, in this experiment, we use 4 for the threshold of the counts.

Algorithm 1 in Figure 5 shows the pseudocode of the SQMI-R. Model(data) means that the model is trained with data. For example, Tester(data) means that a Tester model was trained using data. I.predict(data) means impute by predicting the missing value of the data with the imputing model I. Data[index] represents values corresponding to the index of the data.

Figure 5. Pseudocode of the SQMI-R.

Algorithm 1

Requirements T : teacher, S : student, iters : number of iterations,
Imp : imputation model, Ns : number of sample, Nt : number of test-set,
Inp : input features, Oup : output features

SQMI-R$(T, S, Imp, Iters, Ns, Nt, Inp, oup)$:

$C \leftarrow zeros(length(S)),\ V \leftarrow zeros(shape(S))$

for $iter \leftarrow 1\ to\ Iters$:

$N\_sampling \leftarrow length(S)/Ns,\ I \leftarrow Imp(T)$

$Test\_T \leftarrow sample(T, Nt),\ Train\_T \leftarrow T - Test\_T$

$Imputed\_S \leftarrow I.predict(S)$

for $j \leftarrow 1\ to\ N\_sampling$:

$samples \leftarrow sample(Imputed\_S, Ns)$

$idx \leftarrow S.where(samples)$

$K \leftarrow Tester(Train\_T),\ K' \leftarrow Tester(Train\_T + samples)$

$MSE_K \leftarrow MSE(Test\_T\ [Oup],\ K.predict(Test\_T\ [Inp]))$

$MSE_{K'} \leftarrow MSE(Test\_T\ [Oup],\ K'.predict(Test\_T\ [Inp]))$

if $MSE_{K'} < MSE_K$:

$C[idx] \leftarrow C[idx] + 1$

$V[idx] \leftarrow (C[idx]V[idx] + samples)/(C[idx] + 1)$

else :

$C[idx] \leftarrow C[idx] - 1$

END if

END for

$zero\_count\_index = C.where(C <= 0)$

$full\_count\_index = C.where(C >= 4)$

$V[zero\_count\_index] = 0$

$T = concat(T, V[full\_count\_index])$

$S.drop(full\_count\_index)$

$C.drop(full\_count\_index)$

$V.drop(full\_count\_index)$

END for

$S = I.predict(S)$

END Algorithm1

Results

Dataset

We validated our method with data from CardioNet [25], a real-world EMR. The demographic information from CardioNet appears in Table 1, and we selected 10,000 of the data points as the teacher data and 50,000 of the data points as student data. A teacher dataset with 10,000 data points represents complete data without missing values, and the 50,000 students contain missing values. The actual values in the student dataset are unknown and cannot be evaluated for imputation. For evaluation, we used some of the known values from the students as fake missing. A total of 93 features such as physical information, laboratory tests, and the results of echocardiography were used, and 77 of these were used as inputs to impute the missing values of the remaining 16 targets: chloride, alkaline phosphatase, protein, total CO_2, glucose, uric acid, blood urea

nitrogen, electronic absolute neutrophil count, phosphorus, prothrombin time (PT-INR, PT-%, PT-sec), systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate. The missing rate of the features varied from 0.06% to 85.9%. Table 2 shows the missing rate for each feature. The patterns of missing data include MAR, missing completely at random, and missing not at random [4]. The decision to perform a medical test is usually determined by other observed information. Therefore, the missing laboratory data are related to the observed values, and the pattern is MAR.

Table 1. Demographic information from the CardioNet electronic medical record.

Variables	Asan Medical Center (N=572,811)
Gender, n	
Female	257,160
Male	315,651
Age (years), mean (SD)	56.32 (14.72)
Systolic blood pressure[a] (mm Hg), mean (SD)	123.06 (12.61)
Diastolic blood pressure[a] (mm Hg), mean (SD)	74.29 (7.94)
BMI[b] (kg/m^2), mean (SD)	24.11 (3.50)
CV/CS[c,d] encounter, n	
0	250,160
1	68,037
2	78,406
≥3	174,560
Echocardiography, n (%)	428,004 (74.71)
Pulmonary function, n (%)	265,817 (46.40)
Thallium SPECT[e], n (%)	156,615 (27.34)
Treadmill, n (%)	68,203 (11.90)
CT[f], n (%)	79,064 (13.80)
Holter monitoring, n (%)	46,636 (8.14)
6-minute walk test, n (%)	8871 (1.54)
Cardiac rehabilitation, n (%)	1990 (0.34)
Pediatric echocardiography, n (%)	1720 (0.30)

[a]N=461,693.

[b]N=457,621.

[c]CV/CS: Cardiology or Cardiothoracic Surgery Department.

[d]571,163 total visits.

[e]SPECT: single photon emission computed tomography.

[f]CT: computed tomography.

Table 2. Missing rate and ratio of errors (obtained by dividing the result of 20 iterations by that of 0 iterations).

Feature	Missing rate, %	Normal-MSE[a]	Q-MSE
Chloride	17.60	0.866	0.867
AP[b]	1.00	0.917	0.910
Protein	0.06	0.839	0.837
Total CO_2	28.75	0.906	0.902
Glucose	71.38	0.844	0.844
Uric acid	53.11	0.872	0.865
BUN[c]	59.60	0.713	0.709
E_ANC[d]	74.80	1.007	0.993
PT(INR)[e]	0.10	0.962	0.968
PT (%)	17.71	0.988	0.982
Phosphorus	0.19	0.886	0.884
PT (sec)	27.98	0.950	0.954
SBP[f]	71.38	0.983	0.975
DBP[g]	77.68	0.977	0.977
PR[h]	59.00	0.994	0.993
RR[i]	85.86	1.005	0.993

[a]MSE: mean squared error.

[b]AP: alkaline phosphatase.

[c]BUN: blood urea nitrogen.

[d]E_ANC: electronic absolute neutrophil count.

[e]PT(INR): prothrombin time(international normalized ratio).

[f]SBP: systolic blood pressure.

[g]DBP: diastolic blood pressure.

[h]PR: pulse rate.

[i]RR: respiratory rate.

Experiments on the Effects of the Metric

We experimented on the 2 aforementioned metrics (normal-MSE, Q-MSE) to confirm the change of self-training according to the metric. All experiments were conducted based on a situation where the missing rate was 20% and the number of iterations was 20. Table 2 is the result of dividing the result of 20 iterations by that of 0 iterations when each metric is applied. This ratio indicates how the error decreases when the process ends as compared to the starting point. The smaller ratio values indicate better performance, with a value of 1 indicating that the process has no effect and values greater than 1 indicating that the process is adversely affected. This ratio can be influenced by the degree of ease of prediction, data distribution, and missing rate. We assumed that performance could be affected by IQR, and Q-MSE was suggested to compensate. The results are shown in Table 2. Q-MSE increased the error rate in 3 features compared with normal-MSE but decreased it in 11 features. In this experiment, we can confirm that the assumptions we have set are correct and that the method we have presented is also effective. Furthermore, the results of this experiment suggest that properly setting the evaluation metric of the pseudolabel can improve the performance of the imputation.

Comparison With Existing Methods

The second experiment compared the performance of the existing imputation method and SQMI-R by the missing rate. The self-training iteration was fixed to 20 times, and the metric was normal-MSE. After setting various missing rate situations, we evaluated the performance of the methods in each situation. Then, some of the actual values of the student data missing in the experiments were filled in. Finally, the results of the imputation were evaluated by MSE and the Pearson correlation coefficient.

All experiments were conducted in *Python-3.6.9* environments, and each algorithm was implemented through the *Python* library. We utilized *sklearn-0.23.2* to implement the machine learning models, RF and KNN, and MLP was implemented in *keras-2.24*. The statistical methods, EM and MICE, were implemented through *impyute-0.0.8*. All statistical analyses were performed via *scipy-1.5.2*.

Mean Squared Error

Figure 6 presents the MSE performance of the methods according to the missing rate. As expected, the error increased as the missing rates increased. In the graph, the SQMI-R is the most robust for the increase in the missing rate. Accordingly, the higher the missing rate, the more efficient the SQMI-R. Figure 7 presents the number of features best predicted by the method. Looking at Figure 7, SQMI-R performed better than other methods for most features in all stages. It showed the lowest error in at least 9 and at most 11 features depending on the missing rate. After SQMI-R, MICE had most of the features, followed by RF and MLP.

Figure 6. Total errors from the methods in each missing rate stage. EM: expectation-maximization; KNN: k-nearest neighbor; MICE: multiple imputations by chained equations; MLP: multilayer perceptron; MSE: mean squared; RF: random forest.

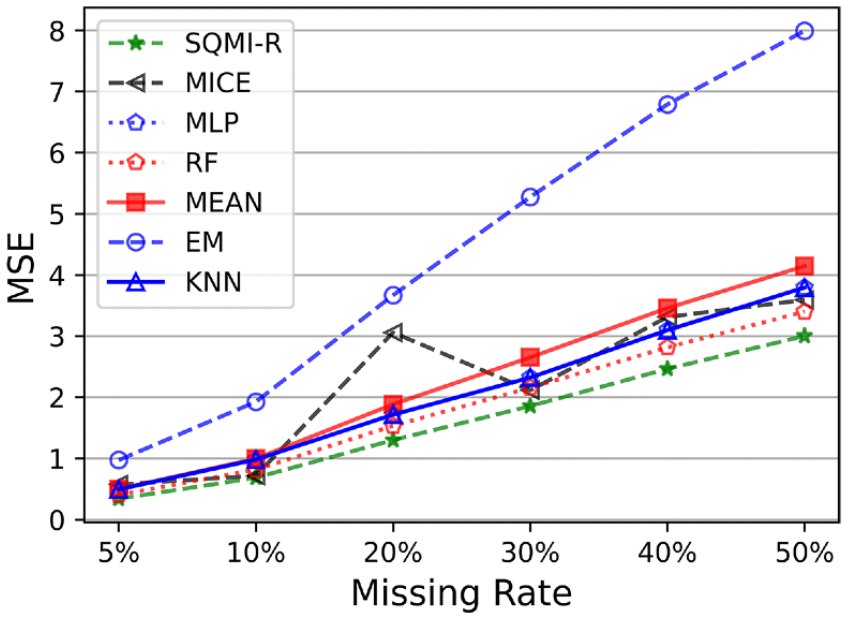
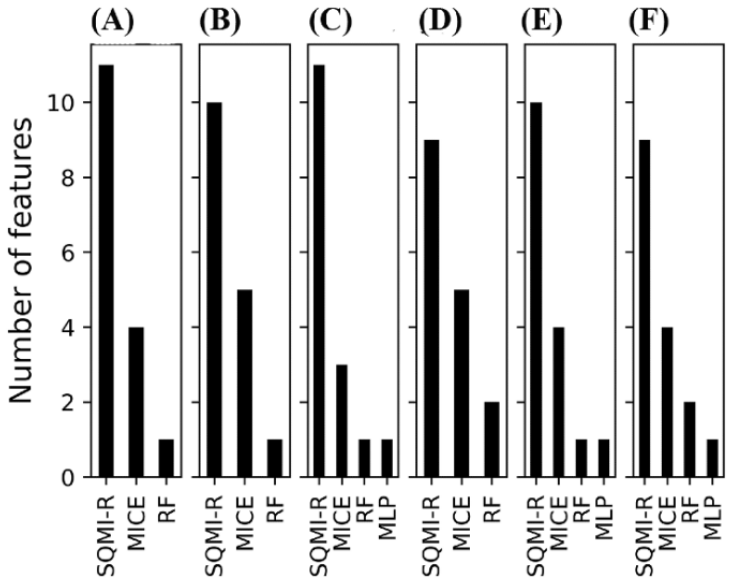


Figure 7. The number of features that the method predicted best in each missing rate stage: (A) 5%, (B) 10%, (C) 20%, (D) 30%, (E) 40%, (F) 50%. MICE: multiple imputations by chained equations; MLP: multilayer perceptron; RF: random forest.



To more accurately evaluate the differences between the methods, we performed the Friedman test [26] on the most powerful 3 algorithms: RF, MICE, SQMI-R. The Friedman test is a nonparametric test that verifies the significance of differences between N algorithms. The Friedman test is used to detect differences between algorithms in multiple test attempts. Columns (repeated tests attempts) rank rows (algorithms) and analyze these ranks to detect differences between algorithms. If there is a superior algorithm, it will rank high in most columns. The Friedman test requires results for iterative experiments such as cross-validation. However, in this study, both student data and teacher data are defined, making this iterative experiment difficult. Therefore, instead of using the results from iterative experiments, the rankings of multiple features were compared. There is no difference between the algorithms under the null hypothesis. Table 3 presents the results

of the Friedman test at each step. The *P* values from the Friedman tests were <.05 in all missing rate situations, and the null hypothesis was rejected, which means that there is a significant effect on the method in all steps. This result demonstrates that SQMI-R is statistically superior to other powerful algorithms, referring to other results that will be presented later.

Table 3. Friedman test *P* values for self-training, multiple imputations by chained equations (MICE), and random forest.

Missing rate	*P* value
5%	.003
10%	.005
20%	.003
30%	.02
40%	.007
50%	.02

Additionally, we conducted Wilcoxon signed-rank tests [27] to verify that there are significant differences between mean imputation and the 6 methods. The Wilcoxon signed rank test is a nonparametric test method that determines whether the medians of paired data are the same. The test calculates the difference between paired data and then the signed rank of the difference to obtain the test statistic. In the null hypothesis, the difference between 2 paired data forms a symmetrical distribution around zero. In this study, we used the imputation results for multivariate target features to determine significant differences between each method and mean imputation. Table 4 presents the results of the Wilcoxon signed-rank test at each step. For MLP, the *P* value was larger than .05 at most stages, which means that this method is not significantly different from the mean imputation. Whether KNN and MICE reject the null hypothesis depends on the missing rate, which means that in some cases, there may be no difference from the mean imputation. SQMI-R, RF, and EM showed the smallest possible *P* values at all stages. In Figure 6, EM had a higher error compared to mean imputation, and a small *P* value means that EM is inferior to mean imputation for all features. The single imputation EM is unstable when the missing rate is large, which is consistent with the experimental results. Only RF and SQMI-R are methods superior to mean imputation for all features in all situations. The comparison between these 2 models is meaningful as RF is used as the impute model in SQMI-R. At 50%, as seen in Figure 6, SQMI-R improved by about 12% when compared to RF. These results proved that self-training could improve the performance of the imputation model while preserving the statistical significance.

Table 4. *P* values from the Wilcoxon signed-rank test for mean imputation.

Missing rate	MLP[a]	RF[b]	MICE[c]	EM[d]	KNN[e]	SQMI-R
5%	.86	<.001	.005	<.001	.463	<.001
10%	.12	<.001	<.001	<.001	.668	<.001
20%	.07	<.001	.375	<.001	.013	<.001
30%	.001	<.001	<.001	<.001	<.001	<.001
40%	.06	<.001	.252	<.001	<.001	<.001
50%	.06	<.001	<.001	<.001	<.001	<.001

[a]MLP: multilayer perceptron.

[b]RF: random forest.

[c]MICE: multiple imputations by chained equations.

[d]EM: expectation-maximization.

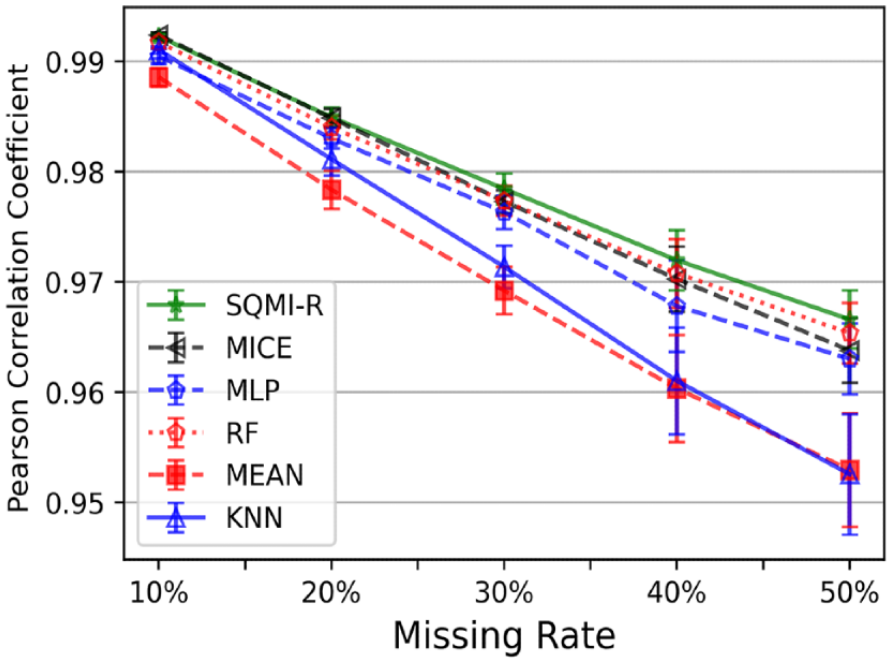
[e]KNN: k-nearest neighbor.

Pearson Correlation Coefficient

We calculated the Pearson correlation coefficient to evaluate the imputation data in another way. We experimented with a situation where the missing rates were 10%, 20%, 30%, 40%, and 50%, and 32,302 data points were used. We used 7000 of these as training data, and randomly created missing data for the rest of the data and used them as test data. Subsequently, the Pearson correlation coefficient between the 25,302 imputed test data points and the original data was calculated to represent the correlation between 2 vectors. The Pearson correlation coefficient has a value between +1 and –1, where +1 means a strong positive linear correlation, 0 means no linear correlation, and –1 means a strong negative linear correlation. In this study, the Pearson correlation coefficient was used as an indicator to measure the degree of preservation of the data structures in the imputed data. It is more important to preserve the data structure when replacing the missing values than simply reducing the integrated error.

As shown in Figure 8, the mean and variance of the Pearson correlation coefficients was almost similar to the results of Figure 6. As the missing rate increases, SQMI-R keeps the Pearson correlation coefficient higher than in the other methods. At each point on the graph, the vertical line represents the variance, while the SQMI-R has the lowest variance. This result implies that SQMI-R is most strongly correlated with the original data, which has great significance in terms of data utilization.

Figure 8. Pearson correlation efficient in various missing rate situations. KNN: k-nearest neighbor; MICE: multiple imputations by chained equations; MLP: multilayer perceptron; RF: random forest.



Discussion

In this study, we proposed multiple self-training regression imputation methods. The proposed algorithm used 3 models. We named the complete data set the teacher and the data set with missing values the student. The missing value of students was predicted with imputation model I, and these predicted values were then evaluated with test models K and K'. If this prediction is determined to be valid, the student becomes a teacher. The data remaining as a student until the end were predicted and imputed by the final imputation model. The first experimental result showed that the metric we presented, Q-MSE, works better than normal-MSE. In the second experimental result, it was confirmed that the self-training imputation was statistically significantly superior to the existing statistics and machine learning methods.

Self-training is one independent process, but it is also a process that further enhances existing methods. The relationship between RF and SQMI-R demonstrates this well. Our method can be easily combined with other algorithms as well as RF and is expected to improve these algorithms. The most important thing in this process is the metric. The purpose or aspect of self-training can vary greatly depending on the metric, so the appropriate metric should be used. In this work, we proposed a metric assuming that all target features are continuous, but for general use, we need a metric that can be used when continuous and discrete values are mixed. And our algorithm requires repeated measurements, which are time-consuming. This limitation is one of the challenges that we need to optimize. Furthermore, experiments on whether the proposed imputation is well applied to practical statistical analysis or machine learning problems are also needed. Applying our method to real machine learning problems with complex data will be the main subject of our future research.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

DT: decision tree
EM: expectation-maximization
EMR: electronic medical record
IQR: interquartile range
KNN: k-nearest neighbor
MAR: missing at random
MI: multiple imputation
MICE: multiple imputations by chained equations
MLP: multilayer perceptron
MSE: mean squared error

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Original Paper

Adoption of Preventive Measures During the Very Early Phase of the COVID-19 Outbreak in China: National Cross-sectional Survey Study

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Abstract

Background: The outbreak of COVID-19 in China occurred around the Chinese New Year (January 25, 2020), and infections decreased continuously afterward. General adoption of preventive measures during the Chinese New Year period was crucial in driving the decline. It is imperative to investigate preventive behaviors among Chinese university students, who could have spread COVID-19 when travelling home during the Chinese New Year break.

Objective: In this study, we investigated levels of COVID-19–related personal measures undertaken during the 7-day Chinese New Year holidays by university students in China, and associated COVID-19–related cognitive factors.

Methods: A cross-sectional anonymous web-based survey was conducted during the period from February 1 to 10, 2020. Data from 23,863 students (from 26 universities, 16 cities, 13 provincial-level regions) about personal measures (frequent face-mask wearing, frequent handwashing, frequent home staying, and an indicator that combined the 3 behaviors) were analyzed (overall response rate 70%). Multilevel multiple logistic regression analysis was performed.

Results: Only 28.0% of respondents (6684/23,863) had left home for >4 hours, and 49.3% (11,757/23,863) had never left home during the 7-day Chinese New Year period; 79.7% (19,026/23,863) always used face-masks in public areas. The frequency of handwashing with soap was relatively low (6424/23,863, 26.9% for >5 times/day); 72.4% (17,282/23,863) had frequently undertaken ≥2 of these 3 measures. COVID-19–related cognitive factors (perceptions on modes of transmission, permanent bodily damage, efficacy of personal or governmental preventive measures, nonavailability of vaccines and treatments) were significantly associated with preventive measures. Associations with frequent face-mask wearing were stronger than those with frequent home staying.

Conclusions: University students had strong behavioral responses during the very early phase of the COVID-19 outbreak. Levels of personal prevention, especially frequent home staying and face-mask wearing, were high. Health promotion may modify cognitive factors. Some structural factors (eg, social distancing policy) might explain why the frequency of home staying was higher than that of handwashing. Other populations might have behaved similarly; however, such data were not available to us.

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KEYWORDS

COVID-19; health behavior; prevention; control; cognition; face mask; hand hygiene; interpersonal contacts; China; protection; public health; behavior; infectious disease; cross-sectional; survey

Introduction

The World Health Organization (WHO) declared the COVID-19 outbreak a Public Health Emergency of International Concern on January 30, 2020 and declared a pandemic on March 11, 2020 [1,2]. Globally, there were 177.9 million infections and 3.8 million deaths (June 22, 2021), respectively [3]. In China, the outbreak coincided with the critical 7-day Chinese New Year holidays (January 25 to February 1), during which billions of trips were made across the country. On January 20, 2020, the government announced evidence of human-to-human transmission. Wuhan (the epicenter) was immediately locked down, and subsequently, other cities were also locked down [4]. Comprehensive control measures were enacted (eg, testing, quarantining, contact tracing, cancelling public events, closing of public areas, extending Chinese New Year holidays, and mandatory face-mask wearing [5,6]), and patients with COVID-19 were treated in more than 30 speedily built hospitals by medical specialists in different provinces across the country [7]. Many countries soon used similar standard strategies to combat COVID-19.

During the 7-day Chinese New Year period (January 25 to February 1), which began only 5 days after the start of the Wuhan lockdown (thus, during the very early phase of the outbreak among university students in China), the daily number of newly detected clinical or suspected COVID-19 infections in China reached its peak (n=17,959) on February 12, 2020, and then declined rapidly, to only 100 new infections on March 8 (ie, week 6 since the Wuhan lockdown) [8,9]. The daily figure for indigenous confirmed cases reached zero on March 22, 2020 [9] and remained very low afterward [10]. Thus, the first wave of the COVID-19 outbreak in mainland China had been effectively controlled within 6 to 8 weeks. The use of preventive behaviors might have led to the sharp decline. Worldwide, almost all governments have implemented some testing and social distancing measures [11]; their effectiveness, however, varied by country. Since March 2020, outbreaks have occurred in every continent [3,12].

Effective control of severe acute respiratory syndrome (SARS) outbreaks depended on community-level behavioral responses (ie, general adoption of protective measures, such as face-mask use, good hand hygiene, and social distancing [13,14]). Unfortunately, strong public health messages (eg, the importance of urgent uptake of the aforementioned preventive measures) throughout the COVID-19 pandemic have been blurred by politics and have not always been well received by governments and citizens in many countries. The identification of factors associated with preventive behaviors facilitates health promotion to improve preventive behaviors. Cognitive factors related to SARS and influenza A (H1N1) of preventive measures during such epidemic periods have been identified (eg, perceived risk of SARS infection) [13-19]. Similar factors have been identified during the COVID-19 pandemic [20-22].

The rationale of this study was to understand and document the behavioral responses among university students during the very early phase of the COVID-19 outbreak in China. During the Chinese New Year (the peak travel season in China), university students could have transmitted and spread the virus across the country because of their travel during that time period. It is essential to examine Chinese university students' behavioral responses to understand why their travel movements did not appear to cause COVID-19 outbreaks countrywide. There is a dearth of such studies. Although generalization to the general population is impossible, the findings are potentially illustrative of what might have occurred in other populations in China, and thus, might to some extent provide some clues about how the pandemic was controlled within a short period of time in China.

We aimed to investigate the frequency with which 3 key preventive measures—face-mask wearing, frequent handwashing, and frequent home staying—were practiced, as well as related cognitive factors among university students

across mainland China during the critical 7-day Chinese New Year period.

Methods

Study Design

A cross-sectional anonymous web-based survey was conducted during the period from February 1 to 10, 2020. At the time of the study, there were a total of 1272 universities in China. Convenience sampling was used to select the same faculties (medicine, arts, science, engineering, social science, and others) from 26 universities (16 cities in 13 out of 32 provinces, municipalities, or autonomous regions); altogether, selected faculties contained 36,560 students, who were invited through WeChat to complete an anonymous web-based questionnaire, which included an informed consent statement (invitations per university: median 1165, IQR 2271). Methodological details have been previously described in other papers based on the same data set [23,24].

A total of 25,647 participants returned completed questionnaires. The overall response rate was 70.2% (25,647/36,560). The mean response rate for cities was 70% (SD 17%), with 12 of the 16 cities having response rates >60%, while the average response rate for the 26 universities was 68.4%. Of 25,647 completed questionnaires, 1784 were excluded (due to failure to pass the built-in consistency checks: n=1197; respondents were diagnosed with COVID-19: n=47; respondents were quarantined due to COVID-19 exposure: n=515; respondents had been outside mainland China during the 7-day Chinese New Year period: n=25); therefore, the effective sample size for analysis was 23,863 (93.0%). Ethics approval was obtained from the Chinese University of Hong Kong.

Measures

Background Information

Background information about sociodemographic characteristics, school, where respondents were located at the time of the survey (ie, staying in their universities' cities or with the family), self-perceived physical health status, living arrangements during the 7-day Chinese New Year holidays (ie, whether staying in their universities' cities and whether staying with their family from January 25 to February 1, 2020), and the lockdown status of the community where they were located at the time of the survey.

Dependent Variables

We assessed the frequency of uptake of various preventive measures during the period from January 25 to February 1, 2020 (ie, the 7-day Chinese New Year holidays). Frequency of face-mask wearing was assessed with the question: "Have you worn a mask when going out, no matter whether you have symptoms or not?" Respondents answered using a scale from 1 (definitely no) to 5 (definitely yes), which was recoded into 1 (definitely yes) and 0 (other responses). Daily frequency of handwashing with water, soap, or disinfectant was assessed, with 0 to 2, 3 to 5, 6 to 10, 11 to 15, >15 times as response options; responses were then categorized as frequent (>10) or less frequent (0-10). Frequency of home staying was assessed, with 0 to 4 hours or >4 hours at home during the 7-day of the Chinese New Year as response options; responses were recoded into 1 (frequent) and 0 (less frequent). In addition, we used a composite Preventive Measure Indicator—the number of abovementioned measures that were frequently used—which was recoded into a binary variable: low (0 or 1 frequently used preventive measures) or high (2 or 3 frequently used preventive measures).

Independent Variables

We assessed a set of cognitive variables: Perceived Probable Transmission Mode Indicator (the number of appropriate answers about transmission by droplets, touching infected persons, and touching contaminated objects), which ranged from 0 to 3; perceived asymptomatic transmission knowledge (yes or no/don't know); perceived severity of COVID-19 (ie, "Whether COVID-19 would easily cause permanent bodily damage?"), with responses 0 (disagree/don't know) or 1 (agree); perceived risk of contracting COVID-19 in the upcoming year for oneself, family members, and peers, with responses 1 (extremely high/high) or 0 (other); Perceived Risk Indicator (the number of responses equal to 1), which ranged from 0 to 3; perceived nonavailability of effective vaccines, with responses 1 (agree) or 0 (else); and perceived nonavailability of effective vaccine-specific treatment for COVID-19, with responses 1 (agree) or 0 (else).

An Efficacy of Personal Preventive Measure Indicator was obtained by summing 5 scores (frequent face-mask wearing in public areas, frequent handwashing with water, frequent handwashing with soap or disinfectant, household sterilization, and avoiding going to crowded places), where scores less than 15 (0th to 26.4th percentile) were low, scores from 16 to 18 (26.4th to 58.4th percentile) were medium, and scores equal to 19 or 20 (58.4th to 100th percentile) were high. The Efficacy of Governmental Preventive Measure Indicator was obtained by summing 6 measures (cancellation of public events, lockdown of Wuhan, closing public venues such as restaurants and cinemas, home staying, primary school to university class suspension, and mandatory face-mask wearing in public areas), where scores less than 20 (27.4th percentile) were low, scores from 21 to 23 (27.4th -51.4th percentile) were medium, and a score of 24 (51.4th to100th percentile) was high.

Statistical Analysis

Pooled proportions were estimated using meta-analysis techniques that consider random-effects and inverse variance weighting (universities were the pooling units) [25]. Simple (univariate) logistic regression was performed to examine the crude association between background variables and dependent variables. Significant background variables (P<.05) were potential confounders of associations between cognitive variables and dependent variables and were adjusted for in subsequent multivariable logistic regression analysis. Multilevel logistic regression models with random effects, adjusted for background variables, were fit separately for the 4 preventive measure–dependent variables (with university as the first level). Summary models included all independent variables. Adjusted odds ratios (OR) with 95% confidence intervals are reported. SPSS statistical software (version 25; IBM Corp) and R software

(version 3.5.2; the R Project) were used. Significance was defined as a *P* value <.05.

Results

Background Characteristics

At the time of the survey, 53.4% of the participants (12,747/23,863) were located in the same city as their university, 93.5% were staying with their family (22,304/23,863), 70.6% were in communities under lockdown, and 79.4% (18,937/23,863) self-reported good or very good physical health status (Table 1).

Table 1. Background variable descriptive statistics.

Variables	Respondents (n=23,863), n (crude %)	Pooled % (95% CI)
Sociodemographics		
Gender		
Male	7605 (31.9)	29.8 (26.2, 33.4)
Female	16,258 (68.1)	70.2 (66.6, 73.8)
Grade		
First year	9017 (37.8)	36.8 (23.7, 49.9)
Second year	6425 (26.9)	27.5 (21.6, 33.3)
Third year	5061 (21.2)	21.0 (13.7, 28.3)
Fourth year	2281 (9.6)	7.3 (6.2, 8.4)
Fifth year	542 (2.3)	0.8 (0.5, 1.1)
Master or above	537 (2.3)	1.0 (0.6, 1.3)
Major		
Medicine	10,850 (45.5)	34.5 (27.9, 41.2)
Arts	4232 (17.7)	22.3 (18.1, 26.4)
Science	3901 (16.4)	15.1 (11.6, 18.6)
Engineering	1809 (7.6)	8.8 (7.0, 10.5)
Social science	846 (3.6)	4.1 (3.2, 5.0)
Other	2225 (9.3)	8.5 (6.6, 10.5)
Living arrangement during Chinese New Year		
Staying in the same city as their university		
No	11,116 (46.6)	48.1 (42.3, 53.8)
Yes	12,747 (53.4)	51.9 (46.2, 57.7)
Staying with family		
No	1559 (6.5)	5.6 (4.7, 6.5)
Yes	22,304 (93.5)	94.4 (93.5, 95.3)
Self-reported physical health status		
Moderate/poor/very poor	4926 (20.6)	22.5 (20.4, 24.7)
Good/very good	18,937 (79.4)	77.5 (75.3, 79.6)
Local entry and exit control (ie, lockdown)		
No	7081 (29.4)	34.1 (27.2, 40.9)
Yes	16,845 (70.6)	65.9 (59.1, 72.8)

Preventive Measures During the Chinese New Year Period

The majority of respondents (19,026/23,863, 79.7%) always used face masks when going out without flu symptoms (frequent face-mask users); only 7.7% (1842/23,863) had never used face masks during the Chinese New Year (744/1842, 40.4% of whom had not left home). Approximately three-quarters (72.0%) went out for <4 hours per day (0 hours: 11,757/23,863, 49.3%; 1-4 hours: 5422/23,863, 22.7%) during the 7-day period.

Approximately three-quarters (17,439/23,863, 73.1%) washed their hands with soap or disinfectant for 0 to 5 times per day, 28.6% (6836/23,863) washed their hands with soap or disinfectant 0 to 2 times per day, and 43.7% (10,440/23,863) washed hands with either water or soap or disinfectant >10 times per day. Of the 23,863 respondents, 44.7% (10,675/23,863) and 27.7% (6607/23,863) had frequently taken up 2 and 3 key preventive measures, respectively (Table 2).

Table 2. Descriptive statistics for behavioral variables related to COVID-19 among university students in China.

Variables	Respondents (n=23,863), n (crude %)	Pooled % (95% CI)
Frequent face-mask wearing when went out		
Not definitely yes	4837 (20.3)	16.7 (13.7, 19.8)
Definitely yes	19,026 (79.7)	83.3 (80.2, 86.3)
Frequent handwashing (frequencies of washing either soap or water)		
0-10 times/day	13,423 (56.3)	55.6 (52.9, 58.2)
>10 times/day	10,440 (43.7)	44.4 (41.8, 47.1)
Frequent home staying (total number of hours went out during the 7-day Chinese New Year period)		
>4 hours	6684 (28.0)	27.5 (25.1, 29.8)
1-4 hours	5422 (22.7)	25.0 (23.4, 26.7)
Never went out	11,757 (49.3)	46.9 (43.6, 50.2)
Preventive Measure Indicator[a]		
0-1	6581 (27.6)	25.2 (21.8, 28.5)
2-3	17,282 (72.4)	74.8 (71.5, 78.2)

[a]The Preventive Measure Indicator counted the number of the frequently used preventive measures (ie, frequent face-mask wearing, frequent handwashing, and frequent home staying.

COVID-19–Related Cognitions

A majority (21,991/23,863, 92.2%) indicated ≥2 of the 3 key modes of transmission (droplets, touching infected persons, and touching contaminated surfaces) and perceived possibility of asymptomatic transmission (19,549/23,863, 81.9%). Less than 20% (3238/23,863, 13.6%) believed that there was a high risk of themselves, their family members, or their peers contracting the virus; 35.7% (8523/23,863) perceived that COVID-19 would easily cause permanent bodily damage. Approximately 70.0% (18,281/23,863 and 15,015/23,863, respectively) perceived effective vaccines and specific treatments for COVID-19 were not available, and personal and governmental preventive measures were perceived to be highly effective (Table 3).

Table 3. Descriptive statistics for cognitive variables related to COVID-19 among university students in China.

Variables	Respondents (n=23,863), n (crude %)	Pooled % (95% CI)
Transmission-related variables		
Perceived Probable Transmission Mode Indicator (number of appropriate answers)		
0	292 (1.2)	0.9 (0.6, 1.2)
1	1580 (6.6)	6.2 (5.2, 7.1)
2	6171 (25.9)	26.3 (24.1, 28.6)
3	15,820 (66.3)	66.3 (63.5, 69.1)
Perceived asymptomatic transmission		
No or don't know	4314 (18.1)	16.6 (13.7, 19.6)
Yes	19,549 (81.9)	83.4 (80.4, 86.3)
Perceived severity		
Permanent bodily damage		
Disagree/don't know	15,340 (64.3)	66.4 (64.6, 68.2)
Agree	8523 (35.7)	33.6 (31.8, 35.4)
Perceived risk		
Perceived Risk Indicator		
0	18,779 (78.7)	77.4 (75.2, 79.6)
1	1846 (7.7)	8.0 (7.0, 8.9)
2	1707 (7.2)	7.2 (6.2, 8.2)
3	1531 (6.4)	6.6 (5.8, 7.4)
Medical preparedness		
Perceived nonavailability of vaccines		
Disagree or don't know	5582 (23.4)	19.9 (16.4, 23.4)
Agree	18,281 (76.6)	80.1 (76.6, 83.6)
Perceived nonavailability of specific treatment		
Disagree or don't know	8848 (37.1)	34.5 (31.3, 37.8)
Agree	15,015 (62.9)	65.5 (62.2, 68.7)
Perceived efficacy		
Efficacy of Personal Preventive Measure Indicator		
≤15 (<26.4th percentile)	6298 (26.4)	24.4 (22.4, 26.4)
16-18 (26.4th to 58.4th percentile)	7646 (32.0)	33.4 (31.5, 35.2)
19-20 (>58.4th percentile)	9919 (41.6)	41.8 (39.0, 44.5)
Efficacy of Governmental Preventive Measure Indicator		
≤ 20 (<27.4th percentile)	6528 (27.4)	25.4 (23.1, 27.7)
21-23 (27.4th to 51.4th percentile)	5729 (24.0)	25.2 (22.9, 27.4)
24 (>51.4th percentile)	11,606 (48.6)	49.2 (45.3, 53.1)

Background Factors

Female university students were more likely than male university students to have frequently used more preventive measures (univariate OR 1.40). University year, major, staying with family, staying in the same city as their university, self-reported physical health, and lockdown were associated with some or all of the 4 dependent variables (Table 4); subsequent analyses were adjusted for these background variables as they were potential confounders of the associations between the cognitive factors and preventive behaviors.

Table 4. Univariate associations (crude odds ratios) between the background variables (sociodemographics, living arrangement during the Chinese New Year, self-perceived health, and local lockdowns) and preventive measures among university students in China (n=23,863).

Independent variables	Dependent variable, univariate odds ratio (95% CI)			
	Frequent face-mask wearing	Frequent handwashing	Frequent home staying	Preventive measure indicator
Sociodemographic				
Gender				
Male	1.00	1.00	1.00	1.00
Female	1.68 (1.48-1.91)***	1.15 (1.06-1.26)**	1.10 (1.04-1.15)***	1.40 (1.31-1.51)***
Grade				
First year	1.00	1.00	1.00	1.00
Second year	1.12 (1.00-1.25)	1.07 (0.99-1.15)	0.95 (0.88-1.04)	1.05 (0.97-1.15)
Third year	1.15 (1.04-1.28)**	1.13 (1.01-1.26)*	0.97 (0.90-1.05)	1.12 (1.00-1.25)
Fourth year	1.15 (1.01-1.30)*	1.11 (0.97-1.26)	0.94 (0.86-1.04)	1.01 (0.01-1.11)
Fifth year	1.33 (0.96-1.85)	1.19 (1.05-1.34)**	0.77 (0.66-0.91)**	1.10 (0.80-1.51)
Master or above	1.45 (1.03-2.06)*	1.35 (1.26-1.45)***	0.79 (0.71-0.88)***	1.19 (0.96-1.47)
Major				
Medicine	1.00	1.00	1.00	1.00
Arts	1.00 (0.89-1.13)	1.00 (0.93-1.06)	1.04 (0.94-1.14)	1.04 (0.97-1.12)
Science	0.73 (0.66-0.81)***	0.96 (0.90-1.02)	0.91 (0.85-0.98)*	0.82 (0.75-0.90)***
Engineering	0.76 (0.69-0.84)***	0.85 (0.77-0.94)**	0.93 (0.83-1.05)	0.80 (0.70-0.92)**
Social science	0.88 (0.73-1.05)	0.84 (0.75-0.94)**	0.82 (0.69-0.98)*	0.77 (0.63-0.94)**
Other	0.99 (0.89-1.10)	0.99 (0.92-1.07)	1.00 (0.88-1.14)	0.97 (0.89-1.06)
Living arrangement during the Chinese New Year				
Staying in the same city as their university				
No	1.00	1.00	1.00	1.00
Yes	0.93 (0.87-0.98)*	0.93 (0.87-0.99)*	0.77 (0.73-0.83)***	0.82 (0.76-0.87)***
Staying with the family				
No	1.00	1.00	1.00	1.00
Yes	1.26 (1.10-1.45)**	0.72 (0.65-0.81)***	0.77 (0.65-0.92)**	0.91 (0.77-1.07)
Self-perceived physical health status				
Moderate/poor/very poor	1.00	1.00	1.00	1.00
Good/very good	1.42 (1.33-1.51)***	1.34 (1.27-1.42)***	1.30 (1.23-1.38)***	1.48 (1.36-1.61)***
Local lockdown (entry/exit control)				
No	1.00	1.00	1.00	1.00
Yes	0.93 (0.81-1.06)	1.00 (0.92-1.09)	1.21 (1.14-1.28)***	1.06 (0.97-1.15)

*P<.05.
**P<.01.
***P<.001.

Adjusted Associations Between Cognitive Factors and Preventive Measures

Perceived knowledge about probable modes of transmission of COVID-19 was significantly associated with the number of frequently used preventive measures (adjusted OR ranged from 2.50 to 3.06) and frequent face-mask wearing (adjusted OR ranged from 4.32 to 6.25) (Table 5). Perceived knowledge about asymptomatic transmission was associated with frequent face-mask wearing (adjusted OR 1.54, 95% CI 1.34-1.76) and more frequently used preventive measures (adjusted OR 1.27, 95% CI 1.18-1.36). Perceived permanent bodily damage was mildly associated with frequent face-mask wearing (adjusted OR 1.24, 95% CI 1.14-1.35), frequent handwashing (adjusted OR 1.07, 95% CI 1.02-1.12), and the number of frequently used preventive measures (adjusted OR 1.17, 95% CI 1.11-1.22), but was not associated with frequent home staying (adjusted OR 1.02, 95% CI 0.96-1.08). Perceived risks of infection was

associated with less preventive behaviors (adjusted OR ranged from 0.76 to 0.83).

Perceived nonavailability of vaccines or specific treatments was significantly and mildly associated with frequent face-mask wearing (adjusted OR 1.43 and 1.27, respectively) and number of frequently used preventive measures (adjusted OR 1.18 and 1.15, respectively). Perceived efficacy of the personal measures was strongly associated with frequent face-mask wearing (adjusted OR ranged from 1.86 to 3.51) and number of frequently used preventive measures (adjusted OR ranged from 1.44 to 2.08), and mildly with frequent handwashing (adjusted OR ranged from 1.07 to 1.33) and frequent home staying (adjusted OR ranged from 1.05 to 1.14). Perceived efficacy of governmental measures was similarly associated with the 4 dependent variables.

A summary logistic regression model, which contained all the independent variables and was adjusted for background variables (potential confounders), exhibited largely similar results (Multimedia Appendix 1).

Table 5. Adjusted associations between cognitive factors and preventive measures among university students in China (n=23,863).

Independent variables	Dependent variables, adjusted odds ratio[a] (95% CI)			
	Frequent face-mask wearing	Frequent handwashing	Frequent home staying	Preventive measure indicator
Transmission-related variables				
Perceived Probable Transmission Mode Indicator (No. of appropriate answers)				
0	1.00	1.00	1.00	1.00
1	4.32 (2.81-6.65)***	0.89 (0.68-1.17)	1.25 (0.92-1.69)	2.50 (2.00-3.12)***
2	5.31 (3.31-8.54)***	0.89 (0.74-1.07)	1.27 (0.91-1.79)	2.62 (2.03-3.38)***
3	6.25 (3.77-10.36)***	1.01 (0.84-1.21)	1.33 (0.96-1.83)	3.06 (2.35-3.98)***
Perceived asymptomatic transmission				
No/don't know	1.00	1.00	1.00	1.00
Yes	1.54 (1.34-1.76)***	1.03 (0.98-1.09)	1.08 (1.00-1.18)	1.27 (1.18-1.36)***
Perceived severity				
Permanent bodily damage				
Disagree/don't know	1.00	1.00	1.00	1.00
Agree	1.24 (1.14-1.35)***	1.07 (1.02-1.12)*	1.02 (0.96-1.08)	1.17 (1.12-1.22)***
Perceived risk				
Perceived Risk Indicator				
0	1.00	1.00	1.00	1.00
1	0.81 (0.74-0.90)***	0.95 (0.91-1.00)*	0.84 (0.75-0.95)**	0.83 (0.73-0.94)**
2	0.78 (0.71-0.85)***	0.90 (0.78-1.03)	0.80 (0.71-0.92)**	0.76 (0.68-0.85)***
3	0.82 (0.63-1.06)	0.94 (0.86-1.03)	0.76 (0.67-0.87)***	0.76 (0.67-0.86)***
Medical preparedness				
Perceived nonavailability of vaccines				
Disagree/don't know	1.00	1.00	1.00	1.00
Agree	1.43 (1.32-1.54)***	1.05 (1.00-1.10)	1.00 (0.92-1.07)	1.18 (1.10-1.28)***
Perceived nonavailability of specific treatment				
Disagree/don't know	1.00	1.00	1.00	1.00
Agree	1.27 (1.18-1.36)***	1.00 (0.94-1.05)	1.02 (0.97-1.08)	1.15 (1.09-1.21)***
Perceived efficacy of preventive measures				
Efficacy of Personal Preventive Measure Indicator				
≤15 (26.4 percentile)	1.00	1.00	1.00	1.00
16-18 (58.4 percentile)	1.86 (1.62-2.14)***	1.07 (1.01-1.14)*	1.05 (0.99-1.12)	1.44 (1.33-1.55)***
19-20 (100 percentile)	3.51 (3.06-4.02)***	1.33 (1.25-1.43)***	1.14 (1.08-1.21)***	2.08 (1.93-2.23)***
Efficacy of Governmental Preventive Measure Indicator				
≤20 (27.4 percentile)	1.00	1.00	1.00	1.00
21-23 (51.4 percentile)	2.07 (1.82-2.36)***	1.10 (1.03-1.18)**	1.04 (0.97-1.12)	1.15 (1.35-1.65)***
24 (100 percentile)	4.05 (3.58-4.58)***	1.28 (1.22-1.35)***	1.17 (1.11-1.22)***	2.23 (2.10-2.36)***

[a]Adjusted for gender, grade, major, living arrangement during Chinese New Year, self-perceived physical health status, and local entry and exit control.
*P<.05.
**P<.01.
***P<.001.

Discussion

We found that some preventive behaviors, especially social distancing (staying at home) and face-mask use, were frequently practiced by the majority of university student respondents during the 7-day Chinese New Year holiday week. Cognitive factors—perceived knowledge about probable modes of transmission and perceived knowledge about asymptomatic transmission, perceived permanent bodily damage, perceived nonavailability of vaccines or specific treatment, perceived efficacy of the personal measures, and perceived efficacy of governmental measures—were associated with practicing the 3 preventive behaviors. Unexpectedly, perceived risks of infection was associated with less preventive behaviors.

One of the key findings was the amount that people remained home during the 7-day Chinese New Year holiday period. The time frame for investigating preventive behaviors in the very early phase of the COVID-19 outbreak in China was set during the holiday period (which was 2-9 days into the Wuhan lockdown). This holiday period is typically filled with travel, celebrations, dining, gatherings, open markets, and mutual family visits, which would have entailed a very high risk of COVID-19 transmission and spread across provinces via university students when they traveled home. Such risks, however, seem to have been mitigated—the majority of university students stayed home all or most of the time and frequently wore face masks in public areas. As the responses from quarantined individuals were excluded from the study and there was, then, no penalty for going out, most home staying was likely to be voluntary, although possibly based on governmental advice. Frequent home staying was not used to control SARS and H1N1; the massive scale of voluntary home staying is unprecedented. Consistent face-mask wearing was much higher than the 61.2% to 64.3% recorded during the SARS period in Hong Kong [26,27]. Neither social norms nor governmental policy about the use of face masks existed during the initial period of the COVID-19 outbreak in China, which suggests that, to some extent, spontaneous behavioral responses to practice COVID-19 preventive measures might have commonly occurred among university students nationwide, as 31 of the 32 provincial-level regions in China were represented by respondents. The potential spontaneity is remarkable as only a low number of 381 newly confirmed infections were detected outside Hubei province (where Wuhan is located) on February 10 [28]. It is notable that good knowledge about the key transmission modes and high perceived efficacies of personal and governmental measures in preventing COVID-19 were significantly associated with the number of frequently used preventive measures (all $P<.001$), indicating that it is potentially important to disseminate information to increase COVID-19–related knowledge to promote positive behavioral responses.

The findings further suggest that health education about transmission via fomites is required, as the level of washing hands with soap or disinfectants was much lower than that of mask-wearing. The frequency of handwashing could be improved, as 73.1% (17,439/23,863) had only washed their hands with soap or disinfectant for 0 to 5 times per day, compared to 91.4% of the Hong Kong general public had washed hands for >6 times per day to prevent H1N1 [15]. Handwashing was widely publicized during the SARS period in Hong Kong [29]. Interestingly, handwashing was less practiced than home staying and face-mask wearing, possibly because handwashing is a privately performed behavior while home staying and face-mask wearing are visible behaviors that protect both the doer and other people. Handwashing might be less subjected to social norms and controls.

Corroborating literature with respect to knowledge about COVID-19, perceived permanent bodily damages (severity) [30], perceived nonavailability of vaccines or specific treatments [31], perceived efficacy of personal measures, and perceived efficacy of governmental measures [32] were associated with practicing preventive measures frequently. Unexpectedly, high perceived risk of infection was mildly associated with fewer preventive behaviors. As the use of preventive measures may reduce perceived risk, cross-sectional studies have often reported similar negative associations (eg, association between condom use and lower perceived risk of contracting HIV [33]). It is interesting that cognitive factors exhibited stronger associations with frequent face-mask wearing than frequent home staying. It is plausible that because some governmental social distancing measures (eg, lockdown, extended holidays, suspending events, and closing venues) had removed reasons to go out and the government encouraged staying at home (eg, for personal safety, to be a good citizen, and to contribute to controlling the national pandemic), home staying may hence be influenced less by individual-level cognitive factors than face-mask wearing and more so by structural policy factors and interpersonal norm factors. Such a contention needs to be confirmed in the future. If true, global public health workers may need to pay more attention to the structural and interpersonal factors in controlling the COVID-19 pandemic.

It is noteworthy that 70% of the respondents (16,845/23,863) reported some entry and exit restrictions in their communities. It is possible that social distancing policies had already been implemented in many parts of China very soon after the COVID-19 outbreak. Other studies [34-36] have also reported high levels of preventive behaviors in different populations in China (eg, general population, factory workers, and teachers) from February to May 2020. We speculate that the nation started responding to COVID-19 shortly after the initial outbreak. This study has thus documented active positive behavioral responses to COVID-19 in one important population of university students in China, while social distancing and face-mask use remain controversial even now, due to potential infringement on personal freedoms, in many countries [37-40].

The study has some limitations. Although it included respondents from universities in 16 cities in 13 provinces, this still did represent truly national coverage. Selection bias may exist, as classes and departments were not randomly selected. We were unable to include universities in Hubei Province, the epicenter. The sample only included university students and cannot be generalized to other populations. The subsample sizes of the participating universities varied; the weighted data were very similar to the observed frequencies. The uptake of preventive measures was self-reported and refined measurement

was not allowed (eg, the exact amount of time spent outside the home). We did not cover important interpersonal factors (eg, subjective norms and social support), which are associated with many health-related behaviors [41]. The cross-sectional study design does not allow for causal inferences. In addition, information bias might exist due to recall and social desirability.

The sample of university students in China demonstrated very strong behavioral prevention responses, especially home staying (social distancing) and face mask use, during the initial phase of the COVID-19 outbreak in China. Such preventive behaviors may have averted subsequent outbreaks that could have arisen from a large volume of nationwide travel by university students during Chinese New Year holidays. Potential determinants of the preventive behaviors were identified. Prompt health education, given the findings of this study, should be provided to university students through social media in the very early phase of outbreaks of future pandemics. The strong behavioral responses that were observed might be, to some extent, spontaneous and may indicate the importance of structural factors (eg, strong governmental policies, mobilization, and social capital). Although there were substantial hardships during the early phase of the pandemic, the entire country remained supportive, united, orderly, and harmonious—altruism and patriotism appeared to be wide-spread [42]. Good social capital (eg, trust in the government and mutual help) might have played an important role in initiating the positive responses among university students. Further studies are warranted to understand the roles of social capital in controlling the spread of COVID-19 infections in and outside China.

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Authors' Contributions

JL conceived the research questions, designed this study, assembled the team of collaborators, and supervised the project's implementation. JL, YY, XM, RS, and SL conducted the statistical analysis and drafted the manuscript; JL finalized the manuscript. All authors assisted in questionnaire design, data collection, and data interpretation and provided comments with respect to intellectual content of the manuscript. JL, YY, XM, RS, and SL have full access to all data and are responsible for the integrity of the data and the accuracy of data analysis.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary models entering all cognitive factors as independent variables (n=23,863).
[DOCX File , 17 KB - publichealth_v7i10e26840_app1.docx]

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Abbreviations

H1N1: influenza A
HIV: human immunodeficiency virus
OR: odds ratio
SARS: severe acute respiratory syndrome
WHO: World Health Organization

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Statin Use and COVID-19 Infectivity and Severity in South Korea: Two Population-Based Nationwide Cohort Studies

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Abstract

Background: Basic studies suggest that statins as add-on therapy may benefit patients with COVID-19; however, real-world evidence of such a beneficial association is lacking.

Objective: We investigated differences in SARS-CoV-2 test positivity and clinical outcomes of COVID-19 (composite endpoint: admission to intensive care unit, invasive ventilation, or death) between statin users and nonusers.

Methods: Two independent population-based cohorts were analyzed, and we investigated the differences in SARS-CoV-2 test positivity and severe clinical outcomes of COVID-19, such as admission to the intensive care unit, invasive ventilation, or death, between statin users and nonusers. One group comprised an unmatched cohort of 214,207 patients who underwent SARS-CoV-2 testing from the Global Research Collaboration Project (GRCP)-COVID cohort, and the other group comprised an unmatched cohort of 74,866 patients who underwent SARS-CoV-2 testing from the National Health Insurance Service (NHIS)-COVID cohort.

Results: The GRCP-COVID cohort with propensity score matching had 29,701 statin users and 29,701 matched nonusers. The SARS-CoV-2 test positivity rate was not associated with statin use (statin users, 2.82% [837/29,701]; nonusers, 2.65% [787/29,701]; adjusted relative risk [aRR] 0.97; 95% CI 0.88-1.07). Among patients with confirmed COVID-19 in the GRCP-COVID cohort, 804 were statin users and 1573 were matched nonusers. Statin users were associated with a decreased likelihood of severe clinical outcomes (statin users, 3.98% [32/804]; nonusers, 5.40% [85/1573]; aRR 0.62; 95% CI 0.41-0.91) and length of hospital stay (statin users, 23.8 days; nonusers, 26.3 days; adjusted mean difference –2.87; 95% CI –5.68 to –0.93) than nonusers. The results of the NHIS-COVID cohort were similar to the primary results of the GRCP-COVID cohort.

Conclusions: Our findings indicate that prior statin use is related to a decreased risk of worsening clinical outcomes of COVID-19 and length of hospital stay but not to that of SARS-CoV-2 infection.

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KEYWORDS

COVID-19; statin; susceptibility; severe clinical outcomes; length of hospital stay

Introduction

COVID-19 is caused by SARS-CoV-2, and started in Wuhan, China. The World Health Organization (WHO) declared COVID-19 a pandemic on March 12, 2020 [1,2]. In Korea, the first COVID-19 patient was diagnosed on January 20, 2020. During the period from January 1, 2020, to May 31, 2020, the number of daily confirmed COVID-19 cases was less than 2000 and the cumulative number of COVID-19 cases was 11,468 with 270 deaths [3,4]. During this pandemic phase, efficient strategies for triage and therapeutics are crucial due to the high number of patients with SARS-CoV-2 infection, and the relatively limited facilities and medical resources [1,2]. The effective treatment of patients with COVID-19 has still not been established. Previous studies have suggested potential therapeutic candidates, including antimalarial drugs [5], antivirals such as lopinavir and ritonavir in combination [6], remdesivir [7], previous bacillus Calmette–Guérin (BCG) vaccination [8], famotidine [9], and immunoglobulin-containing sera from convalescent patients with COVID-19 [10]. However, antimalarial drugs and the lopinavir–ritonavir combination proved ineffective in clinical trials [5,6], and previous studies on BCG vaccination, famotidine, and immunoglobulin-containing sera had small sample sizes and preliminary study designs [8-10]. Remdesivir improved clinical outcomes in patients with COVID-19, but it is not readily available [7].

In this context, statins are inexpensive and easily available therapeutic agents, and their multiple pharmacologic mechanisms include anti-inflammation, antioxidation, inhibition of the angiotensin-converting enzyme 2 (ACE2) pathway, and lowering bodily lipid levels [11]. Statins are recommended for the primary prevention of cardiovascular diseases according to the American College of Cardiology/American Heart Association guidelines [12], and a recent retrospective cohort study has reported on their protective roles in preventing both all-cause mortality and cardiovascular-related mortality in the elderly [13]. The pleiotropic effects of statin on anti-inflammation and immune modulation, in addition to their inhibition of viral entry via ACE2, indicate the potential beneficial effects of statins on patients with COVID-19 [11,14]. In line with this, a recent study on patients with COVID-19 presented a negative association between statin use and risks of all-cause mortality [15]; however, the study was limited by the relatively small study population and the potential selection bias due to the unconcerned variables including lifestyle factors such as obesity, smoking, and alcohol consumption.

We hypothesized that prior statin use could either decrease the risks of COVID-19 or of severe clinical outcomes of COVID-19 (ie, death, admission to the intensive care unit, and invasive ventilation). Through 2 independent nationwide cohort studies on Korean patients, with propensity score matching, we investigated the potential association of previous statin use with the likelihood of a positive SARS-CoV-2 test result (viral infectivity) in all patients who underwent the test. Furthermore, we aimed to clarify the difference in clinical outcomes of patients with laboratory-confirmed SARS-CoV-2 infection who were and who were not administered statins.

Methods

Study Design

Two independent cohorts were analyzed: the Global Research Collaboration Project on COVID-19 (GRCP-COVID) cohort [16,17] and the National Health Insurance Service-COVID-19 (NHIS-COVID) cohort. The study protocol was approved by the Institutional Review Board of Sejong University (SJU-HR-E-2020-003). The requirement for written informed consent was waived by the ethics committee due to the urgent medical needs during the COVID-19 pandemic.

GRCP-COVID Cohort (Claims-Based Cohort)

During the COVID-19 pandemic, the Korean Government shared the first nationwide claims-based database consisting of all people who were tested for SARS-CoV-2 in South Korea. This high-quality, large-scale nationwide cohort included all people who tested through medical or Korea Centers for Disease Control referrals (excluding self-referral) in South Korea via services facilitated by the Health Insurance Review and Assessment Service of Korea, the Korea Centers for Disease Control and Prevention, and the Ministry of Health and Welfare, Republic of Korea [16,18,19]. This cohort study has the following characteristics: (1) The Korean Government provided obligatory and complimentary medical health insurance for all patients with COVID-19; (2) therefore, this database has records of personal data, health care records of inpatients and outpatients for 3 years before the first SARS-CoV-2 test (including health care visits, prescriptions, diagnoses, and procedures), pharmaceutical visits, COVID-19-associated outcomes, and death records; and (3) all claim-based data were anonymous to maintain patient confidentiality with the Ministry of Health and Welfare and the Korean Government.

We identified all patients older than 20 years who underwent tests for SARS-CoV-2 infection in South Korea between January 1, 2020, and May 15, 2020 (n=214,207). As the pathophysiology of COVID-19 differs between children and adults, we excluded pediatric patients from the analysis [20]. The positive SARS-CoV-2 test results were based on real-time reverse transcriptase-polymerase chain reaction assays of nasal or pharyngeal swabs, following the WHO guidelines [8]. For each identified patient who was tested for SARS-CoV-2 infection,

the cohort entry data (individual index data) included the date of the first SARS-CoV-2 test. Health care records of inpatients and outpatients between January 1, 2017, and May 15, 2020, were combined, and personal data on the age, sex, and region of residence were extracted from the insurance eligibility data.

A history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), hypertension, or chronic kidney disease was identified in at least two claims of inpatients or outpatients, or both, within 1 year using the appropriate International Classification of Disease 10th revision (ICD-10) codes [16,18]. The Charlson Comorbidity Index score was calculated using ICD-10 codes, as reported previously [21]. Use of medication (aspirin, metformin, and systemic glucocorticoids) was defined as taking any of these medications at 1-30 days before the index data. Demographics such as age, sex, and region of residence were obtained from the insurance eligibility data. The region of residence was classified as either urban (Seoul, Sejong, Busan, Incheon, Daegu, Gwangju, Daejeon, and Ulsan) or rural (Gyeonggi, Gangwon, Gyeongsangbuk, Gyeongsangnam, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, and Jeju) [22].

NHIS-COVID-19 Cohort (Interview-Based Cohort)

Data were from individuals aged 20 years or older who underwent a SARS-CoV-2 test through a medical or Korea Centers for Disease Control referral (excluding self-referral) between January 1, 2020, and May 31, 2020, or through a general health examination between January 1, 2019, and December 31, 2019, as registered by the National Health Insurance Service of Korea (n=74,866).

Baseline information was obtained for each individual at the time of the general health examination. A history of diabetes mellitus, stroke, or cardiovascular disease; previous use of medication for hypertension, diabetes mellitus, or cardiovascular disease; smoking habit; physical activity; and frequency of alcohol consumption were obtained via self-reported questionnaires [21]. Body mass index and blood pressure were measured; data on serum glucose, creatinine, total cholesterol, low-density lipoprotein-cholesterol, and high-density lipoprotein-cholesterol were obtained from fasting blood samples [21].

Exposure

We identified all lipophilic (atorvastatin, simvastatin, fluvastatin, lovastatin, and cerivastatin) and hydrophilic (rosuvastatin and pravastatin) statins, prescribed within 1 year before the index data [23]. Statin users were defined as patients who took statins 1-30 days before the index data. Patients who received statins 31-365 days before the index data were excluded [24]. Nonusers were defined as patients who did not take statins 1-365 days before the index data.

Outcomes

The primary outcome was a laboratory-confirmed SARS-CoV-2 positivity, among all patients who were tested. The secondary outcomes were severe outcomes of COVID-19 [25], consisting of intensive care unit admission, invasive ventilation, or death, among patients who tested positive for SARS-CoV-2.

Statistical Analysis

In the GRCP-COVID cohort, we performed each propensity score matching twice to compare SARS-CoV-2 test positivity (primary outcome) with severe clinical outcomes of patients with COVID-19 (secondary outcome), to minimize potential confounding factors and balance the baseline covariates of the 2 groups. First, we assessed the predicted probability of statin users versus nonusers among patients who underwent the SARS-CoV-2 test (n=214,207) using a logistic regression model with adjustment for potential confounding factors by age; sex; region of residence (rural or urban); a history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, COPD, hypertension, or chronic kidney disease; Charlson Comorbidity Index (0, 1, or ≥2); use of aspirin, metformin, or systemic glucocorticoids. Second, we assessed the predicted probability of statin users versus nonusers among patients who tested positive for SARS-CoV-2 (n=7566) with the aforementioned adjustments for potential confounding factors. We performed the matching in the 2 groups in a 1:1 or 1:2 ratio using a "greedy nearest-neighbor" algorithm among all individuals who underwent the SARS-CoV-2 test and among those who tested positive for SARS-CoV-2, respectively, using random selection without replacement within caliper widths of 0.01 SDs.

In the NHIS-COVID cohort, we performed each propensity score matching twice, using the same methods as those used for the GRCP-COVID cohort, with adjustment for potential confounding factors by age (20-59, 60-69, and ≥70 years); sex; region of residence; a history of diabetes mellitus, stroke, cardiovascular disease; Charlson Comorbidity Index; body mass index (<25, 25-30, and ≥30 kg/m^2); systolic blood pressure (continuous); diastolic blood pressure (continuous); fasting blood glucose (continuous); serum total cholesterol (continuous); serum low-density lipoprotein-cholesterol (continuous); serum high-density lipoprotein-cholesterol (continuous); estimated glomerular filtration rate (normal, mildly decreased, and moderately to severely decreased); household income (low, middle, and high); smoking status (never smoker, ex-smoker, and current smoker); frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week); physical activity (0, 1-2, 3-4, 5-6, and 7 sessions per week); and medication for hypertension, diabetes mellitus, or cardiovascular disease.

Adequate propensity score matching was confirmed by comparing propensity score densities (Multimedia Appendix 1) and standardized mean differences (SMDs) [23]. This approach assessed by SMDs is more meaningful than assessing *P* values from *t* tests [21,23]. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.) and R software version 3.1.1 (R Foundation). Two-sided *P* values <.05 were considered statistically significant.

Main Analysis

The "exposure" considered the current use of statin, and the "primary endpoint" was the positive test results for SARS-CoV-2 among all patients who were tested for SARS-CoV-2. The "secondary endpoint" was the severe clinical

outcomes and the length of hospital stay among patients with laboratory-confirmed COVID-19. Data were analyzed using modified Poisson regression models, and adjusted relative risks (aRRs) with 95% CIs for the 2 groups in each propensity score–matched cohort were estimated after adjusting for potential covariates.

Results

Unmatched GRCP-COVID Cohort

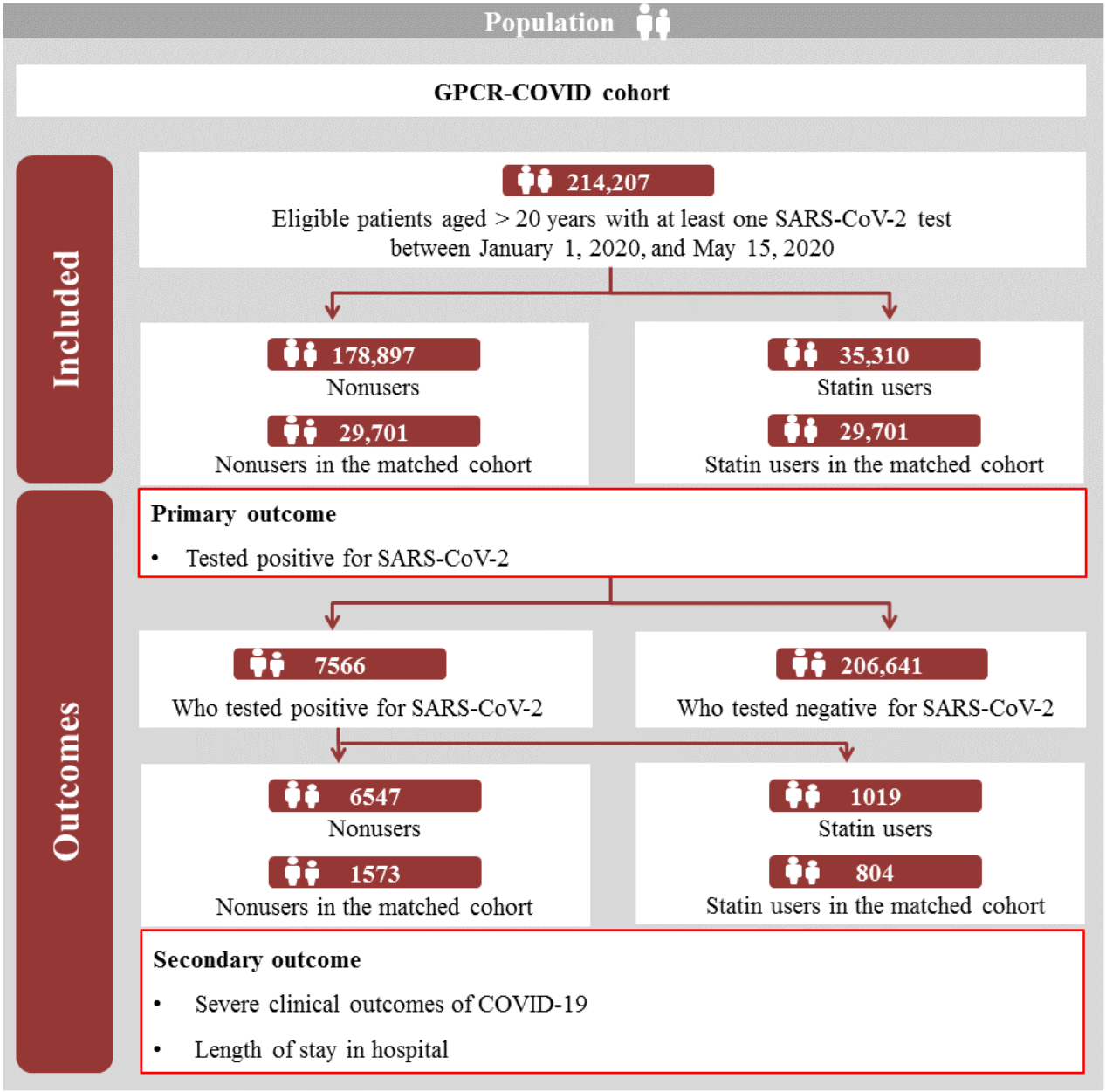
Among patients who underwent SARS-CoV-2 testing (n=214,207), we identified 178,897 nonusers and 35,310 statin users in the full unmatched cohort (Table 1 and Figure 1 and Multimedia Appendix 1). Among patients with laboratory-confirmed COVID-19 (n=7566), we identified 6547 nonusers and 1019 statin users in the full unmatched cohort.

Table 1. Baseline characteristics of all patients who were tested for SARS-CoV-2 infection and of those with laboratory-confirmed SARS-CoV-2 infection in the GRCP[a]-COVID cohort (South Korea; January 1 to May 15, 2020).

Characteristic	Patients tested for SARS-CoV-2 infection (n=214,207)		Patients with laboratory-confirmed SARS-CoV-2 infection (n=7566)	
	Nonusers of statin	Users of statin	Nonusers of statin	Users of statin
Total, n (%)	178,897 (83.52)	35,310 (16.48)	6547 (86.53)	1019 (13.47)
Age in years, mean (SD)	46.0 (19.0)	67.6 (13.6)	43.5 (17.8)	65.5 (13.7)
Sex, n (%)				
Male	84,477 (47.22)	17,004 (48.16)	2996 (45.76)	490 (48.09)
Female	94,420 (52.78)	18,306 (51.84)	3551 (54.24)	529 (51.91)
Region of residence, n (%)				
Rural	79,786 (44.60)	14,216 (40.26)	2492 (38.06)	423 (41.51)
Urban	99,111 (55.40)	21,094 (59.74)	4055 (61.94)	596 (58.49)
History of cardiovascular disease, n (%)	15,969 (8.93)	14,339 (40.61)	448 (6.84)	343 (33.66)
History of cerebrovascular disease, n (%)	10,745 (6.01)	9582 (27.14)	304 (4.64)	250 (24.53)
History of diabetes mellitus, n (%)	17,949 (10.03)	17,293 (48.97)	559 (8.54)	472 (46.32)
History of chronic obstructive pulmonary disease, n (%)	12,106 (6.77)	5511 (15.61)	368 (5.62)	137 (13.44)
History of hypertension, n (%)	35,166 (19.66)	26,694 (75.60)	1083 (16.54)	729 (71.54)
History of chronic kidney disease, n (%)	7856 (4.39)	6190 (17.53)	372 (5.68)	172 (16.88)
Charlson Comorbidity Index, n (%)				
0	116,359 (65.04)	3915 (11.09)	4557 (69.60)	129 (12.66)
1	20,728 (11.59)	4418 (12.51)	717 (10.95)	157 (15.41)
≥2	41,810 (23.37)	26,977 (76.40)	1273 (19.44)	733 (71.93)
Use of medication, n (%)				
Aspirin	5502 (3.08)	9066 (25.68)	112 (1.71)	243 (23.85)
Metformin	7090 (3.96)	10,664 (30.20)	210 (3.21)	322 (31.60)
Systemic glucocorticoids	64,441 (36.02)	14,149 (40.07)	2085 (31.85)	390 (38.27)

[a]GRCP: Global Research Collaboration Project.

Figure 1. Graphical depiction of patient enrollment in the GRCP-COVID cohort (South Korea; January 1 to May 15, 2020). GRCP: Global Research Collaboration Project.



SARS-CoV-2 Test Positivity and Statins in the Matched GRCP-COVID Cohort

After propensity score matching among patients who underwent SARS-CoV-2 testing, we found there were no major imbalances in the baseline covariates between the 2 groups assessed by SMD (Table 2; SMD all <0.1). Among all patients, we identified 29,701 statin users (mean age 67.5 [SD 15.0] years; men, 50.39% [14,966/29,701]) and matched nonusers (mean age, 66.1 [SD 13.8] years; men, 48.89% [14,522/29,701]) in the propensity score–matched cohort. The SARS-CoV-2 test positivity rate was 2.82% (837/29,701) and 2.65% (787/29,701; fully aRR 0.97; 95% CI 0.88-1.07) for statin users and nonusers, respectively (Figure 2).

Table 2. Propensity score–matched baseline characteristics, positive SARS-CoV-2 infection test results, and statin use in all patients who were tested for SARS-CoV-2 infection in the GRCP[a]-COVID cohort (n=59,402; South Korea; January 1 to May 15, 2020).

Characteristic	Nonusers of statin (n=29,701)	Users of statin (n=29,701)	Standardized mean difference[b]
Age, years (SD)	67.5 (15.0)	66.1 (13.8)	0.094
Sex, n (%)			0.030
Male	14,966 (50.39)	14,522 (48.89)	
Female	14,735 (49.61)	15,179 (51.11)	
Region of residence, n (%)			0.005
Rural	12,095 (40.72)	12,031 (40.51)	
Urban	17,606 (59.28)	17,670 (59.49)	
History of cardiovascular disease, n (%)	10,079 (33.93)	10,660 (35.89)	0.049
History of cerebrovascular disease, n (%)	6988 (23.53)	7210 (24.28)	0.021
History of diabetes mellitus, n (%)	12,176 (41.00)	12,597 (42.41)	0.034
History of chronic obstructive pulmonary disease, n (%)	4733 (15.94)	4557 (15.34)	0.019
History of hypertension, n (%)	22,250 (74.91)	21,180 (71.31)	0.087
History of chronic kidney disease, n (%)	4613 (15.53)	4705 (15.84)	0.010
Charlson Comorbidity Index, n (%)			0.015
0	4664 (15.70)	3859 (12.99)	
1	4526 (15.24)	4322 (14.55)	
≥2	20,511 (69.06)	21,520 (72.46)	
Use of medication, n (%)			
Aspirin	4865 (16.38)	5738 (19.32)	0.076
Metformin	5835 (19.65)	6938 (23.36)	0.090
Systemic glucocorticoids	11,923 (40.14)	11,923 (40.14)	<0.001
COVID-19, n (%)[c,d]	787 (2.65)	837 (2.82)	

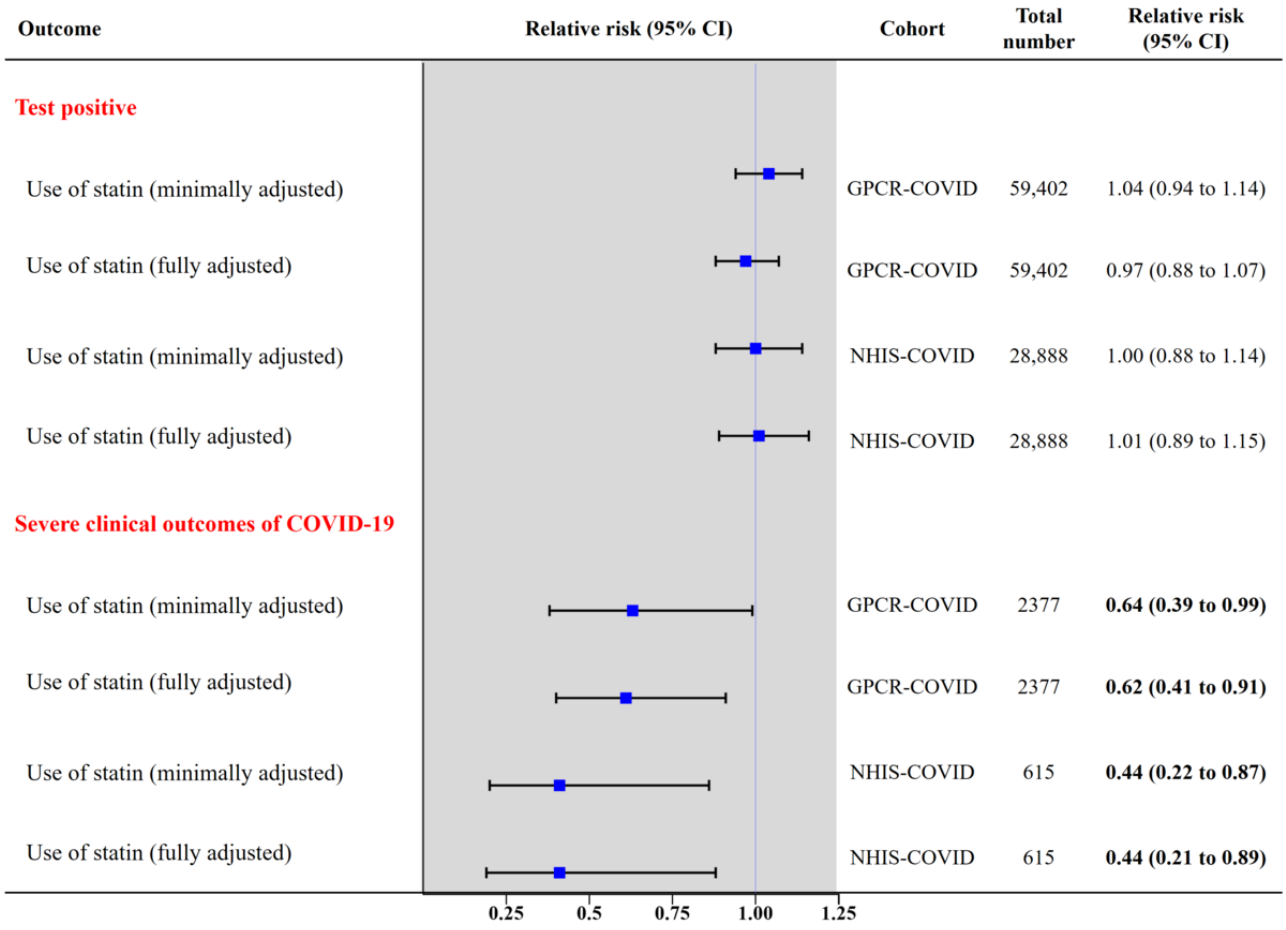
[a]GRCP: Global Research Collaboration Project.

[b]A standardized mean difference (SMD) below 0.1 indicates no major imbalance. All SMD values were less than 0.1 in the propensity score–matched cohort.

[c]Minimally adjusted relative risk (95% CI): 1.04 (0.94-1.14), *P*=.43; risk factors were adjusted for age and sex.

[d]Fully adjusted relative risk (95% CI): 0.97 (0.88-1.07), *P*=.55; risk factors were adjusted for age; sex; region of residence (rural or urban); history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, or chronic kidney disease; Charlson Comorbidity Index (0, 1, or ≥2); and use of aspirin, metformin, or systemic glucocorticoid.

Figure 2. Propensity score-matched association of statin use with (1) positive SARS-CoV-2 test result among patients who underwent SARS-CoV-2 testing (primary outcome), and (2) severe clinical outcomes of COVID-19 among patients who tested positive for SARS-CoV-2 (secondary outcome) in the GPCR-COVID cohort and in the NHIS-COVID cohort (South Korea). Significant values are in bold. GRCP: Global Research Collaboration Project; NHIS: National Health Insurance Service.



Clinical Outcomes in Patients With Laboratory-Confirmed SARS-CoV-2 in the Matched GRCP-COVID Cohort

After propensity score matching among patients who tested positive for SARS-CoV-2, we found there were no major imbalances in the baseline covariates between the 2 groups assessed by SMD (Table 3; SMD all <0.1). Among the patients with laboratory-confirmed COVID-19, the severe clinical outcomes were 3.98% (32/804) and 5.40% (85/1573) for statin users and nonusers, respectively (Figure 2; fully aRR 0.62; 95% CI 0.41-0.91). Moreover, statin users were hospitalized for an average of 23.8 days compared with 26.3 days for nonusers (adjusted mean difference –2.87; 95% CI –5.68 to –0.93).

Table 3. Propensity score–matched baseline characteristics and the composite endpoint with statin use among patients with laboratory-confirmed SARS-CoV-2 infection in the GRCP[a]-COVID cohort (n=2377; South Korea; January 1 to May 15, 2020).

Characteristic	Nonusers of statin (n=1573)	Users of statin (n=804)	Standardized mean difference[b]
Age, years (SD)	63.6 (15.7)	63.7 (13.9)	0.003
Sex, n (%)			0.009
Male	745 (47.4)	377 (46.9)	
Female	828 (52.6)	427 (53.1)	
Region of residence, n (%)			0.006
Rural	647 (41.1)	333 (41.4)	
Urban	926 (58.9)	471 (58.6)	
History of cardiovascular disease, n (%)	410 (26.1)	229 (28.5)	0.054
History of cerebrovascular disease, n (%)	259 (16.5)	163 (20.3)	0.098
History of diabetes mellitus, n (%)	501 (31.8)	294 (36.6)	0.100
History of chronic obstructive pulmonary disease, n (%)	198 (12.6)	103 (12.8)	0.008
History of hypertension, n (%)	957 (60.8)	525 (65.3)	0.093
History of chronic kidney disease, n (%)	263 (16.7)	133 (16.5)	0.006
Charlson Comorbidity Index, n (%)			0.099
0	489 (31.1)	122 (15.2)	
1	203 (12.9)	142 (17.7)	
≥2	881 (56.0)	540 (67.2)	
Use of medication, n (%)			
Aspirin	105 (6.7)	75 (9.3)	0.099
Metformin	194 (12.3)	123 (15.3)	0.087
Systemic glucocorticoids	622 (39.5)	305 (37.9)	0.034
Severe outcomes of COVID-19[c,d,e], n (%)	85 (5.4)[g]	32 (4.0)[g]	
Length of stay for patients in hospital (days), mean (SD)[f]	26.3 (15.7)[g]	23.8 (14.2)[g]	

[a]GRCP: Global Research Collaboration Project.

[b]A standardized mean difference (SMD) below 0.1 indicates no major imbalance. All SMD values were less than 0.1 in the propensity score–matched cohort.

[c]Severe outcomes of COVID-19 consisted of admission to the intensive care unit, invasive ventilation, or death.

[d]Minimally adjusted relative risk (95% CI): 0.64 (0.40 to 0.96), *P*=.04; risk factors were adjusted for age and sex.

[e]Fully adjusted relative risk (95% CI): 0.62 (0.41 to 0.91), *P*=.02; risk factors were adjusted for age; sex; region of residence (rural or urban); histories of diabetes mellitus, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, hypertension, or chronic kidney disease; and Charlson Comorbidity Index (0, 1, or ≥2); and use of aspirin, metformin, or systemic glucocorticoid.

[f]The fully adjusted mean difference (95% CI) was –2.87 (–5.68 to –0.93). Risk factors were adjusted for age and sex.

[g]Statistically significant differences (*P*<.05).

Unmatched NHIS-COVID Cohort

Among patients who underwent SARS-CoV-2 testing (n=74,866), we identified 57,416 nonusers and 17,450 statin users in the full unmatched cohort (Table 4 and Figure 3 and Multimedia Appendix 1). Among patients with laboratory-confirmed COVID-19 (n=2666), we identified 2105 nonusers and 561 statin users in the full unmatched cohort.

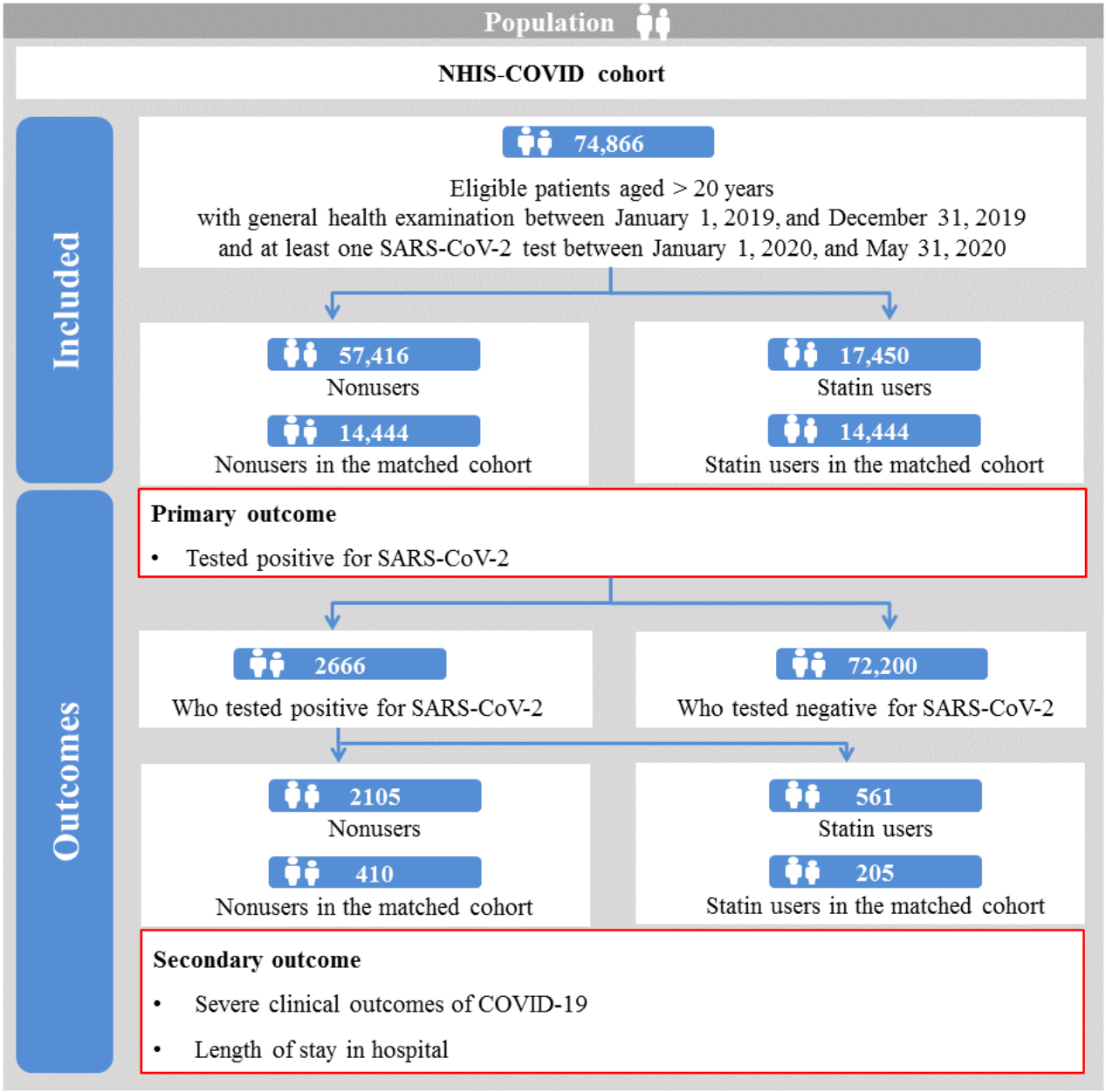
Table 4. Baseline characteristics of all patients who were tested for SARS-CoV-2 infection and of those with laboratory-confirmed SARS-CoV-2 infection in the NHIS[a]-COVID cohort (South Korea; January 1 to May 31, 2020).

Characteristics	Patients tested for SARS-CoV-2 infection (n=74,866)		Patients with laboratory-confirmed SARS-CoV-2 infection (n=2666)	
	Users of statin	Nonusers of statin	Users of statin	Nonusers of statin
Total, n (%)	57,416 (76.69)	17,450 (23.3)	2105 (79.0)	561 (21.0)
Age (years), n (%)				
20-59	38,120 (66.39)	4443 (25.46)	1401 (66.56)	169 (30.12)
60-69	7987 (13.91)	4721 (27.05)	422 (20.05)	187 (33.33)
≥70	11,309 (19.70)	8286 (47.48)	282 (13.40)	205 (36.54)
Sex, n (%)				
Male	28,092 (48.93)	8289 (47.50)	770 (36.58)	202 (36.01)
Female	29,324 (51.07)	9161 (52.50)	1335 (63.42)	359 (63.99)
Region of residence, n (%)				
Rural	20,892 (36.39)	6385 (36.59)	216 (10.26)	39 (6.95)
Urban	36,524 (63.61)	11,065 (63.41)	1889 (89.74)	522 (93.05)
History of diabetes mellitus, n (%)	3603 (6.28)	5227 (29.95)	103 (4.89)	169 (30.12)
History of stroke, n (%)	694 (1.21)	881 (5.05)	13 (0.62)	22 (3.92)
History of cardiovascular disease, n (%)	1215 (2.12)	2531 (14.50)	25 (1.19)	52 (9.27)
Charlson Comorbidity Index, n (%)				
0	37,320 (65.00)	1939 (11.11)	1201 (57.05)	56 (9.98)
1	6660 (11.60)	2181 (12.50)	362 (17.20)	100 (17.83)
≥2	13,436 (23.40)	13,330 (76.39)	542 (25.75)	405 (72.19)
BMI (kg/m^2), n (%)				
<25	38,976 (67.88)	9467 (54.25)	1427 (67.79)	309 (55.08)
25-30	15,524 (27.04)	6652 (38.12)	587 (27.89)	223 (39.75)
>30	2916 (5.08)	1331 (7.63)	91 (4.32)	29 (5.17)
Systolic blood pressure (mmHg), mean (SD)	121.4 (15.2)	128.2 (15.5)	120.4 (15.2)	127.6 (15.4)
Diastolic blood pressure (mmHg), mean (SD)	74.9 (10.1)	76.8 (10.2)	74.4 (10.1)	77.0 (10.1)
Fasting blood glucose (mg/dL), mean (SD)	98.6 (24.7)	112.8 (37.4)	98.5 (25.6)	112.7 (33.5)
Serum total cholesterol (mg/dL), mean (SD)	191.5 (37.1)	182.4 (50.0)	195.3 (35.7)	188.3 (46.5)
Serum low-density lipoprotein cholesterol (mg/dL), mean (SD)	110.8 (33.0)	101.5 (45.5)	115.3 (31.5)	106.6 (42.0)
Serum high-density lipoprotein cholesterol (mg/dL), mean (SD)	56.9 (18.8)	53.5 (16.5)	57.9 (27.3)	56.5 (38.4)
Estimated glomerular filtration rate (mL/min/1.73m^2), n (%)				
Normal (≥90)	29,258 (51.96)	5693 (32.62)	1066 (50.64)	216 (38.50)
Mildly decreased (60-89)	24,714 (43.04)	8962 (51.36)	958 (45.51)	289 (51.52)
Moderately to severely decreased (<59)	3444 (6.00)	2795 (16.02)	81 (3.85)	56 (9.98)
Household income, n (%)				
Low (0th-39th percentile)	15,480 (27.96)	4771 (27.34)	784 (37.24)	185 (32.98)
Middle (40th-79th percentile)	21,313 (37.12)	5227 (29.95)	685 (32.54)	178 (31.73)
High (80th-100th percentile)	20,623 (35.92)	7452 (42.70)	636 (30.21)	198 (35.29)
Smoking, n (%)				

Characteristics	Patients tested for SARS-CoV-2 infection (n=74,866)		Patients with laboratory-confirmed SARS-CoV-2 infection (n=2666)	
	Users of statin	Nonusers of statin	Users of statin	Nonusers of statin
Never smoker	37,145 (64.69)	11,270 (64.58)	1681 (79.86)	419 (74.69)
Ex-smoker	9278 (16.16)	3708 (21.25)	280 (13.30)	101 (18.00)
Current smoker	10,993 (19.15)	2472 (14.17)	144 (6.84)	41 (7.31)
Alcoholic drinks per week, n (%)				
<1	32,184 (56.05)	12,667 (72.59)	1472 (69.93)	423 (75.40)
1-2	18,048 (31.43)	3152 (18.06)	489 (23.23)	94 (16.76)
3-4	4981 (8.68)	1021 (5.85)	103 (4.89)	32 (5.70)
≥5	2203 (3.84)	610 (3.50)	41 (1.95)	12 (2.14)
Physical activity sessions per week, n (%)				
0	29,958 (52.18)	10,061 (57.66)	1154 (54.82)	331 (59.00)
1-2	14,079 (24.52)	2943 (16.87)	469 (22.28)	86 (15.33)
3-4	7563 (13.17)	2301 (13.19)	286 (13.59)	73 (13.01)
5-6	3846 (6.70)	1253 (7.18)	141 (6.70)	39 (6.95)
7	1970 (3.43)	892 (5.11)	55 (2.61)	32 (5.70)
Use of medication, n (%)				
Medication for hypertension, n (%)	9074 (15.80)	8939 (51.23)	266 (12.64)	263 (46.88)
Medication for diabetes mellitus, n (%)	3328 (5.80)	4989 (28.59)	93 (4.42)	159 (28.34)
Medication for cardiovascular disease, n (%)	1028 (1.79)	2400 (13.75)	18 (0.86)	52 (9.27)

[a]NHIS: National Health Insurance Service.

Figure 3. Graphical depiction of patient enrollment in the NHIS-COVID cohort (South Korea; January 1 to May 31, 2020). NHIS: National Health Insurance Service.



SARS-CoV-2 Test Positivity and Statins in the Matched NHIS-COVID Cohort

After propensity score matching among patients who underwent SARS-CoV-2 testing, we found there were no major imbalances in the baseline covariates between 2 groups assessed by SMD (Table 5; SMD all <0.1). Among all patients, we identified 14,444 statin users and matched nonusers in the propensity score–matched cohort. The SARS-CoV-2 test positivity rate was 3.3% (483/14,444) and 3.4% (492/14,444; fully aRR 1.01; 95% CI 0.89-1.15) for statin users and nonusers, respectively (Figure 2).

Table 5. Propensity score–matched baseline characteristics, positive SARS-CoV-2 infection test results, and statin use in all patients who were tested for SARS-CoV-2 infection in the NHIS[a]-COVID cohort (n=28,888; South Korea; January 1 to May 31, 2020).

Characteristic	Nonusers of statins	Users of statins	Standardized mean difference[b]
Total, n	14,444	14,444	
Age (years), n (%)			0.099
20-59	4524 (31.32)	4479 (31.01)	
60-69	2938 (20.34)	3505 (24.27)	
≥70	6982 (48.34)	6460 (44.72)	
Sex, n (%)			0.019
Male	7107 (49.20)	6967 (48.23)	
Female	7337 (50.80)	7477 (51.77)	
Region of residence, n (%)			0.009
Rural	5341 (36.98)	5277 (36.53)	
Urban	9103 (63.02)	9167 (63.47)	
History of diabetes mellitus, n (%)	3002 (20.78)	3434 (23.77)	0.082
History of stroke, n (%)	537 (3.72)	580 (4.02)	0.017
History of cardiovascular disease, n (%)	1013 (7.01)	1367 (9.46)	0.089
Charlson Comorbidity Index, n (%)			0.049
0	2549 (17.65)	1341 (9.28)	
1	1524 (10.55)	1879 (13.01)	
≥2	10,371 (71.80)	11,224 (77.71)	
Body mass index (kg/m^2), n (%)			0.049
<25	7966 (55.15)	8154 (56.45)	
25-30	5167 (35.77)	5331 (36.91)	
>30	1311 (9.08)	959 (6.64)	
Systolic blood pressure (mmHg), mean (SD)	128.5 (16.0)	127.3 (15.3)	0.082
Diastolic blood pressure (mmHg), mean (SD)	77.4 (10.4)	76.6 (10.1)	0.075
Fasting blood glucose (mg/dL), mean (SD)	109.5 (38.2)	109.9 (34.2)	0.013
Serum total cholesterol (mg/dL), mean (SD)	189.7 (38.9)	186.0 (50.9)	0.083
Serum low-density lipoprotein cholesterol (mg/dL), mean (SD)	108.4 (33.5)	105.0 (46.7)	0.088
Serum high-density lipoprotein cholesterol (mg/dL), mean (SD)	53.5 (15.5)	54.0 (17.0)	0.025
Estimated glomerular filtration rate (mL/min/1.73 m^2), n (%)			0.018
Normal (≥90)	5214 (36.10)	5018 (34.74)	
Mildly decreased (60-89)	6976 (48.30)	7468 (51.70)	
Moderately to severely decreased (<59)	2254 (15.61)	1958 (13.56)	
Household income, n (%)			0.005
Low (0th-39th percentile)	3802 (26.32)	4002 (27.71)	
Middle (40th-79th percentile)	4688 (32.46)	4368 (30.24)	
High (80th-100th percentile)	5954 (41.22)	6074 (42.05)	
Smoking, n (%)			0.007
Never smoker	9319 (64.52)	9250 (64.04)	
Ex-smoker	2845 (19.70)	3058 (21.17)	

Characteristic	Nonusers of statins	Users of statins	Standardized mean difference[b]
Current smoker	2280 (15.79)	2136 (14.79)	
Alcoholic drinks per week, n (%)			0.002
<1	10,174 (70.44)	10,192 (70.56)	
1-2	2817 (19.50)	2794 (19.34)	
3-4	909 (6.29)	918 (6.36)	
≥5	544 (3.77)	540 (3.74)	
Physical activity sessions per week, n (%)			0.007
0	8268 (57.24)	8241 (57.05)	
1-2	2555 (17.69)	2541 (17.59)	
3-4	1781 (12.33)	1917 (13.27)	
5-6	1066 (7.38)	1063 (7.36)	
7	774 (5.36)	682 (4.72)	
Use of medication, n (%)			
Medication for hypertension, n (%)	6758 (46.79)	6515 (45.11)	0.038
Medication for diabetes mellitus, n (%)	2797 (19.36)	3246 (22.47)	0.086
Medication for cardiovascular disease, n (%)	904 (6.26)	1280 (8.86)	0.099
COVID-19, n (%)[c,d]	483 (3.34)	492 (3.41)	

[a]NHIS: National Health Insurance Service.

[b]A standardized mean difference (SMD) of less than 0.1 indicates no major imbalance. All SMD values were less than 0.1 in each propensity score–matched cohort.

[c]Minimally adjusted relative risk (95% CI): 1.00 (0.88-1.13), *P*=.99; risk factors were adjusted for age and sex.

[d]Fully adjusted relative risk (95% CI): 1.01 (0.89-1.15), *P*=.89; risk factors were adjusted for age; sex; region of residence (rural and urban); history of diabetes mellitus, stroke, cardiovascular disease; Charlson Comorbidity Index (0, 1, or ≥2); body mass index (<25, 25-30, and ≥30 kg/m^2); systolic blood pressure (continuous); diastolic blood pressure (continuous); fasting blood glucose (continuous); serum total cholesterol (continuous); serum low-density lipoprotein (continuous); serum high-density lipoprotein (continuous); estimated glomerular filtration rate (normal, mildly decreased, and moderately to severely decreased); household income (low, middle, and high); smoking (never smoker, ex-smoker, and current smoker); frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week); physical activity (0, 1-2, 3-4, 5-6, and 7 sessions per week); and medication for hypertension, diabetes mellitus, and cardiovascular disease.

Clinical Outcomes in Patients With Laboratory-Confirmed SARS-CoV-2 in the Matched NHIS-COVID Cohort

After propensity score matching among patients who tested positive for SARS-CoV-2, we found there were no major imbalances in the baseline covariates between the 2 groups assessed by SMD (Table 6; SMD all <0.1), except medication for cardiovascular disease among nonusers versus statin users (SMD 0.120). Among the patients with laboratory-confirmed COVID-19, the severe clinical outcomes were 5.4% (11/205) and 12.2% (50/410) for statin users and nonusers, respectively (Figure 2; fully aRR 0.44; 95% CI 0.21-0.89). Moreover, statin users were hospitalized for an average of 23.9 days compared with 26.3 days for nonusers (adjusted mean difference –2.53; 95% CI –5.54 to –0.37).

Table 6. Propensity score–matched baseline characteristics and the severe clinical outcomes with statin use among patients with laboratory-confirmed SARS-CoV-2 infection in the NHIS[a]-COVID cohort (n=615; South Korea; January 1 to May 31, 2020).

Characteristic	Nonusers of statins (n=410)	Users of statins (n=205)	Standardized mean difference[b]
Age (years), n (%)			0.011
20-59	175 (42.7)	88 (42.9)	
60-69	121 (29.5)	61 (29.8)	
≥70	114 (27.8)	56 (27.3)	
Sex, n (%)			0.081
Male	132 (32.2)	74 (36.1)	
Female	278 (67.8)	131 (63.9)	
Region of residence, n (%)			0.043
Rural	39 (9.5)	17 (8.3)	
Urban	371 (90.5)	188 (91.7)	
History of diabetes mellitus, n (%)	40 (9.8)	24 (11.7)	0.063
History of stroke, n (%)	4 (1.0)	3 (1.5)	0.044
History of cardiovascular disease, n (%)	8 (2.0)	7 (3.4)	0.091
Charlson Comorbidity Index , n (%)			0.077
0	98 (23.9)	42 (20.5)	
1	107 (26.1)	59 (28.8)	
≥2	208 (50.7)	104 (50.7)	
Body mass index (kg/m^2), n (%)			0.090
<25	251 (61.2)	128 (62.4)	
25-30	140 (34.1)	71 (34.6)	
>30	19 (4.6)	6 (2.9)	
Systolic blood pressure (mmHg), mean (SD)	125.1 (15.6)	123.7 (15.5)	0.090
Diastolic blood pressure (mmHg), mean (SD)	77.2 (10.4)	76.3 (10.4)	0.086
Fasting blood glucose (mg/dL), mean (SD)	105.6 (29.4)	102.8 (20.6)	0.093
Serum total cholesterol (mg/dL), mean (SD)	201.0 (37.8)	203.0 (49.5)	0.050
Serum low-density lipoprotein cholesterol (mg/dL), mean (SD)	117.9 (33.3)	121.5 (43.7)	0.093
Serum high-density lipoprotein cholesterol (mg/dL), mean (SD)	58.2 (16.8)	58.2 (52.1)	<0.001
Estimated glomerular filtration rate (mL/min/1.73 m^2), n (%)			0.067
Normal (≥90)	171 (41.7)	81 (39.5)	
Mildly decreased (60-89)	207 (50.5)	110 (53.7)	
Moderately to severely decreased (<59)	32 (7.8)	14 (6.8)	
Household income, n (%)			0.096
Low (0th-39th percentile)	141 (34.4)	68 (33.2)	
Middle (40th-79th percentile)	141 (34.4)	64 (31.2)	
High (80th-100th percentile)	128 (31.2)	73 (35.6)	
Smoking, n (%)			0.084
Never smoker	318 (77.6)	155 (75.6)	
Ex-smoker	66 (16.1)	39 (19.0)	
Current smoker	26 (6.3)	11 (5.4)	

Characteristic	Nonusers of statins (n=410)	Users of statins (n=205)	Standardized mean difference[b]
Alcoholic drinks per week, n (%)			0.080
<1	314 (76.6)	153 (74.6)	
1-2	70 (17.1)	39 (19.0)	
3-4	19 (4.6)	8 (3.9)	
≥5	7 (1.7)	5 (2.4)	
Physical activity sessions per week, n (%)			0.085
0	233 (56.8)	118 (57.6)	
1-2	85 (20.7)	37 (18.0)	
3-4	59 (14.4)	34 (16.6)	
5-6	22 (5.4)	11 (5.4)	
7	11 (2.7)	5 (2.4)	
Use of medication, n (%)			
Medication for hypertension, n (%)	102 (24.9)	46 (22.4)	0.057
Medication for diabetes mellitus, n (%)	36 (8.8)	22 (10.7)	0.066
Medication for cardiovascular disease, n (%)	5 (1.2)	6 (2.9)	0.120
Severe clinical outcomes of COVID-19, n (%)[c,d]	50 (12.2)[e]	11 (5.4)[e]	
Length of stay for patients in hospital (days), mean (SD)	26.3 (15.7)[e]	23.9 (14.3)[e]	

[a]NHIS: National Health Insurance Service.

[b]A standardized mean difference (SMD) below 0.1 indicates no major imbalance. All SMD values were less than 0.1 in the propensity score–matched cohort, except medication for cardiovascular disease among nonusers versus statin users.

[c]Minimally adjusted relative risk (95% CI): 0.44 (0.22-0.87), *P*=.02; risk factors were adjusted for age and sex.

[d]Fully adjusted relative risk (95% CI): –2.53 (–5.54 to –0.37); *P*=.03; risk factors were adjusted for age; sex; region of residence (rural and urban); history of diabetes mellitus, stroke, cardiovascular disease; Charlson Comorbidity Index (0, 1, or ≥2); body mass index (<25, 25-30, and ≥30 kg/m^2); systolic blood pressure (continuous); diastolic blood pressure (continuous); fasting blood glucose (continuous); serum total cholesterol (continuous); serum low-density lipoprotein (continuous); serum high-density lipoprotein (continuous); estimated glomerular filtration rate (normal, mildly decreased, and moderately to severely decreased); household income (low, middle, and high); smoking (never smoker, ex-smoker, and current smoker); frequency of alcohol consumption (<1, 1-2, 3-4, 5-6, and 7 times per week); physical activity (0, 1-2, 3-4, 5-6, and 7 sessions per week); and medication for hypertension, diabetes mellitus, and cardiovascular disease.

[e]Statistically significant differences (*P*<.05).

Discussion

Principal Findings

Among those in the GRCP-COVID cohort (n=214,207) and NHIS-COVID cohort (n=74,866) who underwent SARS-CoV-2 testing, 16.5% (35,310/214,207) and 23.3% (17,450/74,866) were currently taking statins, respectively. We examined the potential association between positive SARS-CoV-2 test results with the current use of statins in the propensity score–matched cohort (GRCP-COVID, n=59,402; NHIS-COVID, n=28,888) and clinical outcomes of patients with COVID-19 taking statins in the propensity score–matched cohort (GRCP-COVID, n=2377; NHIS-COVID, n=615). After controlling for various confounding variables using propensity matching and statistical adjustment, the use of statins was associated with improved clinical outcomes of COVID-19 and decreased length of hospital stay but not with the risk of susceptibility to SARS-CoV-2 infection.

This study demonstrated that statin use was associated with improved clinical outcomes and decreased length of hospital stay in patients with COVID-19. Many plausible pathophysiology could contribute to the association of statin use with COVID-19 outcomes.

The entry of SARS-CoV-2 is initiated by the binding of viral spike protein to the cellular receptor ACE2 [26]. The intracellular invasion of SARS-CoV-2 via ACE2 downregulates the expression of ACE2, which results in disinhibition of angiotensin II [27]. This, in turn, induces vasoconstriction of lung vasculatures as well as increases vascular permeability and inflammation, thereby leading to lung injury [28]. Statins are known to upregulate ACE2, and thus are recognized as promising antiviral agents [11].

Immune modulatory effects of statins may influence recovery from COVID-19. COVID-19 is accompanied by the activation of the immune system and the elevation of inflammatory cytokines, such as C-reactive protein, ferritin, and interleukin-6 (IL-6) [29], and could induce a severe catastrophe response with hyperinflammation, namely, the “cytokine storm” [30]. Thus, controlling host response and restoring immune homeostasis may be crucial to reduce the severity of COVID-19. In this

context, the control of host response using immune modulation is a promising therapeutic option for SARS-CoV-2 infection [31]. By affecting chemokine secretion and expression of adhesion molecules, such as lymphocyte function–associated antigen 1 and intercellular adhesion molecule 1, statins could modulate immune cell trafficking to the airways [32]. Moreover, statins could suppress the activation of Th1 cells and interferon-γ (a key player of the chronic inflammation) [33], and downregulate major histocompatibility complex class II expression in the airway including B cells [31]. Therefore, statins were reported to be effective in treating immune disorders, such as multiple sclerosis [34] and rheumatoid arthritis [35]. This evidence of widespread anti-inflammatory effects implies that long-term use of statins could act as a shield to protect patients from severe cascades of inflammation represented by the cytokine storm [11].

Statins are a well-known class of drugs that protect the vascular endothelium from reactive oxygen species [36]. A major effect of statins on endothelial cells is the decreased number of reactive oxygen species due to the downregulation of endothelin-1 expression, and decreased proinflammatory cytokines (eg, IL-1β, IL-6) [36]. Additionally, statins are known to suppress the expression of caveolin-1, a key component of endothelial cell transcytosis [37], which may ameliorate the vascular hyperpermeability induced by the inflammatory manifestations of SARS-CoV-2 infection. These vasoprotective effects of statins may prevent pulmonary edema and other lung injuries that may eventually lead to acute respiratory distress syndrome, a major cause of death in COVID-19.

Numerous studies have reported the effects of statins on clinical improvements in viral infections, namely, Ebola (positive association) [38], influenza (no association) [39], pneumonia (positive association [40] and no association [41,42]), acute respiratory distress syndrome (no association in the entire group [43], but positive association in a subgroup analysis, namely, a hyperinflammatory subphenotype [44]), hepatitis (positive association [45]), and hepatocellular carcinoma in patients with hepatitis (positive association [23]). However, previous studies on the association of statins with the clinical outcomes of pneumonia were limited by limited sample size [42], restricted clinical outcomes (mortality in ventilator-associated patients with pneumonia [41] or elevation of cytokine levels [42]), or by a focus on specific statin types [41,42].

A recent previous study reported the beneficial association between in-hospital use of statin and mortality in patients with COVID-19 [15], which is consistent with our results. However, unlike our study, this previous study did not analyze statin use before SARS-CoV-2 infection contraction.

Limitations

This study has some limitations. First, the GRCP-COVID cohort had a maximum follow-up duration less than 3 years, whereas the history of statin use can span decades. For rapid data acquisition and real-time analysis in this global crisis, the Korean Government provides relatively short-term histories (maximum 3 years) of patients with COVID-19. Second, in the GRCP-COVID cohort, the serum lipid profiles of patients were not accessible. However, the Korean National Health Insurance program has strict regulations regarding reimbursement for the treatment of hyperlipidemia that count the risk factors and consider the serum cholesterol levels. This makes the inclusion of the patients with dyslipidemia very robust. Third, important missing covariates included smoking status, blood pressure levels, biomarkers including basal sugar levels, and factors that could influence the outcomes of COVID-19. To overcome this issue, we adjusted the statistics by obtaining the histories of hypertension, diabetes, and COPD, a well-known smoking-associated disorder, verified by ICD codes. Fourth, our analysis lacked the evaluation of patient adherence to statins based on either the medical record or the questionnaire. Further meticulous review of data including the drug adherence is necessary to overcome this issue. Fifth, our analysis lacked personal information of the socioeconomic status (education level and household income) of the patients, which might affect the treatment compliance of patients with COVID-19. However, all COVID-19–related costs were provided complimentarily by the Korean Government; thus, the impact of the socioeconomic status of the patients on the clinical outcomes of COVID-19 may be minimal. Sixth, we were unable to obtain full information about all baseline variables on the index date in the NHIS-COVID cohort; therefore, the values of time-varying variables might differ from their values on the index date. To overcome this issue, we used the data measured on the date closest to the index date as the baseline data. Besides, we did not investigate whether statin medication was continued while the patients were hospitalized. A further study is warranted to clarify this issue. Seventh, as our study cohort involves patients tested for SARS-CoV-2, there was potential for ascertainment bias wherein those who have pre-existing health conditions (some necessitating statins) may have greater COVID-19 awareness, and be more likely to undergo screening, and be referred to care settings. However, the prevalence of patients with statin use (GRCP-COVID cohort, 16.48% [35,310/214,207]) is comparable to a nationally representative cohort of the general US population aged over 20 years (17.23%) [46]. Furthermore, we performed meticulous adjustment of systemic factors by using double-propensity score matching and fully adjusted regression analysis to overcome prevalence-related bias in the group comparisons. Eighth, the possibility of selection bias during the propensity matching process cannot be excluded. Because statins are one of the popular drugs for chronic diseases, such as cardiovascular disease, cerebrovascular disease, and diabetes mellitus, matching on these covariates could select control participants who had similar medical profiles but were not prescribed statins. Although similar medical profiles between nonusers and statin users reveal the direct effect of statin usage, the possibility of selection bias remains. Lastly, every patient involved in this study was Asian in ethnicity. Therefore, our results may not be extrapolatable to different ethnicities. However, the effect of statin use was reported to be effective regardless of the ethnic background [47]. Further studies of large cohorts involving diverse populations are warranted to clarify this issue.

Another limitation was that although the NHIS-COVID cohort had more key covariates than the GRCP cohort (ie, serum glucose, lipid profile, body mass index, household income, smoking status, physical activity status, and frequency of alcohol

consumption), the total sample size (n=74,866) was less than that of the GRCP-COVID cohort (n=214,207). Finally, although 2 organizations (NHIS and Health Insurance Review and Assessment Service [HIRA]) independently constructed the cohorts, there is a possibility that patient data may have been duplicated.

Conclusions

Statins are inexpensive and readily available therapeutic agents. Despite the aforesaid limitations, our study highlights for the first time the potential protective effects of previous statin use on the clinical outcomes of patients with COVID-19. Two large cohort studies provided clinical evidence that previous and current statin use is associated with decreased risks of severe COVID-19 outcomes; one study used claims-based data (GRCP-COVID cohort) and the other used interview-based data (NHIS-COVID cohort), with propensity score matching. Furthermore, our study included a large number of patients and well-designed statistical techniques were implemented. Thus, our use of 2 independent cohorts increases the generalizability and reliability of our results, and this makes the results of this study robust and reliable.

Prior statin use was associated with a decreased likelihood of severe clinical outcomes of COVID-19 and a shorter length of hospital stay. Our well-designed observational study suggests that the use of statins may play a potential protective role for patients with COVID-19 and that randomized controlled trials of the therapeutic use of statins for COVID-19 are warranted.

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Authors' Contributions

DY, JY, and SL had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. DY was responsible for study concept and design. SL and SM performed acquisition, analysis, or interpretation of data. SK, JY, and DY drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. SL, SM, and DY performed statistical analysis. DY, JY, and SL are corresponding authors (DY, yonkkang@gmail.com; JY, jeemang87@gmail.com; and SL, swlsejong@sejong.ac.kr).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary figures.
[DOCX File , 1389 KB - publichealth_v7i10e29379_app1.docx]

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Abbreviations

ACE2: angiotensin-converting enzyme 2
aRR: adjusted relative risk
BCG: bacillus Calmette–Guérin
COPD: chronic obstructive pulmonary disease
GRCP: Global Research Collaboration Project
HIRA: Health Insurance Review and Assessment Service
ICD-10: International Classification of Disease 10th revision
IL: interleukin
NHIS: National Health Insurance Service
SMD: standardized mean difference
WHO: World Health Organization

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Original Paper

Development and Actionability of the Dutch COVID-19 Dashboard: Descriptive Assessment and Expert Appraisal Study

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Abstract

Background: Web-based public reporting by means of dashboards has become an essential tool for governments worldwide to monitor COVID-19 information and communicate it to the public. The actionability of such dashboards is determined by their fitness for purpose—meeting a specific information need—and fitness for use—placing the right information into the right hands at the right time and in a manner that can be understood.

Objective: The aim of this study was to identify specific areas where the actionability of the Dutch government's COVID-19 dashboard could be improved, with the ultimate goal of enhancing public understanding of the pandemic.

Methods: The study was conducted from February 2020 to April 2021. A mixed methods approach was carried out, using (1) a descriptive checklist over time to monitor changes made to the dashboard, (2) an actionability scoring of the dashboard to pinpoint areas for improvement, and (3) a reflection meeting with the dashboard development team to contextualize findings and discuss areas for improvement.

Results: The dashboard predominantly showed epidemiological information on COVID-19. It had been developed and adapted by adding more in-depth indicators, more geographic disaggregation options, and new indicator themes. It also changed in target audience from policy makers to the general public; thus, a homepage was added with the most important information, using news-like items to explain the provided indicators and conducting research to enhance public understanding of the dashboard. However, disaggregation options such as sex, socioeconomic status, and ethnicity and indicators on dual-track health system management and social and economic impact that have proven to give important insights in other countries are missing from the Dutch COVID-19 dashboard, limiting its actionability.

Conclusions: The Dutch COVID-19 dashboard developed over time its fitness for purpose and use in terms of providing epidemiological information to the general public as a target audience. However, to strengthen the Dutch health system's ability to cope with upcoming phases of the COVID-19 pandemic or future public health emergencies, we advise (1) establishing timely indicators relating to health system capacity, (2) including relevant data disaggregation options (eg, sex, socioeconomic status), and (3) enabling interoperability between social, health, and economic data sources.

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KEYWORDS

COVID-19; dashboard; performance intelligence; Netherlands; actionability; communication; government; pandemic; public health

Introduction

In response to the COVID-19 pandemic, caused by the infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that emerged in 2019, governments worldwide have been forced to take measures that impact the lives of individuals in order to protect the health of their citizens. Making the right COVID-19 policy decisions requires a balanced trade-off between protecting the population from infection and its consequences, ensuring that non-COVID-19 care needs are met (dual-track capacity monitoring), and minimizing socioeconomic impacts [1]. Web-based public reporting by means of dashboards has become an essential tool for monitoring COVID-19 information and communicating it to the public [2-4]. Moreover, dashboards are used to support individuals in informed decision making, for instance to educate citizens on whether they need to adapt their behaviors to minimize individual and population risk [5]. As such, dashboards are a powerful communication tool, and they are also frequently used by media as key information sources. If, however, information in dashboards is based on suboptimal reporting practices (eg, incomplete or unreliable reporting of data), it could produce undesirable effects, such as misleading perceptions, stress, or anxiety [6-9]. Users of dashboards must therefore be assured of complete, valid, reliable, and balanced information that can support them in making informed decisions as they deal with the pandemic. Information can be actionable only if it is fit for purpose and fit for use. Important determinations in the development of dashboards therefore include the selection and standardization of indicators at national and international levels, sources of data collection, analysis of data, and visualization techniques chosen to display the data [9,10]. The World Health Organization (WHO) advised 4 key types of information needed to effectively manage transitions and modulate restrictive measures over the course of the COVID-19 pandemic: (1) public health and epidemiological, (2) health system management, (3) behavioral insights, and (4) social and economic impact [11].

In mid-2020, an international network of performance intelligence researchers [12], to which the authors of this paper belong, carried out a global study to assess the actionability of 158 COVID-19 dashboards at international, national, and regional levels in 53 countries worldwide [13]. Actionability refers to a dashboard's potential to inform decision making by way of providing information that is both *fit for purpose*—meeting a specific information need—and *fit for use*—placing the right information into the right hands at the right time and in a manner that can be understood [14]. The study identified 7 features that were common to highly actionable dashboards: (1) knowing the audience and their information needs; (2) managing the type, volume, and flow of displayed information; (3) reporting data sources and methods clearly; (4) linking time trends to policy decisions; (5) providing "data close to home"; (6) disaggregating the information into relevant subgroups; (7) using storytelling and visual cues.

The international dashboard study also found that there was overlap in indicators between the international dashboards, being that most dashboards portrayed case numbers, hospital admissions, and deaths due to COVID-19. Yet, little is currently known about how dashboards have improved their content and actionability over the course of the pandemic and what guided the decisions that were made in the development of the dashboards. This will very likely be context-dependent, thus a closer look at a specific country context can provide insight into the "why" of COVID-19 dashboard development. One study has looked at the development of Canadian COVID-19 dashboards and concluded that data availability and dashboard technology witnessed the most improvements. However, no improvements were found in communicative elements [15]. The development of the Dutch government's COVID-19 dashboard, led by the Ministry of Health, Welfare and Sport, is continuously evolving in which publicly available feedback from expert panels [16] and from surveys among the public [17,18] are used to further develop the dashboard's content and its communication strategy. This makes it an interesting case study for research. With this study, we set out to evaluate how the Dutch COVID-19 dashboard developed from its launch on June 5, 2020 through January 31, 2021, to assess its actionability, and to understand what factors guided decisions during the dashboard's development.

Those objectives translated into the following research questions: (1) How did the Dutch COVID-19 dashboard develop over the course of the pandemic from its launch on June 5, 2020 to January 31, 2021? (2) How actionable is the Dutch COVID-19 dashboard, based on its December 2020 version, reflecting on features of highly actionable COVID-19 dashboards? (3) What decisions were made in the development of the COVID-19 dashboard by its developers and why?

This study aimed to improve the Dutch COVID-19 dashboard's actionability in order to enhance public understanding of the pandemic.

Methods

Scope and Study Setting

This study focused on the development of the Dutch government's COVID-19 dashboard [19] from June 5, 2020 (launch) to January 31, 2021. The first confirmed COVID-19 patient in the Netherlands was reported on February 27, 2020 to the House of Representatives by the Minister for Medical Care [20]. Hygiene and safety recommendations announced on March 9, 2020 at a press conference by the Dutch prime minister, accompanied by the director of the National Institute for Public Health and the Environment (RIVM), were rapidly followed by a number of policy measures to enforce physical distancing, impose travel restrictions, and establish case management and quarantine policies to contain the spread of the SARS-CoV-2 virus. In the weekly COVID-19 mortality numbers, a first peak was seen from mid-March to late May 2020, followed by relatively low numbers during the summer months of June to September, with numbers increasing again from October 2020 [21]. The COVID-19 measures taken by the government reflect these 2 high-burden periods, showing a pause or partial loosening for most measures in the June to September period [22,23]. In the management of the pandemic, the national government is advised by an Outbreak Management Team coordinated by the RIVM and works closely together

with the 25 safety regions that, by law, have a responsibility for regional disaster management [24].

In May 2020, in addition to existing Dutch websites providing information on the pandemic [25-27], the Minister of Health, Welfare and Sport proposed a dedicated COVID-19 dashboard with the aim of keeping track of the pandemic and informing policy decisions to the House of Representatives [21]. On June 5, 2020, a test version of the official Dutch government dashboard for COVID-19 (entitled *Coronadashboard*) was launched for the general public [21].

Descriptive Assessment of the Development of the COVID-19 Dashboard by the Netherlands Ministry of Health, Welfare and Sport Over Time

To examine the development of the Dutch COVID-19 dashboard, 3 points in time were chosen for our descriptive assessment. The first was conducted on July 16, 2020, approximately 1 month after the dashboard's launch, and was part of our international study of COVID-19 dashboards [28]. The second was on December 23, 2020, amid new containment measures, and the third was on January 31, 2021, just after vaccinations had commenced. The dashboard website was archived at these time points (Multimedia Appendix 1). We used the descriptive checklist developed and validated in the international dashboard study (see Multimedia Appendix 2 for the checklist and its measures) [28]. The tool was based on communication theory (notably on Lasswell's Model from 1948 [29]), the discipline of performance intelligence in health [30,31], and existing evidence on performance indicators, public reporting, and the use of dashboards [28]. In addition to general and context aspects, the tool focuses on whether the purpose of the dashboard and the type of users are noted, what indicators are presented, whether metadata and the sources are made available, what disaggregation options are presented, and the use of visualization techniques.

Actionability Appraisal of the COVID-19 Dashboard

To appraise the actionability of the Dutch COVID-19 dashboard, we rated it in terms of the 7 common features of highly actionable COVID-19 dashboards (Table 1) [28].

Table 1. Seven common features of highly actionable dashboards.

Number	Feature[a]	Explanation
1	Knowing the audience and their information needs	Dashboards with a known audience and explicit aim had focus and continuity in their content, analysis, and delivery. Techniques such as guiding key questions or overall composite scores clearly communicated the decision they intended to support. Multilanguage functionality and exact timing of updating signaled an awareness and intent to encourage their regular use by the intended decision maker.
2	Managing the type, volume, and flow of displayed information	The selection of a concise number of indicators brought focus and importance to the information and the possibility to view indicators together at a glance. The use of indicators in moderation, although still spanning varied types of information, was especially effective. The ordering of information, from general to specific or in sections based on theme, made the flow of information intuitive.
3	Reporting data sources and methods clearly	A clear source of data and explanation of an indicator's construction, including potential limitations, was found to be an important component of trust in the dashboard and clarity in its reporting. This information can be provided in short narratives that support users to understand what is in fact being presented.
4	Linking time trends to policy decisions	Reporting data over time together with the introduction of key infection control measures facilitated an understanding of their effect (or lack thereof). This was found to be conducive to generating public support for infection control measures.
5	Providing data "close to home"	To inform individuals of risks in their immediate surroundings, granular geographic breakdowns are needed. Data that are highly aggregated are difficult to understand. Maps (over tables and charts) were most effective to provide geographic information.
6	Disaggregating the information into relevant subgroups	Providing data with the possibility to explore varied population characteristics made indicators relatable to individual users. It enables understanding of risks and trends based on one's own demographics. It can also facilitate equity-driven decision making by exposing differences among the population.
7	Using storytelling and visual cues	A concise narrative explaining the significance of a trend supports users to understand the importance of the information. Bare statistics without a narrated analysis leave the burden of interpretation solely to the user. Brief explanations on the meaning of trends used in combination with visual techniques, such as intuitive color schemes and icons, supported ease of interpretation.

[a]As identified by [28].

Two individual researchers (VB and TJ) marked these as either not present, somewhat present, or clearly present and provided argumentation for the ratings in free text. The actionability scoring was performed on December 17, 2020 (see Multimedia Appendix 2 for links to the archive). After their individual scorings, they shared and discussed their findings. Discrepancies in scorings were discussed between the 2 researchers and resulted in either an agreement for the score or an agreement to clarify discrepancies in the concluding qualitative appraisal for each of the 7 features.

Appraisal Validation and Expert Reflections on the Decisions Made Throughout the Development Process of the COVID-19 Dashboard

A reflection meeting with the project team of the Ministry of Health, Welfare and Sport responsible for the COVID-19 dashboard was organized on April 23, 2021, with the following

aims: to verify the appraisal of the dashboard's actionability, to reflect on the development of the COVID-19 dashboard, and to understand decisions that were made towards the development of the dashboard. The project lead and 2 members of the team were present at the meeting. First, the study team presented the previously identified 7 key features of actionable dashboards. Second, the dashboard team shared their general reflection on the development of the dashboard from launch to date. Finally, the actionability appraisal of the 7 features of actionable dashboards were discussed in-depth. Due to COVID-19 restrictions, the meeting was conducted digitally. The meeting was moderated by NK, and notes were taken by TJ and VB. The Dutch dashboard scoring and appraisal for the 7 features were shared with the team in advance.

Results

Development of the COVID-19 Dashboard Over Time

Table 2 shows the findings of the descriptive assessment of the Dutch COVID-19 dashboard at 3 points in time.

Table 2. Descriptive checklist for the Dutch COVID-19 dashboard at 3 points in time.

Checklist items	Assessment date		
	1 (July 16, 2020)	2 (December 23, 2020)	3 (January 31, 2021)
Purpose and users			
Purpose of dashboard use specified	Yes	Yes	Yes
Intended audience or users specified	No	No	No
Content	2 themes, 10 indicators (80% epidemiological)	6 themes, 14 subthemes, and 59 indicators (78% epidemiological)	1 title page, 6 themes, 14 subthemes, and 63 indicators (79% epidemiological)
Indicator themes: subthemes (in order of occurrence on dashboard)	Intensive care admissions[a], hospital admissions[a], positive tested cases per 100,000 inhabitants[a], reproduction number R[a], amount of infectious people (estimated total and per 100,000 inhabitants)[a]; other data: number of patients for which GP[b] suspects COVID-19 and sewage measurements of COVID-19 presence; nursing homes: amount of infections among nursing home residents, amount of nursing homes with at least one infection, deaths among nursing home residents	General: latest developments and active measures; infections: confirmed cases, infectious people, reproduction number, deaths; hospitals: hospital admissions and intensive care admissions; vulnerable groups: nursing care, disability care, people over 70 years old living at home; early signals: sewage water testing, GP-reported symptoms; behavior: compliance and behavior	Measures[a]; vaccinations; infections: confirmed cases, infectious people, reproduction number, deaths; hospitals: hospital admissions and intensive care admissions; vulnerable groups: nursing care, disability care, people over 70 years old living at home; early signals: sewage water testing, GP-reported symptoms; behavior: compliance and behavior
Data sources	Data sources specified: yes; data open-source: yes, most data; metadata specified: yes	Data sources specified: yes; data open-source: yes, most data; metadata specified: yes	Data sources specified: yes; data open-source: yes, most data; metadata specified: yes
Analysis and display			
Time trends	Time trend analysis available: yes, after a few clicks; customizable: No	Time trend analysis available: yes, after a few clicks; customizable: yes	Time trend analysis available: yes, directly available; customizable: yes
Geographic levels of analysis	National: yes, full; safety regions: yes, very limited; municipalities: no	National: yes, full; safety regions: yes, partial; municipalities: yes, partial	National: yes, full; safety regions: yes, partial; municipalities: yes, partial
Disaggregation options	1 disaggregation option: long-term care facilities	4 disaggregation options: age, long-term care facilities, disability care facilities, over-70s living at home	4 disaggregation options: age, long-term care facilities, disability care facilities, over-70s living at home
Type of visualization	Maps, graphs, and charts to visualize indicators	Maps, graphs, and charts to visualize indicators	Maps, graphs, and charts to visualize indicators
Interpretation	Clarifying the quality of data: yes, in separate document and occasionally on dashboard itself; clarifying the meaning: yes, for some indicators; providing contextualization: no	Clarifying the quality of data: yes, in separate document and occasionally on dashboard itself; clarifying the meaning: yes, for almost every indicator; providing contextualization: no	Clarifying the quality of data: yes, in separate document and occasionally on dashboard itself; clarifying the meaning: yes, for every indicator; providing contextualization: yes, via news-like “stories”
Simplification techniques	Color coding: yes; icons: large icons for themes (eg, a head-and-test swab icon denoting testing indicators)	Color coding: yes; icons: large icons for themes (eg, a head-and-test swab icon denoting testing indicators) and small icons (eg, up and down arrows for changes)	Color coding: yes; icons: large icons for themes (eg, a head-and-test swab icon denoting testing indicators) and small icons (eg, up and down arrows for changes)
Interactive options	More information: yes; change of information: no; change of display: no	More information: yes; change of information: yes; change of display: yes	More information: yes; change of information: yes; change of display: yes

[a]Presented as subthemes.

[b]GP: general practitioner.

Purpose and Users

A general statement of purpose was found at all 3 points in time. The statement highlighted the severity of the COVID-19 pandemic and explained the need to create a dashboard in order to use information to monitor the virus and to ensure that measures would be taken only where appropriate. The statement also emphasized that a political assessment of all relevant aspects was to include broader social and economic interests (see Multimedia Appendix 1 for archives). The target audience for the dashboard was not explicitly stated.

Content and Data

The number of indicators available on the dashboard increased over time, from 10 to 63 indicators. Both new themes were included (such as behavior and vaccinations), and the level of detail and stratification of previously available indicator themes was expanded (such as deaths, with an added indicator of excess mortality). The dashboard's focus was mainly on epidemiological indicators (at different time points: 80%, 78%, and 79%, respectively), such as infection incidence numbers, reproduction rate, estimated number of infectious persons, and deaths. Health system capacity indicators included COVID-19 patients (such as numbers admitted to hospitals) and did not address non-COVID care needs. During our study, 4 social and behavioral indicators were added (added from December 10, 2020), such as percentage supporting wearing masks in public transport and percentage adhering to wearing a mask in public transport. These indicators showed self-reported survey outcomes on the compliance with and support for the COVID-19 measures taken by the government, based on data collected by the RIVM. No indicators relating to the social and economic impacts of the pandemic were observed.

Data sources were noted at all 3 points in time, and the data used in the dashboard were largely open-source. Metadata were provided in a separate document.

Analysis and Display of Data

The time trend information became more detailed over time. Customizable time trends and comparisons of indicator outcomes with outcomes for previous weeks, days, 2-day periods, or 3-day periods were provided. Geographic information became more granular over time. For instance, additional indicators on municipal and safety region levels alongside the primarily available national level were provided at the last 2 assessment dates. Disaggregation options were also expanded over time, as age groups and multiple vulnerable groups (eg, disability care homes and people over 70 years old living at home) were added.

Although visualization options were not adapted, during the second and third descriptive assessments, we observed additional interactive options providing change of information and display and more use of simplification techniques through small icons. For example, absolute numbers of infections and a relative number per 100,000 inhabitants were used at all 3 time points of the descriptive assessment. At all 3 time points, a scale was used to visualize the relative numbers, but at the last 2 time points, interpretation of these numbers was simplified by adding a norm value and color coding (red colors for "bad" and green colors for "good") to the scale.

Actionability of the COVID-19 Dashboard

Table 3 provides the initial researcher ratings and our consolidated appraisal of the Dutch government's COVID-19 dashboard, version December 17, 2020, in terms of the 7 established features of highly actionable COVID-19 dashboards.

Table 3. Common features of highly actionable COVID-19 dashboards: appraisal of the Dutch government dashboard, version December 17, 2020.

Feature	Assessment			Combined qualitative assessment of the researchers
	Not present	Somewhat present	Clearly present	
Knowing the audience and its information needs	0	2	0	The dashboard's purpose is stated, and, because it is a public website, the general public is implicitly the audience. That is not explicitly stated, however, nor is the dashboard sufficiently adapted to the audience, as professional jargon limits usability by the general public.
Managing the type, volume, and flow of information	0	1	1	The volume of information necessitates clicking and scrolling multiple times to view dashboard components. However, 2 types of navigation options simplify information searches: (1) 3 tabs for national, safety region, and municipal geographic disaggregation; (2) a left-hand menu to click on indicator themes or subthemes.
Making data sources and methods clear	0	0	2	Data sources and methods are explicitly noted per indicator, and many datasets are open-access.
Linking time trends to policy and policy decisions	2	0	0	Time trends are displayed, but there are no links from time trends to policy decisions. Solely the current policy measures are specified, together with the current risk levels by safety region.
Providing data "close to home"	0	2	0	The dashboard provides information down to municipal levels. Neighborhood-level information or information by postal code is not given.
Breaking down the population into relevant subgroups	0	2	0	Breakdowns of information are available for (1) age (only for current daily new infections) and (2) 3 vulnerable groups: nursing home residents, disability facility residents, and people over 70 years old living at home. Disaggregation of information by gender, socioeconomic status, or ethnicity is not available.
Using storytelling and visual cues	0	1	1	Narratives are present and explain why an indicator is presented and how it should be interpreted. However, interlinkages between indicators are not available. Visual cues such as color schemes and icons are used to show an indicator's outcome severity. Information volumes and wordings are not adapted for easy navigation by the general public.

Decisions Made in the Development of the COVID-19 Dashboard by its Developers

Various reflections were made in the meeting with the COVID-19 dashboard team of the Ministry of Health, Welfare and Sport in the spring of 2021. The following sections include the considerations the dashboard development team made in their decisions to shape the COVID-19 dashboard, ordered by the 7 features of actionable dashboards.

Knowing the Audience and Their Information Needs

At the outset of the dashboard, policy makers, notably in the 25 safety regions, were the primary target audience. Even though much of the same indicators were used over time, there is currently a different medium to provide daily updates to policy makers. Thus, the dashboard was found to be gradually adjusted to addressing the general public. The dashboard has been designed for the purpose of high-frequency (daily) updates in a focused area, which, from the perspective of the COVID-19 dashboard team, is less fitting for the purpose of more broadly reporting on (health) systemwide performance to a wider public. The data infrastructure of the dashboard can be re-used in future situations in which high-frequency daily data updates might be necessary for reporting on other (health) system performance areas.

Managing the Type, Volume, and Flow of the Information

The letter to the House of Representatives in May 2020 has been the leading document in guiding choices on type, volume, and flow of information displayed on the COVID-19 dashboard. The information on the dashboard was found to be organized in chronological order of the infection and successive COVID-19 disease process (estimate infected persons, COVID-19 positive test results, hospital admissions, intensive care unit admission, deaths). To increase quick access to the most important information, a homepage was added when the audience of the dashboard changed from policy makers to the broader public. To facilitate navigation, visits to the different subtabs of the dashboards were reported to be monitored. When a certain subtheme had become more popular, the sidebar could be amended to prioritize that particular subject. For example, when the vaccination subtab was visited more often, it was moved to the top of the page.

Making Data Sources and Methods Clear

It was a political decision to foster transparency in data sources and methods. To ensure that the data sources and methods would not yield discussion, transparency of data was maximized by making it largely available as open source.

Linking Time Trends to Policy Decisions

The dashboard development team was very careful not to link time trends to policy decisions. A caveat of linking policy

decisions to time trends is that correlation is suggested. From the perspective of the dashboard development team, it was a deliberate choice not to make these assumptions. Instead, formal interpretations were handled by political decision makers, who were advised by multidisciplinary experts via the Outbreak Management Team.

Providing Data "Close to Home"

The dashboard team explained that, in some phases of the pandemic, as in the summer 2020 period when case numbers were low, more disaggregated information should ideally be provided in order to act locally to prevent the spread of the virus. However, the team did not have access to neighborhood-level data from all municipalities. Another consideration was that the more an individual zooms in at the local level, the lower the numbers become. For the perception of severity of the transmission and due to privacy issues, disaggregation could challenge its usefulness. The dashboard team did not think it was wise in this stage of the pandemic to invest in more locally available data. The team anticipated that in the future, when most of the population of the Netherlands is vaccinated, attention will turn to investing in information on the international status of the virus. Doing so may provide insights into possible mutation effects that can arise from international travel.

Breaking Down Population Data Into Relevant Subgroups

Disaggregating the data, for example by sex, has not been high on the agenda for the dashboard's development. The dashboard team explained that data for socioeconomic status or ethnicity are not available in their database and would require integration of data on a personal identifier level, which was not available to the dashboard team.

Using Storytelling and Visual Cues

News-like items were added when the audience of the dashboard changed from policy makers to the broader public. This decision was made to enhance public understanding of the information provided, especially for visitors to the dashboard with less affinity towards numbers. During the development of the dashboard, ongoing research on public interpretation and understanding of different features of the dashboard were conducted in order to enhance actionability.

Discussion

Principal Findings

We assessed the COVID-19 dashboard provided by the Dutch government in terms of its development during the pandemic and its actionability for conveying information on the pandemic and supporting data-driven decision making. We found that the dashboard predominantly showed epidemiological information on COVID-19. It had been developed and adapted by adding more in-depth indicators, more geographic disaggregation options, and new indicator themes. It also changed in target audience from policy makers to the general public; thus, a homepage was added with the most important information, using news-like items to explain the provided indicators and conducting research to enhance public understanding of the dashboard.

Two of the 4 key components advised by the WHO Regional Office for Europe for monitoring and managing the pandemic were still missing from the dashboard 10 months after the first patient with COVID-19 was reported in the Netherlands: (1) indicators of available capacity for dual-track health system management to safeguard non-COVID care and (2) indicators of social and economic impact. As COVID-19 care needs draw on limited health system resources, non-COVID care needs must also be taken into account when weighing options to take policy decisions [32,33]. Although information on health care service utilization for other conditions (dual-track monitoring) as well as socioeconomic impact is available via a variety of other government-linked organizations—including the Dutch Health Authority (NZA), Statistics Netherlands (CBS), and the Netherlands Institute for Social Research (SCP)—such information is not provided on the COVID-19 dashboard, thus constraining an overall assessment of the situation. As the pandemic persists, the monitoring of both non-COVID care access and socioeconomic impact is of growing importance to adequately inform policy decisions [11]. Several Dutch political parties have emphasized the need to obtain and discuss such information in a more "overall" format.

Experiences from other countries have shown the importance of relevant disaggregation into subgroups, such as socioeconomic status and ethnicity, in order to highlight inequalities within populations [34-38]. Reported data from the United States on negative changes in life expectancy and the substantial differences between ethnic groups have underscored the relevance of transparent, differential data [39,40]. Ethnicity is not represented in the established data infrastructure on health; thus, the Dutch COVID-19 dashboard does not provide this disaggregation option. In the Netherlands, cohort studies are used to gain insights into ethnic inequalities [41], but such studies carry significant time delays for accessing valuable information needed at the time of a pandemic. Two policy briefs released in May 2021 on the COVID-19 impact among ethnic groups underscore that disaggregating data on COVID-19 impact for ethnic groups can lead to valuable insights for policy decision making [42,43]. The dashboard development team also noted that disaggregation of data by sex and gender was not high on their agenda. COVID-19 outcomes have shown to be affected by sex and gender differences, for example in increased mortality in men compared with women [44]. Taking into account data on sex and gender is needed in order to distinguish potential sex-based immunological differences or gender-based differences in behavior that require tailored care or policy actions [45,46].

The dashboard requires timely data to inform the public of the constantly evolving context, as was the case with the indicators on administered vaccinations and percentages of infected individuals with mutated virus variants. Communicating a constantly changing message to a wide public is complex. Dashboards therefore need to promptly adapt and evolve so as to take the most important considerations of "today" into account, while also providing "stable" trend indicators to highlight the changing circumstances. When data reporting or

data infrastructure lagged behind, the Dutch government chose in many instances to show estimated or not yet contextualized data, for example on estimated numbers of infectious people or on sewage water testing [47]. By our third assessment of the dashboard, news-like text items had been added to bridge gaps in still-unavailable data and to increase public understanding of the provided indicators, making use of textual explanations such as what impact the new variant might have and why caution was needed. Experts are divided as to whether it is wise to publish work-in-progress data for indicators such as sewage water testing. Some ask why an indicator should be shown if it does not lead to consequences in policy decisions [48], while others argue that it could provide early warnings to the general public [49,50]. Experts in health communication emphasize that information should be presented in a way that assumes that citizens have a choice in their behavior [51,52]. Then, a dashboard can not only communicate a general picture of fear but also acknowledge the freedom of individuals to make a choice, which appeals to their responsibility for the collective.

The duration of the COVID-19 pandemic and the pressing need for immediate action have exposed weaknesses in the health and social care data infrastructure of the Netherlands in terms of its timeliness and accessibility to (and interoperability of) health and social care data and socioeconomic data for the benefit of public health. These gaps are evident in the limited availability of timely dual-track indicators, data on social and economic impact, and possibilities for relevant population breakdowns. We advise (1) establishing timely indicators relating to health system capacity in the Dutch health information infrastructure, (2) including relevant data disaggregation options, and (3) enabling interoperability between social, health, and economic data sources.

Strengths and Limitations

A particular strength of this study is that the checklist and the features of actionable dashboards that we applied were developed on the basis of a large sample of international COVID-19 dashboards (158 dashboards in 53 countries) [28]. A number of limitations has to be taken into account in interpreting the presented findings. Both the pandemic and the dashboard are constantly developing. As 3 discrete points in time were chosen for the descriptive checklist, some back-and-forth changes to the dashboard between time points could have been missed. Another limitation is that, although the same researcher (VB) filled out the checklist at all 3 time points, the archiving of the dashboard during the first checklist was limited to a copy of its main page, so that the in-depth tabs could not be revisited and checked by other researchers.

Conclusion

The Dutch COVID-19 dashboard developed over time to be fit for purpose and fit for use in terms of providing epidemiological information to the general public as the target audience. This can help to transform the dashboard from a tool of public accountability to an instrument for community action to contain the pandemic. However, to enhance its actionability for monitoring COVID-19 and its social and economic impact, including a broader set of indicators may be considered. Therefore, gaps in the Dutch health information infrastructure need to be addressed. To strengthen the Dutch health system's ability to cope with upcoming phases of the COVID-19 pandemic or future public health emergencies, we advise (1) establishing timely indicators related to health system capacity, (2) including relevant data disaggregation options (eg, sex, socioeconomic status), and (3) enabling interoperability between social, health, and economic data sources.

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Authors' Contributions

This research was drafted by VB, TJ, DK, and TJ and executed by VB and TJ with close collaboration and supervision by DK and NK.

Conflicts of Interest

None declared

Multimedia Appendix 1
Archived copies of the Dutch COVID-19 government dashboard.
[DOCX File , 14 KB - publichealth_v7i10e31161_app1.docx]

Multimedia Appendix 2
Descriptive checklist.
[DOCX File , 20 KB - publichealth_v7i10e31161_app2.docx]

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Abbreviations

CBS: Statistics Netherlands
NZA: Dutch Healthcare Authority
RIVM: National Institute for Public Health and the Environment
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
SCP: Netherlands Institute for Social Research
WHO: World Health Organization

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Review

Effectiveness of Contact Tracing for Viral Disease Mitigation and Suppression: Evidence-Based Review

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Abstract

Background: Contact tracing in association with quarantine and isolation is an important public health tool to control outbreaks of infectious diseases. This strategy has been widely implemented during the current COVID-19 pandemic. The effectiveness of this nonpharmaceutical intervention is largely dependent on social interactions within the population and its combination with other interventions. Given the high transmissibility of SARS-CoV-2, short serial intervals, and asymptomatic transmission patterns, the effectiveness of contact tracing for this novel viral agent is largely unknown.

Objective: This study aims to identify and synthesize evidence regarding the effectiveness of contact tracing on infectious viral disease outcomes based on prior scientific literature.

Methods: An evidence-based review was conducted to identify studies from the PubMed database, including preprint medRxiv server content, related to the effectiveness of contact tracing in viral outbreaks. The search dates were from database inception to July 24, 2020. Outcomes of interest included measures of incidence, transmission, hospitalization, and mortality.

Results: Out of 159 unique records retrieved, 45 (28.3%) records were reviewed at the full-text level, and 24 (15.1%) records met all inclusion criteria. The studies included utilized mathematical modeling (n=14), observational (n=8), and systematic review (n=2) approaches. Only 2 studies considered digital contact tracing. Contact tracing was mostly evaluated in combination with other nonpharmaceutical interventions and/or pharmaceutical interventions. Although some degree of effectiveness in decreasing viral disease incidence, transmission, and resulting hospitalizations and mortality was observed, these results were highly dependent on epidemic severity (R0 value), number of contacts traced (including presymptomatic and asymptomatic cases), timeliness, duration, and compliance with combined interventions (eg, isolation, quarantine, and treatment). Contact tracing effectiveness was particularly limited by logistical challenges associated with increased outbreak size and speed of infection spread.

Conclusions: Timely deployment of contact tracing strategically layered with other nonpharmaceutical interventions could be an effective public health tool for mitigating and suppressing infectious outbreaks by decreasing viral disease incidence, transmission, and resulting hospitalizations and mortality.

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KEYWORDS

contact tracing; non-pharmaceutical interventions; pandemic; epidemic; viral disease; COVID-19; isolation; testing; surveillance; monitoring; review; intervention; effectiveness; mitigation; transmission; spread; protection; outcome

Introduction

Contact tracing has a long history as an effective tool against infectious disease outbreaks, such as severe acute respiratory syndrome (SARS), Ebola, and monkeypox [1-3]. To mitigate the spread of disease, contact tracing involves interviewing people who are infected to identify which other individuals they might have exposed to the virus, finding those exposed contacts, isolating contacts who are infected, and placing exposed contacts in quarantine until they are not deemed infectious [4]. Public health agencies use contact tracing as one strategy among many to break the chain of viral transmission. As the number of vaccinated individuals increases and vaccine hesitancy and access issues persist, contact tracing remains a key strategy in the COVID-19 response to enable surveillance of the evolving COVID-19 pandemic [5].

Efforts to identify and support the contacts of those who have tested positive for COVID-19 and thus pose a risk for infecting others can be both resource- and labor intensive. Approaches to contact tracing have traditionally used telephone and in-person communication; however, newer approaches examine the use of mobile apps and leveraging data to track and trace social connections and potential exposures. Countries such as South Korea and Taiwan have touted the success of technology enablement; however, to date, evidence demonstrating a causal relationship between technology and COVID-19 mitigation is lacking [6-10]. The COVID-19 pandemic continues to overwhelm public health capacity due to the sheer numbers of those infected. Moreover, the pandemic is particularly challenging because of the large number of asymptomatic infections [11]. As such, the private sector will play a role in augmenting the public health response. Universities and businesses can collaborate with government agencies to facilitate contact tracing, and the use of technology can be an important enabler in this direction but concerns regarding privacy and effectiveness remain.

Like other nonpharmaceutical interventions (NPIs), the effectiveness of contact tracing is difficult to measure in real time owing to the lack of direct access to outcomes data and the reliance on surrogate data. Epidemiologists will determine the impact on COVID-19 with time, but in the interim, existing retrospective studies on the effectiveness of contact tracing to mitigate and suppress viral diseases offer a learning opportunity and valuable information to improve preparedness and response.

The objective of this study is to identify and synthesize evidence regarding the effectiveness of contact tracing on infectious viral disease outcomes. This evidence-based review focuses on studies describing the implementation and assessment of all forms of contact tracing with other NPIs and pharmaceutical interventions (PIs) by using single or multiple interventions during viral epidemics or pandemics.

Methods

An evidence-based review was conducted using systematic methodology to identify literature from the PubMed database, including preprint medRxiv server content, related to the effectiveness of all forms and combinations of contact tracing approaches in viral epidemics or pandemics, including the COVID-19 pandemic. The search query (Table 1) included terms for contact tracing (eg, *contact tracing*, *case finding*, *case detection*) AND COVID-19, as well as other viral pandemics or epidemics (eg, *COVID-19*, *SARS-COV-2*, *2019-nCOV*, *severe acute respiratory syndrome coronavirus 2*, *novel coronavirus*, *influenza*, *flu*, *viral pandemic*, *viral epidemic*) AND effectiveness (eg, *effective**, *efficacy*). The search dates were from database inception to July 24, 2020.

Outcomes of interest were measures of incidence, transmission, hospitalization, and mortality. Modeling studies with generalized statements of effectiveness were also included despite the lack of quantitative data. Primary and secondary articles were obtained; however, secondary articles were excluded with the exception of modeling studies and systematic reviews with inclusion criteria identical to this study. Single reviewer (KJTC) screening was conducted using a priori inclusion and exclusion criteria (Table 2). Data abstraction was completed from primary sources by one reviewer (KJTC), and quality control was undertaken by a second reviewer (RR, VCW) by using standardized forms. The study quality was assessed using Oxford Levels of Evidence [12] by a dual review (KJTC, RR, or VCW).

Table 1. Strategy used for the search conducted in MEDLINE (via PubMed).

Search number	Facet	Search terms	Search results (July 24, 2020)
1	Identify articles on NPIs[a] of contact tracing used alone or in combination with other NPIs	*(contact tracing[title] OR case finding[title] OR identify contacts[title]or detect case*[title] OR early detection[title] OR "contact tracing" [MeSH][title]) OR (non-pharmaceutical intervention* AND contact tracing)*	17,896
2	Identify articles on viral epidemics or pandemics with a focus on COVID-19	*covid19[tiab] OR covid-19[tiab] OR severe acute respiratory syndrome coronavirus 2 or SARS-COV-2 OR 2019-nCoV OR novel coronavirus OR "COVID-19"[Supplementary Concept] OR viral epidemic[tiab] OR viral pandemic[tiab] OR influenza[tiab] or flu[tiab]*	140,427
3	Identify effectiveness outcomes	*effective* OR efficacy OR effectiveness*	8,348,810
4	Identify contact tracing effectiveness studies in viral epidemics or pandemics	#1 AND #2 AND #3	122

[a]NPI: nonpharmaceutical intervention.

Table 2. *A priori* inclusion and exclusion criteria applied.

PICOST[a] component	Inclusion criteria	Exclusion criteria
Population	• The study examines infectious viral disease in humans during pandemic or epidemic settings.	• The study examines bacterial, fungal, parasitic, protozoan, and prion diseases. • The study does not explicitly state viral disease has reached epidemic or pandemic status.
Intervention	• The study focuses on the contact tracing aspect of NPIs[b]. Contact tracing is measured in terms of the detection of asymptomatic cases and following testing or diagnosis of a confirmed case they may have had close contacts with or random testing. • The study may examine single or multiple NPIs, and combinations of contact tracing interventions. Combination contact tracing interventions can also include other interventions such as diagnostic testing, pharmaceutical interventions, and other NPIs.	• The study describes NPIs without contact tracing included in the combination intervention.
Comparison	N/A[c]	N/A

Outcomes	The study reports on the following outcomes:
	• Disease incidence:
	  • Incidence proportion or attack rate/risk: The percentage of the population that contracts the disease in an at-risk population during a specified time interval. Other included variations will allow cumulative and peak attack rates.
	  • Infection rate (or incident rate): An incidence rate is typically used to measure the frequency of occurrence of new cases of infection within a defined population during a specified time frame.
	• Disease transmission:
	  • Reproduction number (R0): The basic reproduction number that is used to measure the transmission potential of a disease.
	  • Reduction and risk of transmission (primary or secondary) will be abstracted.
	• Mortality:
	  • Case fatality proportion: The proportion of deaths within a defined population of interest.
	  • Peak excess death rates: A temporary increase in the mortality rate in a given population.
	  • Mortality rate: The total number of deaths from a particular cause in one year divided by the number of people alive within the population at mid-year. An example is cumulative death rate.
	  • Total deaths: The number of deaths considered all-cause mortality.
	• Hospitalization:
	  • This includes both regular and intensive care unit admissions.
	The study may also report qualitative findings of outcomes from modeling studies.
		• The study does not report quantitative or qualitative data on the effectiveness of contact tracing.

Settings	• No study limits on geography, global findings.	N/A
Study limits	• Study type: primary literature (original studies, case studies) or secondary literature (including systematic reviews with the same inclusion criteria) with or without meta-analyses and modeling. • The publications are either already printed in peer-reviewed journals, conference proceedings, or in the prepublication print phase.	• Study types other than a primary study or a secondary study (ie, commentaries, policy reviews, letters, editorials, and reports).

[a]PICOST: Population, Intervention, Control, Outcomes, Study design and Timeframe.

[b]NPI: nonpharmaceutical intervention.

[c]N/A: not applicable.

Results

Study Characteristics

The search strategy yielded a total of 159 unique records, and 45 records (28.3%) were reviewed at the full-text level (Figure 1). A total of 24 (15.1%) studies met the inclusion criteria [13-36], and their characteristics are provided in Table 3 and Table S1 of Multimedia Appendix 1.

Most studies (n=14) [13,16,18,19,21-23,26-28,30,31,34,35] used mathematical modeling, but others were observational

studies (n=8) [14,15,20,24,29,32,33,36] and systematic reviews (n=2) [17,25]. These modeling studies used synthetic populations to provide quantitative analyses primarily of COVID-19 evolution to query the effectiveness of contact tracing with other interventions. Identified study settings were global [16,17,25,28,32], nonspecified [19,22,27,31], or included the following countries: Canada [30,35], China [36], India [33], Korea [20,29], Taiwan [14,24], United Kingdom [15,18,21,23], and the United States [13,26,34]. Intervention duration varied across the studies, and both children and adults were targeted. SARS-CoV-2 (n=18) was the most frequently examined viral outbreak [13,14,16-19,21-24,26,27,29-32,34,35], but Nipah virus (n=1) [33] and various influenza A hemagglutinin (H) and neuraminidase (N) subtypes, including H1N1 (n=4) [17,25,28,36] and H7N2 (n=1) [15], were also studied.

Figure 1. Results of the literature search. Summary of all articles identified by systematic search queries and tracking of articles that were included and excluded across the study screening phases with reasons for exclusion of full texts.

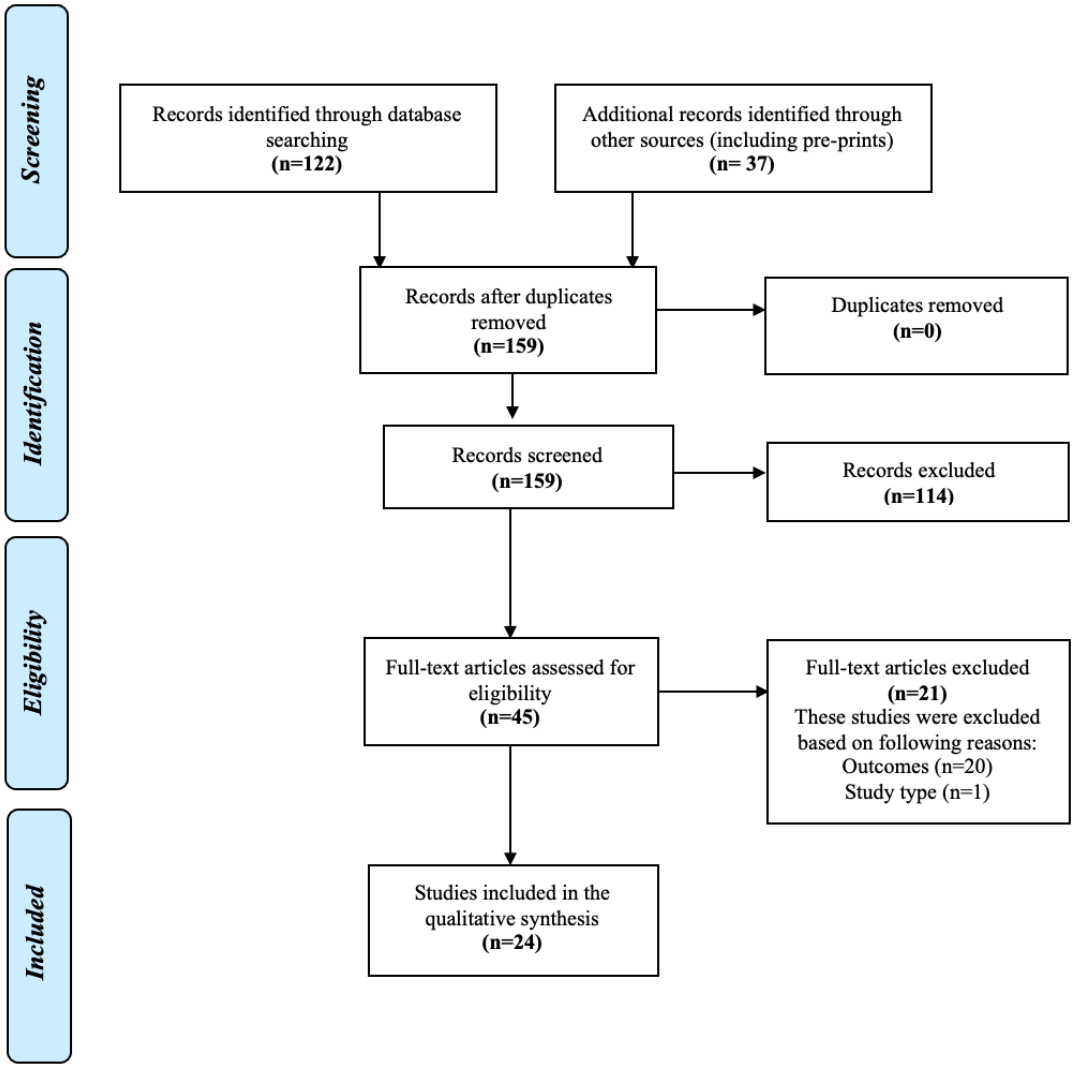

Table 3. Summary of study characteristics.

Serial number	Study reference	Geography		Study design; level of evidence[a]	Causative virus[b]	Effectiveness outcome(s) assessed
		Location	Continent			
1	Aleta, 2020 [13]	United States	North America	Modeling; 2b	SARS-CoV-2	Hospitalization; incidence
2	Cheng, 2020 [14]	Taiwan	Asia	Observational; 4	SARS-CoV-2	Incidence
3	Eames, 2010 [15]	United Kingdom	Europe	Observational; 4	Influenza A (H7N2)	Incidence; transmission
4	Fiore, 2020 [16]	Global	Global	Modeling; 2b	SARS-CoV-2	Incidence; transmission
5	Fong, 2020 [17]	Global	Global	Systematic review; 2a	Varied (included influenza A subtypes)	Incidence; transmission
6	Goscé, 2020 [18]	United Kingdom	Europe	Modeling; 2b	SARS-CoV-2	Mortality; transmission
7	Hellewell, 2020 [19]	N/R[c]	N/R	Modeling; 2b	SARS-CoV-2	Transmission
8	Jung, 2020 [20]	South Korea	Asia	Observational; 4	SARS-CoV-2	Transmission
9	Keeling, 2020 [21]	United Kingdom	Europe	Modeling; 2b	SARS-CoV-2	Transmission
10	Kretzchmar, 2020 [22]	N/R	N/R	Modeling; 2b	SARS-CoV-2	Transmission
11	Kucharski, 2020 [23]	United Kingdom	Europe	Modeling; 2b	SARS-CoV-2	Transmission
12	Liu, 2020 [24]	Taiwan	Asia	Observational; 4	SARS-CoV-2	Incidence; transmission
13	Mizumoto, 2013 [25]	Global	Global	Systematic review; 4	Influenza A (H1N1)	Transmission
14	Ngonghala, 2020 [26]	United States	North America	Modeling; 2b	SARS-CoV-2	Hospitalization; mortality; transmission
15	Peak, 2020 [27]	N/R	N/R	Modeling; 2b	SARS-CoV-2	Transmission
16	Ross, 2015 [28]	Global	Global	Modeling; 2b	Influenza A (H1N1)	Transmission
17	Son, 2020 [29]	South Korea	Asia	Observational; 4	SARS-CoV-2	Incidence
18	Tang, 2020 [30]	Canada	North America	Modeling; 2b	SARS-CoV-2	Transmission
19	Torneri, 2020 [31]	N/R	N/R	Modeling; 2b	SARS-CoV-2	Transmission
20	Wilasang, 2020 [32]	Global	Global	Observational; 4	SARS-CoV-2	Transmission
21	Wilson, 2020 [33]	India	Asia	Observational; 4	Nipah virus (NiV)	Incidence
22	Worden, 2020 [34]	United States	North America	Modeling; 2b	SARS-CoV-2	Transmission
23	Wu, 2020 [35]	Canada	North America	Modeling; 2b	SARS-CoV-2	Transmission
24	Zhang, 2012 [36]	China	Asia	Observational; 4	Influenza A (H1N1)	Incidence

[a]Adapted from Oxford Levels of Evidence [12]. Level 2a: systematic review with homogeneity of 2b or better studies; level 2b: retrospective cohort, simulation, or modeling studies; level 4: case series or systematic review with heterogeneity of studies.

[b]H#N#: hemagglutinin subtype number and neuraminidase subtype number

[c]N/R: not reported.

Types of Contact Tracing Interventions and its Combination With Other Interventions

Five studies [15,24,28,36,37] examined contact tracing in a model as a single intervention. Most studies (n=19) [13,14,16-23,25,26,29-35] used a combination of interventions to assess the effectiveness of contact tracing using NPIs with or without PIs. Isolation (ie, separation of diagnosed individuals) and quarantine (ie, restricted movement of presumably infectious individuals) were most frequently combined with contact tracing as a multipronged approach in public health strategies to combat the outbreak. Case detection by diagnostic testing was an additional consideration for the effectiveness of contact tracing. Other interventions with contact tracing included general social distancing NPIs (eg, school closure, mass gathering bans, travel restrictions, workplace policies to limit contact, and nonspecified social distancing to limit public contact), personal protective equipment (eg, mask wearing), increased hygienic practices (eg, handwashing and sanitization procedures), antiviral prophylaxis and/or treatment, symptom monitoring by public health personnel, and screening practices to identify active cases.

Only two studies [22,23] considered digital approaches that included the use of mobile app technology rather than traditional manual contact tracing interventions. No hybrid approaches of traditional and mobile app–based strategies were identified; however, there were comparative analyses between the two strategies.

Effectiveness of Contact Tracing

Viral disease outcomes associated with the effectiveness of contact tracing were limited to disease incidence, hospitalization, mortality, and transmission (Table 1). The most frequently reported outcomes were transmission (n=19) [13,15-27,30-32,34,35] and incidence (n=9), [13-17,24,28,29,33] whereas hospitalization and mortality outcomes were described in only 3 studies [13,18,26]. All studies reported some degree of effectiveness for contact tracing examined across mild to moderate (R0<1.5) and/or moderate to severe (R0≥1.5) epidemics or pandemics based on the provided R0. Number of contacts traced, timeliness, and compliance with combination intervention implementation, and R0 were found to impact effectiveness. Combination of NPIs with contact tracing was deemed the most effective [26]. One study modeled the effects of contact tracing as a single intervention and it had minimal effects, but the impact was improved by adding social distancing, quarantine, and mask-wearing to case identification. US peak transmission and hospitalizations decreased 10% from the baseline with contact tracing alone and 92%, with a combination of NPIs [26]. Moreover, nationwide mortality changes from baseline improved substantially (US mortality change from baseline: –3% to –64%) by combining contact tracing with other interventions [26]. In a scenario where 50% of symptomatic cases were identified, a 20% effective contact tracing strategy combined with quarantine, isolation, and general social distancing would help reduce the hospital and intensive care unit (ICU) peak daily admissions per 1000 people from 2.35 (95% CI 1.97-2.75) and 1.39 (95% CI, 1.11-1.68) to 0.44 (95% CI 0.28-0.62) and 0.28 (95% CI 0.16-0.42), respectively. With a 40% effective contact tracing strategy, these estimates would further decrease to 0.29 (95% CI 0.18-0.43) and 0.15 (95% CI 0.08-0.26) [13]. Due to intervention heterogeneity and outcome reporting, it was not possible to provide valid head-to-head effectiveness comparisons across studies.

Transmission

Combinations of NPIs with contact tracing decreased viral transmissibility. Countries that implemented widespread diagnostic SARS-CoV-2 testing with active case detection and prompt isolation were more successful in decreasing the R0 than those that did not use contact tracing (decrease in R0: 0.4-2.2) [32]. A higher decrease in transmission was predicted if contact tracing were combined with case isolation strategies rather than with symptom monitoring [17]. Similarly, transmission would decrease by more than 12% to 64% than with mass testing or self-isolation strategies used alone [23]. Simulations indicated that policies to mitigate SARS-CoV-2 transmission, including contact tracing, isolation, and testing, had similar impacts across geographies [16]. As interventions were added, effectiveness was compounded. Simulations indicated that contact tracing prevented 44% of transmissions from a primary case, and the R0 decreased from 1.85 to 1.13, with shelter in place and public mask-wearing policies coupled with contact tracing, isolation, and quarantine in US COVID-19 settings [34]. Similarly, another modeling study conducted in England observed that SARS-CoV-2 transmission decreased substantially following weekly universal testing, mask-wearing, and contact tracing during a lockdown (effective R0: lockdown lifted and no interventions, 2.56; with interventions, 0.27) [18]. Additionally, when antiviral treatments were added to NPIs, the strategy used resulted in a further decrease in transmission and increased the probability of suppressing the COVID-19 pandemic [31].

Compliance or achievement of combination NPIs with contact tracing and severity of the R0 affected their success. The modeling of isolation measures with contact tracing predicted decreased SARS-CoV-2 transmission (preintervention R0: 1.5; post-intervention R0: 0.5-0.9 based on 20%-100% contact tracing achievement) [19]. Moreover, a higher achievement of contact tracing was required as the R0 increased [19]. One simulation study showed that increased case detection by contact tracing reduced the R0 from 3 to 0.5 when used in combination with other community-enforced personal protection measures such as wearing a mask [35]. Additionally, testing efficacy improved the effectiveness of contact tracing. When both presymptomatic and asymptomatic infections occurred, contact tracing was more effective when combined with testing rather than monitoring, provided the diagnostic test was sensitive enough to detect infections during the incubation period in a COVID-19 model [31]. One modeling study identified many simulated conditions that resulted in SARS-CoV-2 suppression (ie, R0<1) of transmission; the parameters included high (≥60%) contact tracing and testing efficacy to accommodate a range of testing capacities (low to high incidence) [16]. Even with short serial intervals, if social distancing NPIs could decrease R0 to 1.25, then adding active monitoring of about 50% of contacts predicted suppressed transmission (R0<1) [27].

Moreover, the duration and timing of contact tracing interventions influenced their effectiveness on limiting transmission. One modeling study noted that the duration of the combined interventions, including contact tracing, was a necessary consideration for its implementation. Although these measures could abate epidemic-level COVID-19 transmission, it would not prevent resurgence if measures were relaxed or removed [13]. A model with combined isolation and contact tracing predicted that the delay between symptom onset and isolation had the largest role in determining whether a COVID-19 outbreak (R0=1.5) was controllable [19]. Further, early detection of asymptomatic cases with high efficiency of contact tracing and SARS-CoV-2 testing adequately limited the observed transmission in nosocomial settings [20]. In ideal scenarios (assuming no testing and tracing delays and 40% of transmissions occurring before symptom onset), contact tracing could achieve COVID-19 suppression (ie, R0<1; effective R0: social distancing NPIs only, 1.2; add contact tracing to NPIs, 0.8; 95% CI 0.7-1.0). However, if testing delays were greater than 3 days, the most efficient combinatory strategies could not suppress transmission (ie, keep R0<1) in COVID-19 models [22].

Logistical and economic burdens were identified in traditional contact tracing interventions, and alternative means of surveillance and monitoring were considered, including the use of digital contact tracing. Keeling et al [21] computed the distribution of epidemiological, social, and contact tracing characteristics across the population using preliminary estimates of severe COVID-19 transmission. The model predicted that with effective contact tracing, less than 1 in 6 cases will generate any subsequent untraced infections. This approach comes with a high logistical burden, given an average of 36 individuals traced per case [21]. In fact, another US modeling study noted that a 75% improvement in contact tracing resulted in a 10% reduction in nationwide pandemic peak, highlighting its potentially limited ability to scale in a cost-effective manner [26]. Recall bias was a further limitation in contact tracing efforts. One COVID-19 modeling study provided comparative effectiveness to overcome these burdens [22]. Digital contact tracing demonstrated limited superiority over traditional methods in simulation. Mobile app–based tracing was more effective than traditional tracing with limited efficacy (ie, 20% coverage; change in R0: digital, –17.6%; traditional, –2.5%) [22].

Incidence

Epidemiological studies examining SARS-CoV-2 [14,24,29] or other viruses [12,15,33,36] described the effectiveness of contact tracing on viral disease incidence. Multiple studies provided the effectiveness of contact tracing as part of mitigation and suppression strategies; some reported the number of cases identified [24,36] and contained [24,29,33] through contact tracing, but noted high resource utilization [36]. Four studies provided secondary attack rates following contact tracing [12,14,15,29] and described the temporal differences based on timing of exposure and contact tracing effectiveness [14]. COVID-19 secondary attack rate was higher when the exposure to an index case started within 5 days of symptom onset (1%, 95% CI 0.6%-1.6%) than when the exposure occurred later (0%, 95% CI 0%-4%). Contact tracing also effectively delineated the associated determinants of COVID-19 secondary attack rates. For example, household and nonhousehold family contacts had higher secondary attack rates than those found in health care or other settings (4.6%-8.2% vs 0.1%-0.9%) [14,29], and attack rates were higher among those older than 40 years [14].

Two modeling studies identified that, when used as part of a combination intervention, contact tracing reduced viral disease incidence [16,17]. A systematic review by Fong et al [17] found that contact tracing of influenza A provided modest benefits when infection rates were high, but it was more effective than symptom monitoring when combined with a quarantine strategy. Fiore et al [16] identified the optimal contact tracing capacities when used in combination with isolation, quarantine, and diagnostic testing with variable efficacies (20%-100%) to determine the predicted impact on incidence when compared to the absence of containment strategies.

Hospitalization and Mortality

The reported effects of contact tracing on COVID-19–related hospitalization and mortality outcomes were limited to three modeling studies [13,18,26]. If contact could be decreased by 40%, then predicted hospitalization and mortality could be reduced by 88% and 64%, respectively, with NPIs including contact tracing [26]. Mortality would be decreased with the addition of contact tracing to suppression and mitigation strategies (ratio of cumulative deaths to no mitigation: 14.5-fold; NPIs with contact tracing: 0.48-fold) [18].

On par with other outcomes, the timing and duration of interventions affected the effectiveness of contact tracing on hospitalization. Compared to no mitigation strategy, substantial reductions in hospitalizations (both normal and ICU admissions) were expected upon the addition of the contact tracing strategy. However, if intervention duration is insufficient (ie, measures are relaxed or removed), then the tracing effort would need to be raised by approximately 50% for hospitals to accommodate the increased number of infections [13].

Study Quality

Using Oxford Levels of Evidence [12], most studies provided level 2b evidence as modeling summarizations [13,16,18,19,21-23,26-28,30,31,34,35]; 1 systematic review with homogeneous interventions provided level 2a evidence [17]; 1 systematic review provided level 4 evidence due to intervention heterogeneity [25]; and the observational studies provided level 4 evidence [14,15,20,24,29,32,33,36]. Furthermore, 3 studies were preprints [13,16,34] The quality of the evidence identified was moderate to low, as 8 studies were classified as level 4.

Discussion

Principal Findings

To the best of our knowledge, this is the first evidence-based review highlighting the impact of contact tracing on the incidence, transmission, hospitalization, and mortality of a viral infectious disease in the context of the COVID-19 pandemic. Contact tracing, in combination with other NPIs or PIs, decreased disease incidence and transmission. A reduction in hospitalizations and mortality of the viral infectious disease was also facilitated by contact tracing. Early, sustained, and layered application of various NPIs, including contact tracing could mitigate and suppress primary outbreaks and prevent more severe secondary or tertiary outbreaks provided that decision-makers consider some important limitations. Retrospective observational and modeling studies suggest the effectiveness of contact tracing and other NPIs are not only largely dependent upon on disease severity and its dynamic R0 values but also on intervention timing, duration, compliance, efficiency, and the number of asymptomatic cases. Thus, an outbreak could be effectively suppressed through strict and early implementation of combined interventions, as long as they can be maintained. The higher the infectivity of the disease and/or the longer the delay in implementation of a measure, the lower would be the resulting effectiveness of the interventions. Additionally, the number of contacts traced and tested without delay and the number of asymptomatic infectious cases are also very important considerations in public health response planning.

It is important to consider these data alongside the limitations of contact tracing—the need for adapting programs based on

the local context, resources, and customs; implementation challenges when disease incidence is very high; and limited scalability. To improve scale, the use of digital surveillance tools to track the contacts of people infected with an infectious disease, such as COVID-19, could be key to reducing the number of people infected and reducing the spread of the virus. More countries are implementing digital tools for contact tracing through mobile apps that allow user data to be shared via the device's GPS and/or Bluetooth capabilities; however, this approach raises concerns about privacy; confidentiality of data; and functional or technological limitations, such as dependency on voluntary adoption, performance-related errors, limited effectiveness in identifying contacts, and restrictions associated with operating systems [38-40]. During our screening, we identified several implementation and theoretical studies regarding the use of digital contact tracing, but most of them lacked outcomes data for inclusion [38,41-49]. A gap remains in understanding the effectiveness of these mobile apps, particularly since limited evidence exists on their effectiveness, although modeling studies have suggested that contact-tracing apps could reduce disease transmission [50]. Notably, there are guidelines set forth by various government agencies to augment traditional contact tracing with digital tools [51].

Strengths and Limitations

This review has several strengths. To our knowledge, this is a novel review using a rigorous methodology to provide a qualitative synthesis of the evidence related to the effects of contact tracing on viral disease outcomes. Synthesis included studies examining the COVID-19 pandemic caused by SARS-CoV-2 (2019-2020), in addition to historic viral epidemics. This examination provides stakeholders with evidence-based findings to better understand the importance and benefits of timely and strategic implementation of contact tracing in the current social context of a severe pandemic.

Our results should be interpreted in the context of their limitations. From a study design perspective, the search was not comprehensive, as only one database (including its preprint contents) was searched, and no handsearching of included studies or conference proceedings was performed to expediently provide synthesis of the available information. Furthermore, the findings are of limited generalizability due to the relatively small number of identified studies, most of which were of moderate to low quality. Additional considerations need to be made for the large number of modeling studies that were used to derive this transmission-based evidence as opposed to epidemiological findings. Finally, the consideration of contact tracing alone and in combination with various other interventions, as observed in the response to the COVID-19 pandemic, limits the interpretation of the causal role of contact tracing in disease mitigation. However, recent work suggests that comparisons between different permutations of NPIs may still be informative [52].

Conclusions

This evidence-based review suggests that the proper deployment of strategically layered NPIs that include contact tracing along with other interventions, such as testing, could mitigate and suppress disease burden by decreasing viral disease incidence, transmission, and resulting hospitalizations and mortality. Strict and timely implementation of NPIs is necessary to minimize inefficiencies associated with their limited ability to scale with the surge of outbreaks. Future work should focus on the ability of digital methods to augment traditional contact tracing and its associated privacy and ethical considerations, the accuracy and assumptions of contact tracing models, and the specific effects of vaccines and other PIs on contact tracing.

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Authors' Contributions

KJTC, RR, WJK, and GPJ conceptualized the study. KJTC was involved in developing the methods (study design) and conducting the literature search. KJTC, RR, and VCW performed data collection, analyses, and interpretation, as well as wrote the original draft of the manuscript; they were also involved in writing the manuscript and editing it, along with WJK and GPJ. KJTC prepared the illustrations; KJTC, RR, and VCW prepared the tables.
KJTC also serves as the project administrator and supervisor.

Conflicts of Interest

The authors are employed by IBM Corporation and declare that they have no competing interests.

Multimedia Appendix 1
Supplementary Table 1: abstractions of included studies.
[DOCX File , 76 KB - publichealth_v7i10e32468_app1.docx]

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Abbreviations

ICU: intensive care unit
NPI: nonpharmaceutical intervention
PI: pharmaceutical intervention
R0: reproduction number
SARS: severe acute respiratory syndrome

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Original Paper

Excess Mortality During the COVID-19 Pandemic in Jordan: Secondary Data Analysis

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Abstract

Background: All-cause mortality and estimates of excess deaths are commonly used in different countries to estimate the burden of COVID-19 and assess its direct and indirect effects.

Objective: This study aimed to analyze the excess mortality during the COVID-19 pandemic in Jordan in April-December 2020.

Methods: Official data on deaths in Jordan for 2020 and previous years (2016-2019) were obtained from the Department of Civil Status. We contrasted mortality rates in 2020 with those in each year and the pooled period 2016-2020 using a standardized mortality ratio (SMR) measure. Expected deaths for 2020 were estimated by fitting the overdispersed Poisson generalized linear models to the monthly death counts for the period of 2016-2019.

Results: Overall, a 21% increase in standardized mortality (SMR 1.21, 95% CI 1.19-1.22) occurred in April-December 2020 compared with the April-December months in the pooled period 2016-2019. The SMR was more pronounced for men than for women (SMR 1.26, 95% CI 1.24-1.29 vs SMR 1.12, 95% CI 1.10-1.14), and it was statistically significant for both genders (P<.05). Using overdispersed Poisson generalized linear models, the number of expected deaths in April-December 2020 was 12,845 (7957 for women and 4888 for men). The total number of excess deaths during this period was estimated at 4583 (95% CI 4451-4716), with higher excess deaths in men (3112, 95% CI 3003-3221) than in women (1503, 95% CI 1427-1579). Almost 83.66% of excess deaths were attributed to COVID-19 in the Ministry of Health database. The vast majority of excess deaths occurred in people aged 60 years or older.

Conclusions: The reported COVID-19 death counts underestimated mortality attributable to COVID-19. Excess deaths could reflect the increased deaths secondary to the pandemic and its containment measures. The majority of excess deaths occurred among old age groups. It is, therefore, important to maintain essential services for the elderly during pandemics.

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KEYWORDS

COVID-19; excess mortality; pandemic

Introduction

The impact of COVID-19 and its response measures on health, economy, and society has been substantial. By the end of 2020, more than 380 million COVID-19 cases were confirmed worldwide, and more than 1.9 million deaths were attributed to COVID-19 [1]. In Jordan, the death toll has reached 3834, with more than 294,000 people diagnosed with COVID-19 at the end of 2020 [1]. The number of officially reported COVID-19 deaths in Jordan [2] does not reflect the true burden of the pandemic because some people with COVID-19 died without

being diagnosed and because of the indirect impact of COVID-19 and its response measures.

All-cause mortality and estimates of excess deaths are commonly used in different countries to estimate the burden of COVID-19 and assess its direct and indirect effects [3,4]. However, the calculation of these measures is challenged by data gaps in some countries. Excess deaths are calculated by subtracting the number of expected deaths in a specific period from the number of observed deaths in the same period. In the context of COVID-19, the number of excess deaths refers to deaths that are directly or indirectly attributed to COVID-19. The indirect effects of the pandemic and its response measures result from denied or delayed diagnosis, management, and prevention of diseases; delayed care for acute emergencies; economic hardship; health care shortages; overburdened health care systems; disruption of essential health services; psychological distress; and domestic violence [5,6].

Previous studies used different methods to estimate excess deaths such as Farrington surveillance algorithms [7], the standardized mortality ratio (SMR) [8], the difference-in-differences econometric approach [9], generalized linear models such as Poisson loglinear and negative binomial with log link models [10], and the relevant excess mortality calculation method [11]. Many previous studies documented the excess mortality attributable to COVID-19. One study in the United States showed that COVID-19 deaths are likely to be twice as high as reported [12]. In Portugal, a study reported that excess deaths are 3-5 times higher than what could be explained by COVID-19 deaths [13]. Studies on the burden of COVID-19 in the Eastern Mediterranean region as well as in Jordan are scarce. This study aimed to analyze excess mortality during the COVID-19 pandemic in Jordan in April-December 2020.

Methods

Official data on deaths in Jordan for 2020 and previous years (2016-2019) were obtained from the Department of Civil Status in March 2021. The data included information on age, sex, and date of death. Data on the number of officially registered COVID-19 deaths in Jordan were obtained from the Ministry of Health (MoH) [2]. The data on COVID-19 deaths were validated from different sources.

Mortality information was grouped by month to assess the temporal trends. Analysis was limited to April-December because the first COVID-19 death in Jordan occurred on March 28, 2020. Crude, gender-specific, and age-specific death rates were calculated. We contrasted mortality rates in 2020 with those in each year and the pooled period 2016-2020 using SMR by calculating the ratio between the observed number of deaths in Jordan in the year 2020 and the number of deaths that would be expected, based on the age- and sex-specific rates in 2016, 2017, 2018, 2019, and a pooled period 2016-2019. A ratio greater than 1.0 indicates excess deaths in the Jordan population in 2020. The 95% CI for SMR was calculated. The SMR was considered statistically significant if the value 1 was not included in the CI.

Expected deaths for 2020 were estimated by fitting the overdispersed Poisson generalized linear models to the monthly death counts for the period of 2016-2019. The model included month and year as variables to capture seasonality and adjust for annual trends. The month was entered in the model as a categorical variable. The model included age and gender as independent variables. Expected deaths were estimated for each gender-age stratum as a difference between observed and expected deaths. The total excess deaths was calculated by summing excess deaths across age categories for each gender. When the excess mortality in some age groups was less than 0 (indicating decreased deaths), the number of excess deaths was set as 0. Excess deaths are reported by gender, age group, and month.

Results

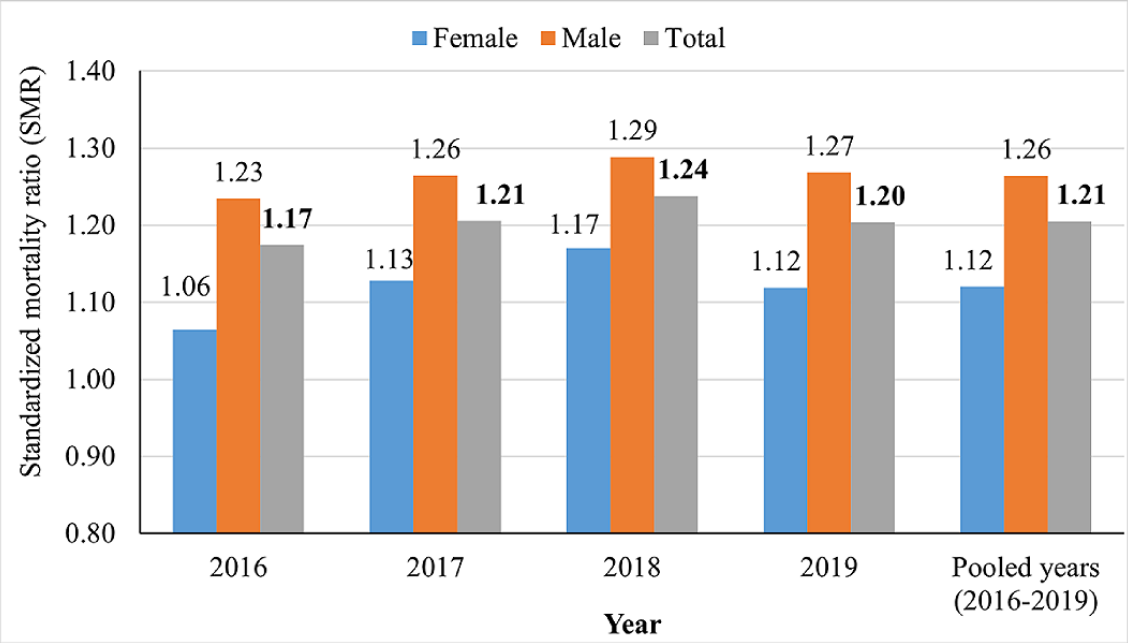
A total of 22,429 deaths were registered in the Department of Civil Registration in April-December 2020. The total number of COVID-19 deaths registered by the MoH during the same period was 3834, accounting for 17.09% of total deaths. The gender-specific and age-specific death rates in April-December 2020 are shown in Table 1.

Table 1. The gender and age-specific death rates in Jordan (April-December 2020).

Age categories (years)	Women			Men		
	Population (n=5,084,000), n	Observed deaths (n=9051), n	Age-specific death rate (per 100,000 population)	Population (n=5,722,000), n	Observed deaths (n=13,378), n	Age-specific death rate (per 100,000 population)
<20	2,317,351	567	24	2,468,981	758	31
20-29	904,139	174	19	1,109,952	320	29
30-39	722,044	252	35	848,784	471	55
40-49	534,417	513	96	638,203	996	156
50-59	317,390	996	314	356,629	2034	570
60-69	168,889	1507	892	174,314	2698	1548
≥70	119,770	5042	4210	125,137	6101	4875

The number of observed deaths in April-December 2020 exceeded the average number of deaths in the period 2016-2019 by 28.0% (4902 deaths). To adjust for changes in age distribution over time and population growth, the SMR was calculated to compare the mortality in April-December 2020 with that in the same months of the years 2016, 2017, 2018, and 2019 and in the pooled years 2016-2019. Overall, a 21% increase in standardized mortality (SMR 1.21, 95% CI 1.19-1.22) occurred in April-December 2020 compared to average mortality in the period 2016-2019. The SMR was more pronounced for men than for women (SMR 1.26, 95% CI 1.24-1.29 vs SMR 1.12, 95% CI 1.10-1.14), and it was statistically significant for both genders (P<.05). Figure 1 shows the comparison of the SMR between April-December 2020 and April-December of the years 2016, 2017, 2018, and 2019 and pooled years 2016-2019.

Figure 1. Comparison of the standardized mortality rate (SMR) between April-December 2020 and the same months in the years 2016, 2017, 2018, 2019, and the pooled years 2016-2019.



Using overdispersed Poisson generalized linear models to consider seasonal and temporal trends, the number of expected deaths in April-December 2020 was 12,845 (7957 in women and 4888 in men). The total number of excess deaths during this period was estimated at 4583 (95% CI 4451-4716), with higher excess deaths in men (3112, 95% CI 3003-3221) than in women (1503, 95% CI 1427-1579). Almost 83.66% (3834/4583) of excess deaths were attributed to COVID-19 in the MoH database. Figure 2 shows the number of excess deaths for men and women according to age group. The vast majority of excess deaths occurred in people aged 60 years or older (total: 3650/4583, 79.64%; women: 1503/1503, 100%; men: 2147/3112, 69.00%). It is worth mentioning that the numbers of deaths that occurred in women aged <60 years and in men aged <30 years in 2020 were less than expected.

Figure 3 shows the number of observed deaths in 2016-2020 and predicted deaths in 2020 according to the month of the year. The observed deaths mainly exceeded the expected deaths during the period September-December 2020 (Figure 3).

Figure 2. The number of excess deaths for men and women according to age group.

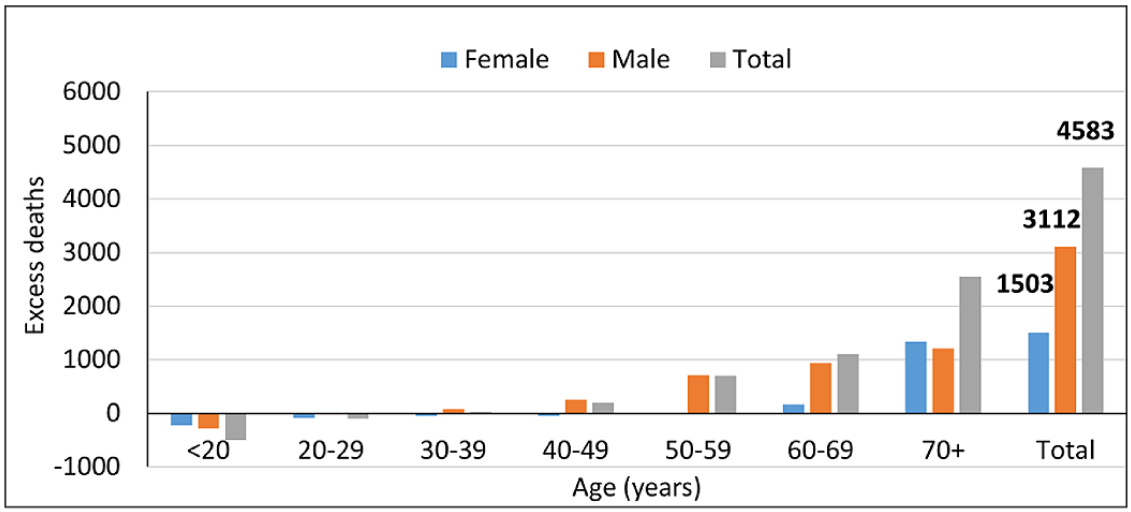
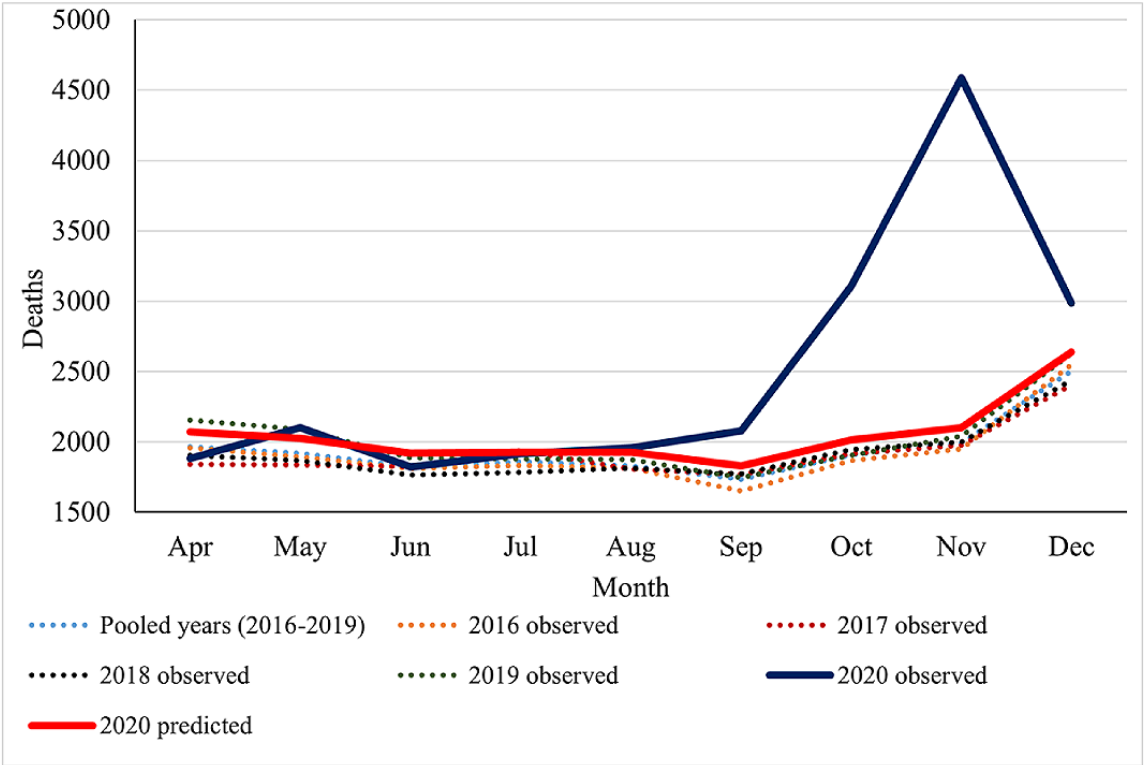


Figure 3. The number of observed deaths in 2016-2020 and predicted deaths in 2020 according to the month of the year.



Discussion

Principal Findings

In this study, we compared the mortality experience in 2020 with that in previous years using indirect standardization of mortality rates and Poisson generalized linear models. We used standardized death ratios of mortality rates to adjust for the effects of differences in population age distributions over years. Age-specific mortality rates were also reported because only reporting standardized rates may mask the age differences in mortality. Poisson models were used to take into account the underlying annual and seasonal trends.

This study showed a 21% increase in standardized mortality in April-December 2020 compared with the same months in the pooled period of 2016-2019. Previous studies had documented increased mortality in some countries. One study in the United States [8] reported a 15.9% increase in the SMR in 2020 compared with 2019. In Switzerland, a study [14] showed that the SMR was 8.8% higher in 2020 than in 2019, returning to the level observed 5-6 years before around the year 2015. Todd

et al [10] showed a 32% increase in deaths, which was above expectations, in Philadelphia during the period from March 22, 2020 to January 2, 2021. The differences in the estimates among different studies including ours might be explained by the differences in the onset of the epidemic in each country, the time at which each country started restrictive measures, and compliance rates.

In our study, higher excess deaths occurred among men and in people aged 60 years or older. The study in the United States [8] reported a sharp increase in mortality rates with increasing age, as well as rates that were higher in men than in women. The Swiss study [12] showed that the increase in deaths was greater for men than for women and was statistically significant only for men over 70 years of age and for women over 75 years of age. Todd et al [10] showed that excess mortality was disproportionately high among older adults. These findings highlight the need for separate analysis for gender- and age-specific strata to determine the groups at risk to be prioritized for interventions. Men were more affected than women, and older people were more affected than younger people.

In Jordan, deaths attributed to COVID-19 accounted for 83.66% of all excess deaths in 2020. In the United States, they accounted for about 75% of all excess deaths in 2020 [15,16]. Todd et al [10] showed that 77% of excess deaths were attributed to COVID-19 on death certificates.

Another finding in this study is that there was a greater reduction in the number of deaths in women aged <60 years and in men aged <30 years in 2020 than what would be expected. This finding might be explained by the reduction in deaths from other common causes in Jordan such as those caused by traffic accidents, due to lockdown and movement restrictions.

It is worth mentioning that the methodological approach we used can be used in other countries that have a strong death registration system. One should consider the limitation of excess death statistics when interpreting the study findings. This measure cannot be used to compare the burden of disease across countries because it depends on the size of the population [17]. Another point to consider is that mortality data might take some time before they become complete.

Conclusion

The reported COVID-19 death counts in Jordan underestimated mortality attributable to COVID-19. The majority of excess deaths occurred among old age groups. Excess deaths could reflect increased deaths secondary to the pandemic and its containment measures. It is, therefore, important to maintain essential services for the elderly during pandemics.

Conflicts of Interest

None declared.

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Abbreviations

MoH: Ministry of Health
SMR: standardized mortality ratio

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Original Paper

Willingness to Receive COVID-19 Vaccination Among People Living With HIV and AIDS in China: Nationwide Cross-sectional Online Survey

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Abstract

Background: HIV infection is a significant independent risk factor for both severe COVID-19 presentation at hospital admission and in-hospital mortality. Available information has suggested that people living with HIV and AIDS (PLWHA) could benefit from COVID-19 vaccination. However, there is a dearth of evidence on willingness to receive COVID-19 vaccination among PLWHA.

Objective: The aim of this study was to investigate willingness to receive COVID-19 vaccination among a national sample of PLWHA in China.

Methods: This cross-sectional online survey investigated factors associated with willingness to receive COVID-19 vaccination among PLWHA aged 18 to 65 years living in eight conveniently selected Chinese metropolitan cities between January and February 2021. Eight community-based organizations (CBOs) providing services to PLWHA facilitated the recruitment. Eligible

PLWHA completed an online survey developed using a widely used encrypted web-based survey platform in China. We fitted a single logistic regression model to obtain adjusted odds ratios (aORs), which involved one of the independent variables of interest and all significant background variables. Path analysis was also used in the data analysis.

Results: Out of 10,845 PLWHA approached by the CBOs, 2740 completed the survey, and 170 had received at least one dose of the COVID-19 vaccine. This analysis was performed among 2570 participants who had never received COVID-19 vaccination. Over half of the participants reported willingness to receive COVID-19 vaccination (1470/2570, 57.2%). Perceptions related to COVID-19 vaccination were significantly associated with willingness to receive COVID-19 vaccination, including positive attitudes (aOR 1.11, 95% CI 1.09-1.12; *P*<.001), negative attitudes (aOR 0.96, 95% CI 0.94-0.97; *P*<.001), perceived support from significant others (perceived subjective norm; aOR 1.53, 95% CI 1.46-1.61; *P*<.001), and perceived behavioral control (aOR 1.13, 95% CI 1.11-1.14; *P*<.001). At the interpersonal level, receiving advice supportive of COVID-19 vaccination from doctors (aOR 1.99, 95% CI 1.65-2.40; *P*<.001), CBO staff (aOR 1.89, 95% CI 1.51-2.36; *P*<.001), friends and/or family members (aOR 3.22, 95% CI 1.93-5.35; *P*<.001), and PLWHA peers (aOR 2.38, 95% CI 1.85-3.08; *P*<.001) was associated with higher willingness to receive COVID-19 vaccination. The overall opinion supporting COVID-19 vaccination for PLWHA on the internet or social media was also positively associated with willingness to receive COVID-19 vaccination (aOR 1.59, 95% CI 1.31-1.94; *P*<.001). Path analysis indicated that interpersonal-level variables were indirectly associated with willingness to receive COVID-19 vaccination through perceptions (β=.43, 95% CI .37-.51; *P*<.001).

Conclusions: As compared to PLWHA in other countries and the general population in most parts of the world, PLWHA in China reported a relatively low willingness to receive COVID-19 vaccination. The internet and social media as well as interpersonal communications may be major sources of influence on PLWHA's perceptions and willingness to receive COVID-19 vaccination.

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KEYWORDS

people living with HIV and AIDS; COVID-19 vaccination; willingness; perceptions; internet and social media influences; interpersonal communication

Introduction

The World Health Organization (WHO) confirmed that HIV infection is a significant independent risk factor for both severe COVID-19 presentation at hospital admission and in-hospital mortality [1]. It is essential to take additional measures to prevent people living with HIV and AIDS (PLWHA) from contracting COVID-19.

The COVID-19 vaccine offers the best hope for ending the pandemic. Simulation experiments showed that when vaccine efficacy was 80%, 75% coverage could end the COVID-19 pandemic without any other control measures [2]. A relatively small number of PLWHA were involved in phase III COVID-19 vaccine trials. The Pfizer study and the Oxford/AstraZeneca study recruited 196 and 157 PLWHA, respectively; however, the data on vaccine efficacy for PLWHA was not included in the publications that led to their approval in the United States and the United Kingdom [3,4]. The Moderna study included 176 PLWHA [5]. Of the PLWHA in the Moderna study, one person who received the placebo and none who received the vaccine developed COVID-19. The Janssen (Johnson & Johnson) study included 1218 PLWHA [6]. Two PLWHA who received the vaccine and four who received the placebo developed COVID-19. There were 201 PLWHA in the Novavax study; the overall vaccine efficacy was 49.4%, with a higher efficacy when PLWHA were excluded from the analysis (60%) [7]. A number of studies observed similar immune responses and adverse events in response to messenger RNA (mRNA) and adenovirus vector COVID-19 vaccines between PLWHA and HIV-negative individuals [8-12]. Despite limited evidence, available information suggests that COVID-19 vaccines recommended by the WHO are safe for PLWHA. There is no evidence to support a less robust response to COVID-19 vaccines among PLWHA. PLWHA could benefit from COVID-19 vaccination.

The recommendations or guidelines regarding COVID-19 vaccination for PLWHA are inconsistent across countries. The WHO, the United States Department of Health and Human Services, the British HIV Association, and health authorities in Australia recommend that PLWHA receive COVID-19 vaccination regardless of their CD4+ T cell counts [1,13-15]. PLWHA comprise one of the priority groups to receive COVID-19 vaccination in the United Kingdom, the United States, and Australia [13-15]. Moreover, the United States Centers for Disease Control and Prevention recommends that PLWHA who are moderately to severely immunocompromised should receive an additional dose of mRNA COVID-19 vaccine after the initial doses [16]. In the Asia-Pacific region, Singapore used to recommend COVID-19 vaccination to PLWHA who are receiving antiretroviral therapy (ART), with suppressed HIV viral load, and with CD4+ T cell counts over 200 cells/μL [17]. Their recommendation expanded to all PLWHA regardless of ART, viral suppression, or CD4+ T cell counts since July 2021 [17]. At the time when this study was conducted, immunodeficiency, including HIV infection, was listed as a precaution for COVID-19 vaccination in China; PLWHA were asked to seek advice from doctors regarding COVID-19 vaccination [18]. The guideline was updated one month after the completion of this study (March 2021) and recommended COVID-19 vaccination for PLWHA, regardless of their CD4+ T cell counts [18].

Vaccine hesitancy hindered the successful control of the COVID-19 pandemic. Therefore, it is helpful for governments to plan interventions to improve people's awareness of the safety

and benefits of the COVID-19 vaccine and to reduce vaccine hesitancy. In order to promote the COVID-19 vaccination of PLWHA, it is necessary to understand their willingness to receive COVID-19 vaccination and related facilitators and barriers. However, most studies investigating willingness to receive COVID-19 vaccination and its associated factors were conducted among the general population and medical professionals [19-21]; therefore, the findings might not be applicable to PLWHA. To our knowledge, only two published studies investigated COVID-19 vaccine hesitancy among PLWHA in the United States and France [22,23]. The results showed that 28.7% of PLWHA in France declared hesitancy to be vaccinated against COVID-19 [22]. Over 30% of PLWHA in the United States indicated that if a vaccine was available to prevent COVID-19, they would not trust it (34%) nor want to get it (32%) [23]. Concerns about their health and the belief that COVID-19 vaccination should be mandatory and is important for people with chronic disease were associated with higher willingness to receive COVID-19 vaccination among PLWHA, while a previous history of vaccination refusal, mistrust in public health information, and concerns related to side effects were shown to be barriers [22,23].

We applied the socioecological model to understand factors associated with willingness to receive COVID-19 vaccination among PLWHA at individual, interpersonal, and sociostructural levels [24]. Interventions addressing influencing factors at multiple levels are more likely to be successful [24]. The socioecological model was used successfully to explain compliance to COVID-19 personal preventive measures among Chinese populations [25]. At the sociostructural level, two COVID-19 vaccination delivery models were implemented simultaneously in China at the time of this study. Individuals could make an appointment to receive COVID-19 vaccination in some cities, while COVID-19 vaccination was mainly arranged by employers and did not allow individuals to make appointments in other Chinese cities. People had the right to refuse such an arrangement. As of the writing of this paper, since the number of vaccines is inadequate to cover the entire Chinese population at the initial phase, priority is given to subgroups with elevated risks of developing COVID-19 (eg, health care workers, pandemic-control staff, and cold-chain workers). Some Chinese cities also reported a shortage of COVID-19 vaccines. We expected that these sociostructural-level factors would influence PLWHA's willingness to receive COVID-19 vaccination. At the individual level, perceived efficacy, concerns about side effects, others' acceptance, and confidence to receive the vaccine influenced people's willingness to receive COVID-19 vaccination [26-30]. At the interpersonal level, people were exposed to information related to COVID-19 vaccination through interpersonal communication or the internet and social media. Higher exposure to positive information related to COVID-19 vaccination on social media was associated with a higher willingness to receive such vaccination among Chinese factory workers [27]. Interpersonal communication, such as receiving advice from doctors and family members, was also positively associated with willingness to receive COVID-19 vaccination among the general population in China [28]. Clinical doctors and staff from community-based organizations (CBOs) are the main service providers for PLWHA [31]. Their advice regarding COVID-19 vaccination may have a great impact on PLWHA's decisions to accept such vaccination. A recent study suggested that exposure to positive information related to COVID-19 vaccination increased perceptions favoring such vaccination [27]. In this study, we hypothesized that exposure to information supporting PLWHA in receiving COVID-19 vaccination through the internet and social media as well as interpersonal communication would influence PLWHA's perceptions of such vaccination and, hence, affect their willingness to receive COVID-19 vaccination.

To our knowledge, no studies have investigated willingness to receive COVID-19 vaccination among PLWHA in China. To address knowledge gaps, this study investigated willingness to receive COVID-19 vaccination among a national sample of PLWHA. We examined the effects of the following factors: sociodemographics, HIV-related characteristics, individual-level factors (ie, perceptions related to COVID-19 vaccination), interpersonal-level variables (ie, exposure to COVID-19 vaccination–related information through the internet and social media as well as interpersonal communication), and sociostructural-level factors (ie, COVID-19 vaccination delivery model, members of priority groups, and shortage in vaccine supply). We further tested the hypothesis that perceptions of COVID-19 vaccination would mediate the association between interpersonal-level variables and willingness to receive COVID-19 vaccination.

Methods

Study Design

This study makes use of a multicenter cross-sectional online survey conducted in eight conveniently selected large Chinese cities between January and February 2021. These cities included two in the north (Tianjin and Beijing), two in the northeast (Shenyang and Hohhot), one in the east (Nanjing), and three in the south (Nanning, Guangzhou, and Shenzhen). Beijing is the capital city of China. Shenzhen is a major special economic zone in China bordering Hong Kong in the south. The other six cities are capital cities of the provinces. Reasons for selecting these cities included the following: (1) each city has a CBO providing services to PLWHA, (2) each city has a large number of PLWHA, and (3) COVID-19 vaccination was first scaled up at these sites. At the time of this study, people in Beijing, Guangzhou, and Shenzhen could make an appointment to receive COVID-19 vaccination. The procedures of making an appointment were simple. People first downloaded a smartphone app developed by the health bureau. After logging in, they could choose the time and location to receive COVID-19 vaccination. In the other five cities, vaccination was arranged by employers and did not allow individuals to make appointments. Only two types of inactivated COVID-19 vaccines—Sinovac-CoronaVac and Sinopharm—were available in China during the study period. They were provided by designated community vaccination centers and people could only receive them at sites in these centers. Immunodeficiency, including HIV infection, was listed as a precaution for COVID-19 vaccination in China during the study period; it was recommended that PLWHA seek

advice from doctors regarding COVID-19 vaccination [18]. Participants who had never received COVID-19 vaccination were asked about their willingness to receive the vaccination. The context of this study is shown in Figures 1 to 3 .

Figure 1. Number of patients living with HIV and AIDS in different study sites.

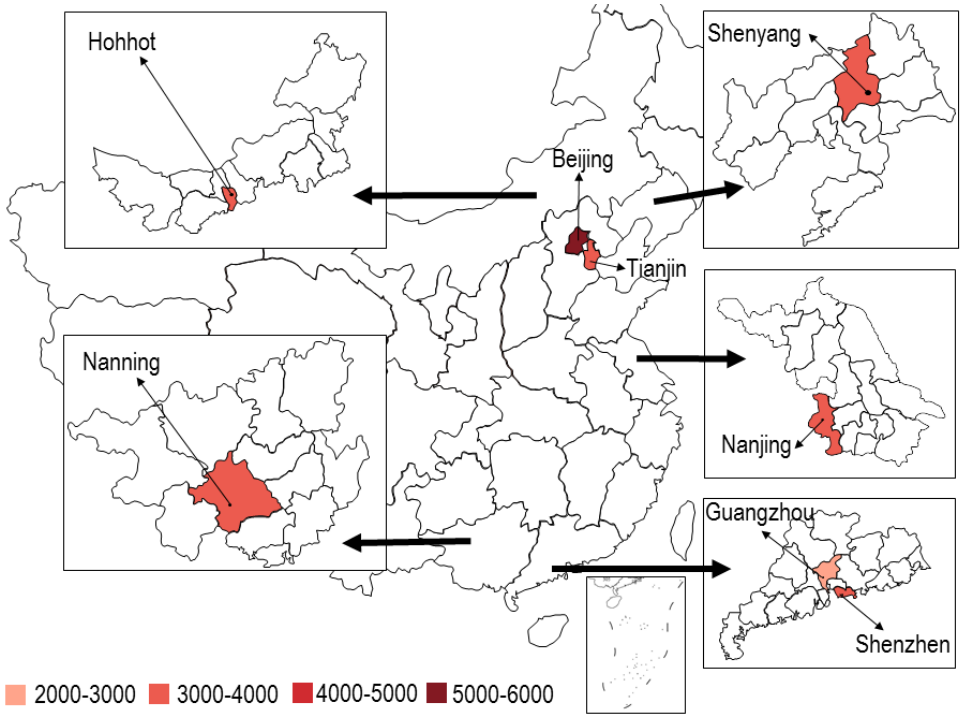


Figure 2. Number of participants in different study sites.

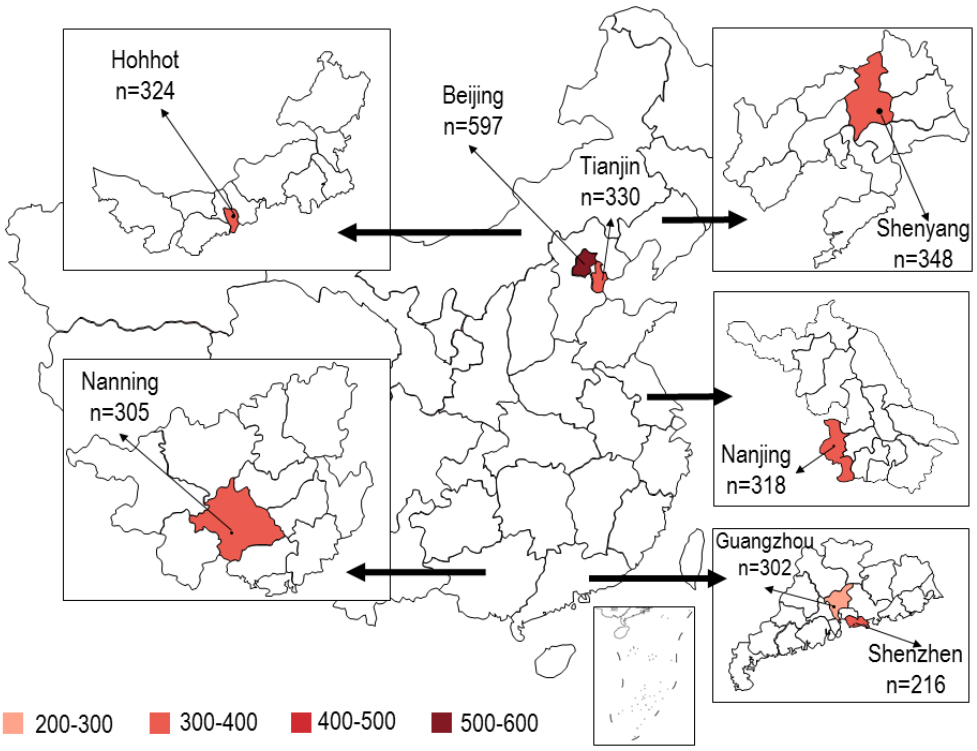
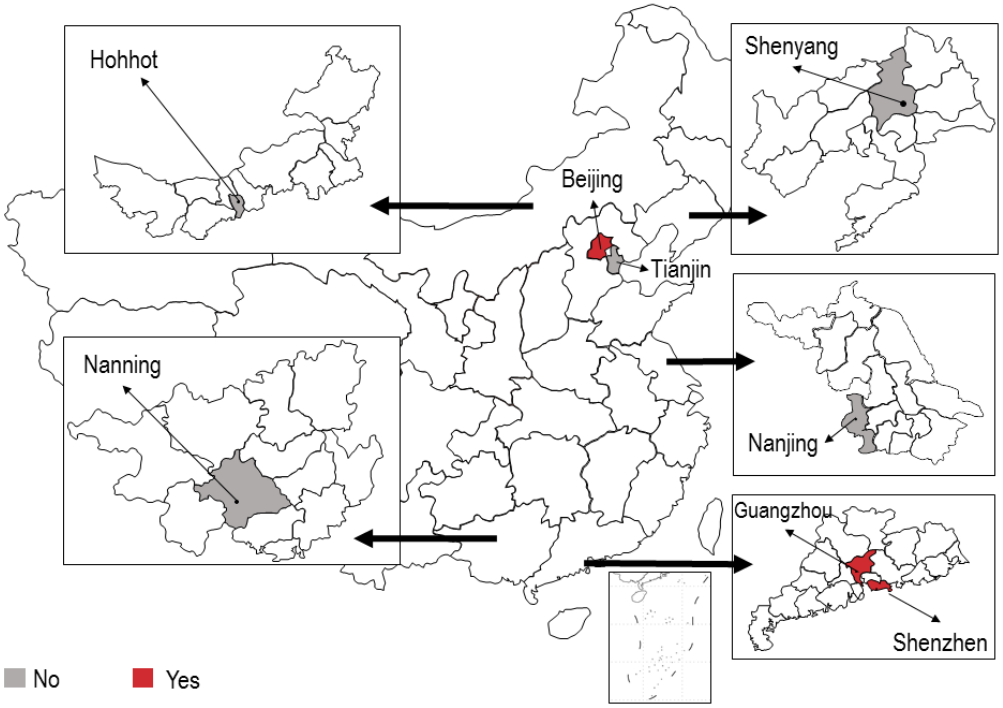


Figure 3. Participants' ability ("Yes") or inability ("No") to make appointments to receive COVID-19 vaccination in different study sites.



Study Population

Study participants included individuals aged 18 to 65 years who have been diagnosed with HIV or AIDS and were living in one of the eight cities. We did not include PLWHA older than 65 years, as COVID-19 vaccination was not approved for this age group in China at the time of the survey. Exclusion criteria included the following: (1) being illiterate and unable to complete the questionnaire survey and (2) being ineligible for COVID-19 vaccination (eg, pregnancy, latency, and severe allergy to previous vaccination).

Recruitment and Data Collection

The eight CBOs that were mainly providing services to marginalized populations (eg, PLWHA and HIV high-risk populations), one in each study site, facilitated recruitment through their networks. These CBOs have been working closely with HIV clinical service providers. CBOs in China are the main providers of HIV outreach services to PLWHA, as these routine tasks have been transferred from government agencies to CBOs [31]. A high proportion of PLWHA are followed up by the CBOs. WeChat is the most common live-chat app used by CBOs to connect with PLWHA clients. The research team provided training for CBO staff who were responsible for communications with PLWHA within the scope of their routine service. Participants were recruited by posting advertisements in the WeChat groups involving PLWHA clients kept by the CBOs. The advertisements contained study information and contacts of project staff (ie, private WeChat account number and telephone number). Interested participants were asked to contact CBO staff either using private WeChat messages or telephone calls. CBO staff screened prospective participants using the eligibility criteria, introduced the study purpose and procedures, answered questions, and explained the confidentiality of study participation. Participation in this study was voluntary, and participants could refuse to answer any of the questions and withdraw from the study at any time without consequences. Participants signed an electronic consent form sent via WeChat messages. A link to access an online self-administered questionnaire was sent to the consented participants.

The survey was carried out through Golden Data, a commonly used, encrypted, web-based survey platform in China. Each individual WeChat account was allowed to access the online questionnaire only once to avoid duplicate responses. The Golden Data tool performed a completeness check before each questionnaire was submitted. Participants could review and change their responses when they completed the questionnaire. The survey took about 13 to 15 minutes to complete. An electronic coupon with a value of 20 Chinese yuan (US $3.1) was sent to each participant upon the completion of the survey. A unique ID was assigned to each participant, which was used to delink the study database from personal identifying data. All data collected by the online surveys were stored in the Golden Data server and protected by a password. Only the designated research team members had access to the database.

Ethics Approval and Consent to Participate

Signed electronic informed consent forms were obtained from all subjects involved in the study. These were kept separately from the empirical data and stored in a password-protected computer or a locked cabinet in the same locked office. This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Boards of Changzhi Medical College (protocol code RT2021003).

Measurements

Development of the Questionnaire

A panel consisting of public health researchers, health psychologists, clinicians, CBO staff, and PLWHA was formed to develop the questionnaire used in this study. The panel revised and finalized the questionnaire based on a pilot test among 10 PLWHA. These 10 PLWHA did not participate in the actual survey.

Background Characteristics

Participants reported sociodemographic characteristics, lifestyles (ie, smoking and alcohol drinking), height and weight, and history of other vaccinations in the past 3 years. Participants were also asked whether they had any chronic conditions, such as chronic cardiovascular, respiratory, kidney, and liver diseases; hypertension; diabetes mellitus and its chronic complications; cancers; lymphoma; leukemia; autoimmune diseases; hemorrhagic diseases; and history of severe allergy. The survey also collected some characteristics related to HIV infection (eg, time since HIV diagnosis, whether they were receiving ART, HIV viral load and CD4+ T cell count in the most recent episode of testing, and self-reported severity of AIDS-related symptoms).

Willingness to Receive COVID-19 Vaccination

Participants were asked about their likelihood of receiving free COVID-19 vaccination in the future; the response categories were as follows: 1 (very unlikely), 2 (unlikely), 3 (neutral), 4 (likely), and 5 (very likely). This study defined willingness to receive COVID-19 vaccination as the responses "likely" or "very likely" [27].

Variables at the Sociostructural, Individual, and Interpersonal Levels Related to COVID-19 Vaccination

The research team interviewed staff from the Chinese Center for Disease Control and Prevention who were responsible for implementing the COVID-19 vaccination program about whether individuals were allowed to make an appointment to receive COVID-19 vaccination and whether there was a shortage of COVID-19 vaccines during the project period at different study sites. Participants were asked whether they belonged to any of the groups who had priority to receive COVID-19 vaccination as listed by the National Health Commission during the project period.

At the individual level, four scales were constructed to measure perceptions related to COVID-19 vaccination. These scales were as follows: (1) the 5-item Positive Attitude Scale, (2) the 5-item Negative Attitude Scale, (3) the 4-item Perceived Subjective Norm Scale (ie, whether significant others would support them to receive COVID-19 vaccination), and (4) the 5-item Perceived Behavioral Control Scale (ie, how much control PLWHA have for receiving COVID-19 vaccination). Response categories were as follows: 1 (strongly disagree), 2 (disagree), 3 (neutral), 4 (agree), and 5 (strongly agree). Positive and negative attitudes, perceived subjective norm, and perceived behavioral control were significantly associated with willingness to receive COVID-19 vaccination among Chinese people [27].

For interpersonal-level variables, participants were asked whether they received advice given by doctors, CBO staff, friends and/or family members, and other PLWHA regarding COVID-19 vaccination. Participants were also asked about the overall opinion regarding COVID-19 vaccination that they found on the internet or social media; response categories were as follows: 1 (against taking up COVID-19 vaccination), 2 (no advice/neutral), and 3 (supportive in taking up COVID-19 vaccination).

Statistical Analysis

Using willingness to receive COVID-19 vaccination as the dependent variable and background characteristics as independent variables, crude odds ratios were obtained by logistic regression models. After adjusting for variables with $P<.05$ in the univariate analysis, associations between independent variables of interest (ie, individual-, interpersonal-, and sociostructural-level variables) and the dependent variable were then assessed by adjusted odds ratios (aORs) and 95% CIs. Each aOR was obtained by fitting a single logistic regression model, which involved one of the independent variables of interest and all significant background characteristics.

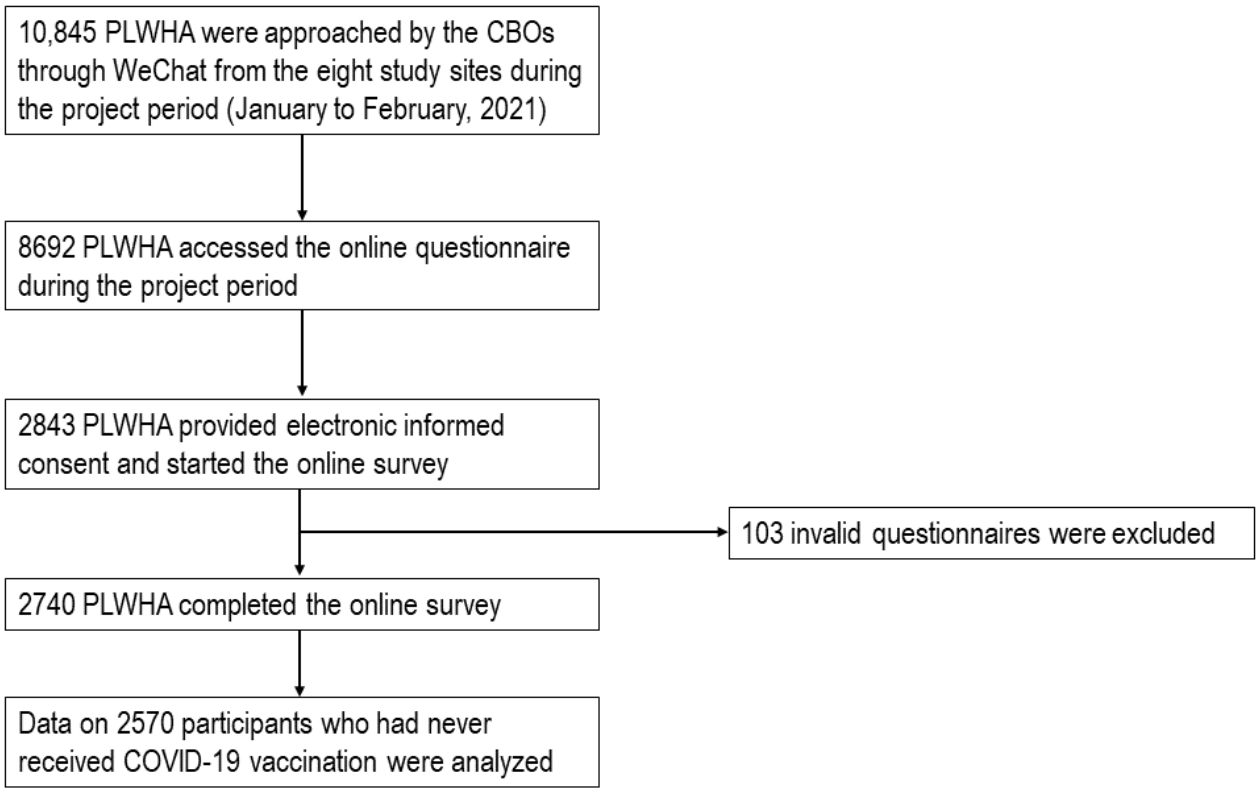
Path analysis was conducted to test the mediation model. The mean scores of the Positive Attitude Scale, the Negative Attitude Scale, the Perceived Subjective Norm Scale, and the Perceived Behavioral Control Scale were used as indicators to represent the latent variable of perceptions related to COVID-19 vaccination. The mean scores of advice given by doctors, CBO staff, friends and/or family members, and other PLWHA, as well as the overall opinion on the internet and social media, were used as indicators to represent the latent variable of interpersonal-level variables. Confirmatory factor analysis was conducted to test goodness of fit of these constructs. The latent variable representing perceptions was used as the independent variable, and willingness to receive COVID-19 vaccination was used as the dependent variable. The significant background characteristics were controlled for the model. Goodness of fit was tested using chi-square tests, the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the root mean square error of approximation (RMSEA). Standardized path coefficients (β) and unstandardized path coefficients (B) were reported. The asymmetric CIs based on the bootstrap method (10,000 times) that were used for significance testing of mediation hypotheses with the 95% bootstrap CI did not include zero, indicating a statistically significant mediation effect. The level of statistical significance was set at $P<.05$. SPSS for Windows (version 21.0; IBM Corp) and Mplus (version 8.3; Muthén and Muthén) were used for all analyses.

Results

Background Characteristics

The CBOs approached 10,845 PLWHA in their WeChat groups, 8692 accessed the online survey, 2740 completed the survey, and 170 received at least one dose of COVID-19 vaccination at the time of the survey. This study was based on 2570 eligible participants who had never received COVID-19 vaccination; the flowchart of this study is presented in Figure 4.

Figure 4. Flowchart of data collection. CBO: community-based organization; PLWHA: people living with HIV and AIDS.



The majority of the 2570 participants were 18 to 39 years of age (n=1916, 74.6%), identified themselves as male (n=2106, 81.9%), were currently single (n=1750, 68.1%), had a full-time job (n=1782, 69.3%), and only had basic health insurance (n=1927, 75.0%). Regarding characteristics related to HIV infection, 17.2% (n=443) of the 2570 participants received their diagnosis within 1 year, 97.3% (n=2501) were receiving ART, 67.9% (n=1746) reported undetectable viral load, and 46.0% (n=1181) reported their CD4+ T cell count level to be above 500/μL. Less than 5% of the participants self-reported having severe AIDS-related symptoms (Tables 1 and 2).

Table 1. Sociodemographic characteristics of 2570 unvaccinated people living with HIV and AIDS in eight Chinese cities.

Characteristic	All participants (N=2570), n (%)	Participants willing to receive COVID-19 vaccination (n=1470), n (%)	Participants unwilling to receive COVID-19 vaccination (n=1100), n (%)	Participants willing versus unwilling, cOR[a] (95% CI)	*P* value
Age group (years)					
18-29	791 (30.8)	456 (31.0)	335 (30.5)	1.0	Ref[b]
30-39	1125 (43.8)	638 (43.4)	487 (44.3)	0.96 (0.80-1.16)	.68
40-49	475 (18.5)	287 (19.5)	188 (17.1)	1.12 (0.89-1.41)	.33
≥50	179 (7.0)	89 (6.1)	90 (8.2)	0.73 (0.53-1.01)	.054
Gender at birth					
Male	2431 (94.6)	1390 (94.6)	1041 (94.6)	1.0	Ref
Female	139 (5.4)	80 (5.4)	59 (5.4)	1.02 (0.72-1.44)	.93
Gender identity					
Male	2106 (81.9)	1224 (83.3)	882 (80.2)	1.0	Ref
Female	228 (8.9)	127 (8.6)	101 (9.2)	0.91 (0.69-1.19)	.48
Transgender	228 (8.9)	114 (7.8)	114 (10.4)	0.72 (0.55-0.95)	.02
Others	8 (0.3)	5 (0.3)	3 (0.3)	1.20 (0.29-5.04)	.80
Relationship status					
Currently single	1750 (68.1)	993 (67.6)	757 (68.8)	1.0	Ref
Cohabitating or married with a same-sex partner	377 (14.7)	217 (14.8)	160 (14.5)	1.03 (0.83-1.30)	.77
Cohabitating or married with an opposite-sex partner	443 (17.2)	260 (17.7)	183 (16.6)	1.08 (0.88-1.34)	.46
Highest education level attained					
Junior high school or below	425 (16.5)	249 (16.9)	176 (16.0)	1.0	Ref
Senior high school or equivalent	574 (22.3)	319 (21.7)	255 (23.2)	0.88 (0.69-1.14)	.34
College and above	1571 (61.1)	902 (61.4)	669 (60.8)	0.95 (0.77-1.18)	.66
Employment status					
Full time	1782 (69.3)	1022 (69.5)	760 (69.1)	1.0	Ref
Part time, unemployed, retired, student, or others	788 (30.7)	448 (30.5)	340 (30.9)	0.98 (0.83-1.16)	.81
Monthly personal income (Chinese yuan[c])					
No fixed income	302 (11.8)	174 (11.8)	128 (11.8)	1.0	Ref
<1000	136 (5.3)	72 (4.9)	64 (5.8)	0.83 (0.55-1.24)	.36
1000-2999	338 (13.2)	199 (13.5)	139 (12.6)	1.05 (0.77-1.44)	.75
3000-4999	736 (28.6)	413 (28.1)	323 (29.4)	0.94 (0.72-1.23)	.66
5000-6999	492 (19.1)	285 (19.4)	207 (18.8)	1.01 (0.76-1.35)	.93
7000-9999	273 (10.6)	174 (11.8)	99 (9.0)	1.29 (0.92-1.81)	.13
≥10,000	293 (11.4)	153 (10.4)	140 (12.7)	0.80 (0.58-1.11)	.19
Type of health insurance					
None	307 (11.9)	166 (11.3)	141 (12.8)	1.0	Ref
Basic health insurance only	1927 (75.0)	1111 (75.6)	816 (74.2)	1.16 (0.91-1.47)	.24
Commercial health insurance only	69 (2.7)	47 (3.2)	22 (2.0)	1.82 (1.04-3.16)	.04

Characteristic	All participants (N=2570), n (%)	Participants willing to receive COVID-19 vaccination (n=1470), n (%)	Participants unwilling to receive COVID-19 vaccination (n=1100), n (%)	Participants willing versus unwilling, cOR[a] (95% CI)	*P* value
Both basic and commercial health insurance	253 (9.8)	140 (9.5)	113 (10.3)	1.05 (0.75-1.47)	.77
Others	14 (0.5)	6 (0.4)	8 (0.7)	0.64 (0.22-1.88)	.41

[a]cOR: crude odds ratio.

[b]Ref: reference.

[c]A currency exchange rate of 1 Chinese yuan=US $0.16 is applicable.

Table 2. Lifestyle and health conditions of 2570 unvaccinated people living with HIV and AIDS in eight Chinese cities.

Condition	All participants (N=2570), n (%)	Participants willing to receive COVID-19 vaccination (n=1470), n (%)	Participants unwilling to receive COVID-19 vaccination (n=1100), n (%)	Participants willing versus unwilling, cOR[a] (95% CI)	*P* value
Current smoker					
No	1855 (72.2)	1069 (72.7)	786 (71.5)	1.0	Ref[b]
Yes	715 (27.8)	401 (27.3)	314 (28.5)	0.94 (0.79-1.12)	.48
Current drinker					
No	2068 (80.5)	1190 (81.0)	878 (79.8)	1.0	Ref
Yes	502 (19.5)	280 (19.0)	222 (20.2)	0.93 (0.77-1.13)	.47
Self-reported BMI (kg/m^2)					
<18.5	235 (9.1)	125 (8.5)	110 (10.0)	1.0	Ref
18.5-23.9	1649 (64.2)	944 (64.2)	705 (64.1)	1.18 (0.90-1.55)	.24
24.0-27.9	558 (21.7)	327 (22.2)	231 (21.0)	1.25 (0.92-1.69)	.16
≥28	127 (4.9)	74 (5.0)	53 (4.8)	1.23 (0.80-1.90)	.36
Presence of chronic disease conditions					
No	1707 (66.4)	1009 (68.6)	698 (63.5)	1.0	Ref
Yes	863 (33.6)	461 (31.4)	402 (36.5)	0.79 (0.67-0.94)	.01
Medication use for treating chronic diseases					
No	2411 (93.8)	1385 (94.2)	1026 (93.3)	1.0	Ref
Yes	159 (6.2)	85 (5.8)	74 (6.7)	0.85 (0.62-1.17)	.33
History of other vaccinations in the past 3 years					
No	2002 (77.9)	1110 (75.5)	892 (81.1)	1.0	Ref
Yes	568 (22.1)	360 (24.5)	208 (18.9)	1.39 (1.15-1.69)	.001
Time since HIV diagnosis (years)					
≤1	443 (17.2)	264 (18.0)	179 (16.3)	1.0	Ref
2-5	1198 (46.6)	685 (46.6)	513 (46.6)	0.91 (0.73-1.13)	.38
>5	929 (36.1)	521 (35.4)	408 (37.1)	0.87 (0.69-1.09)	.22
Receiving antiretroviral therapy					
No	69 (2.7)	40 (2.7)	29 (2.6)	1.0	Ref
Yes	2501 (97.3)	1430 (97.3)	1071 (97.4)	0.97 (0.60-1.57)	.90
HIV viral load in the most recent episode of testing (copies/mL)					
Undetectable (<50)	1746 (67.9)	988 (67.2)	758 (68.9)	1.0	Ref
50-200	154 (6.0)	79 (5.4)	75 (6.8)	0.81 (0.58-1.12)	.21
201-400	69 (2.7)	45 (3.1)	24 (2.2)	1.44 (0.87-2.38)	.16
>400	137 (5.3)	87 (5.9)	50 (4.5)	1.34 (0.93-1.91)	.12
Not sure	464 (18.1)	271 (18.4)	193 (17.5)	1.08 (0.88-1.33)	.48
CD4+ T cell count in the most recent episode of testing (cells/mm^3)					
≥500	1181 (46.0)	669 (45.5)	512 (46.5)	1.0	Ref
350-499	531 (20.7)	320 (21.8)	211 (19.2)	1.16 (0.94-1.43)	.16
200-349	258 (10.0)	150 (10.2)	108 (9.8)	1.06 (0.81-1.40)	.66
<200	89 (3.5)	44 (3.0)	45 (4.1)	0.75 (0.49-1.15)	.19
Unknown	511 (19.9)	287 (19.5)	224 (20.4)	0.98 (0.80-1.21)	.85

Condition	All participants (N=2570), n (%)	Participants willing to receive COVID-19 vaccination (n=1470), n (%)	Participants unwilling to receive COVID-19 vaccination (n=1100), n (%)	Participants willing versus unwilling, cOR[a] (95% CI)	*P* value
Self-reported severity of AIDS-related symptoms					
No symptoms	1306 (50.8)	767 (52.2)	539 (49.0)	1.0	Ref
Mild	839 (32.6)	483 (32.9)	356 (32.4)	0.95 (0.80-1.14)	.60
Moderate	308 (12.0)	157 (10.7)	151 (13.7)	0.73 (0.57-0.94)	.01
Severe	117 (4.6)	63 (4.3)	54 (4.9)	0.82 (0.56-1.20)	.31

[a]cOR: crude odds ratio.

[b]Ref: reference.

Willingness to Receive COVID-19 Vaccination and Variables at the Individual, Interpersonal, and Sociostructural Levels

Over half of the participants were willing to receive free COVID-19 vaccinations in the future (1470/2570, 57.2%). A shortage of COVID-19 vaccines was encountered in Shenyang, Guangzhou, and Shenzhen. Among the participants, 19.0% (488/2570) identified themselves as belonging to a priority group that would receive COVID-19 vaccination. The Cronbach α of the scales for perceptions related to COVID-19 vaccination ranged from .83 to .92; single factors were identified by exploratory factor analysis, explaining 61.1% to 76.4% of the total variance (Table 3 and Multimedia Appendix 1).

Table 3. Willingness to receive COVID-19 vaccination and variables at the sociostructural, individual, and interpersonal levels among 2570 unvaccinated people living with HIV and AIDS (PLWHA).

Variable	All participants (N=2570)	Participants willing to receive COVID-19 vaccination (n=1470)	Participants unwilling to receive COVID-19 vaccination (n=1100)	Participants willing versus unwilling, cOR[a] (95% CI)	*P* value
Willing to receive free COVID-19 vaccination, n (%)					
No (very unlikely, unlikely, or neutral)	1100 (42.8)	0 (0)	1100 (100)	N/A[b]	N/A
Yes (likely or very likely)	1470 (57.2)	1470 (100)	0 (0)	N/A	N/A
Sociostructural-level variables, n (%)					
Individuals could make an appointment to receive COVID-19 vaccination during the study period					
No	1578 (61.4)	887 (60.3)	691 (62.8)	1.0	Ref[c]
Yes	992 (38.6)	583 (39.7)	409 (37.2)	1.11 (0.95-1.30)	.20
There was a shortage of COVID-19 vaccine in the city where the participants were living during the study period					
No	1729 (67.3)	1009 (68.6)	720 (65.5)	1.0	Ref
Yes	841 (32.7)	461 (31.4)	380 (34.5)	0.87 (0.73-1.02)	.09
Participants belonged to priority groups that would receive COVID-19 vaccination in their cities during the study period					
No	2082 (81.0)	1189 (80.9)	893 (81.2)	1.0	Ref
Yes	488 (19.0)	281 (19.1)	207 (18.8)	1.02 (0.84-1.25)	.85
Individual-level variables: perceptions and attitudes toward COVID-19 vaccination, mean (SD)					
Positive Attitude Scale[d] score	18.4 (4.8)	19.3 (4.6)	17.1 (4.7)	1.11 (1.09-1.13)	<.001
Negative Attitude Scale[e] score	18.6 (5.2)	18.1 (5.4)	19.3 (4.8)	0.96 (0.94-0.97)	<.001
Perceived Subjective Norm Scale[f] score	13.3 (2.4)	14.5 (2.5)	12.3 (1.8)	1.53 (1.46-1.61)	<.001
Perceived Behavioral Control Scale[g] score	12.9 (6.1)	14.7 (6.1)	10.6 (5.4)	1.13 (1.11-1.14)	<.001
Interpersonal-level variables, mean (SD)					
Advice from doctors regarding COVID-19 vaccination	2.1 (0.5)	2.2 (0.5)	2.0 (0.4)	2.03 (1.69-2.44)	<.001
Advice from CBO[h] staff regarding COVID-19 vaccination	2.1 (0.4)	2.1 (0.4)	2.0 (0.4)	1.86 (1.49-2.32)	<.001
Advice from friends and/or family members regarding COVID-19 vaccination	2.0 (0.2)	2.0 (0.4)	1.9 (0.2)	3.18 (1.92-5.26)	<.001
Advice from other PLWHA regarding COVID-19 vaccination	2.0 (0.3)	2.1 (0.3)	1.9 (0.4)	2.38 (1.85-3.07)	<.001
Overall opinion regarding COVID-19 vaccination for PLWHA on the internet and social media	2.0 (0.4)	2.1 (0.4)	2.0 (0.4)	1.63 (1.34-1.98)	<.001

[a]cOR: crude odds ratio.

[b]N/A: not applicable; cOR was not calculated for this item.

[c]Ref: reference.

[d]The Positive Attitude Scale includes five items and has a maximum score of 25; Cronbach α=.83; one factor was identified by exploratory factor analysis, explaining 61.1% of the total variance.

[e]The Negative Attitude Scale includes five items and has a maximum score of 25; Cronbach α=.87; one factor was identified by exploratory factor analysis, explaining 66.3% of the total variance.

[f]The Perceived Subjective Norm Scale includes four items and has a maximum score of 20; Cronbach α=.84; one factor was identified by exploratory factor analysis, explaining 63.4% of the total variance.

[g]The Perceived Behavioral Control Scale includes five items and has a maximum score of 25; Cronbach α=.92; one factor was identified by exploratory factor analysis, explaining 76.4% of the total variance.

[h]CBO: community-based organization.

Factors Associated With Willingness to Receive COVID-19 Vaccination

In the univariate logistic regression analysis, transgender persons, those with chronic conditions, and those with more severe AIDS-related symptoms showed lower willingness to receive COVID-19 vaccination. Having commercial health insurance only and a history of other vaccinations in the past 3 years were associated with higher willingness to receive COVID-19 vaccination (Tables 1 and 2).

After adjusting for significant background characteristics, having more positive attitudes toward COVID-19 vaccination (aOR 1.11, 95% CI 1.09-1.12; *P*<.001), stronger perceived support from significant others (perceived subjective norm; aOR 1.53, 95% CI 1.46-1.61; *P*<.001), and higher perceived behavioral control (aOR 1.13, 95% CI 1.11-1.14; *P*<.001) to take up the vaccination were associated with higher willingness to receive COVID-19 vaccination. A negative association was found between negative attitudes toward COVID-19 vaccination and the dependent variable (aOR 0.96, 95% CI 0.94-0.97; *P*<.001). At the interpersonal level, receiving advice supportive of COVID-19 vaccination from doctors (aOR 1.99, 95% CI 1.65-2.40; *P*<.001), CBO staff (aOR 1.89, 95% CI 1.51-2.36; *P*<.001), friends and/or family members (aOR 3.22, 95% CI 1.93-5.35; *P*<.001), and other PLWHA (aOR 2.38, 95% CI 1.85-3.08; *P*<.001) were associated with higher willingness to receive COVID-19 vaccination. The overall opinion supporting COVID-19 vaccination for PLWHA on the internet and social media was also positively associated with the dependent variable (aOR 1.59, 95% CI 1.31-1.94; *P*<.001; Table 4).

Table 4. Factors associated with willingness to receive COVID-19 vaccination among 2570 unvaccinated people living with HIV and AIDS (PLWHA).

Variable	aOR[a] (95% CI)	*P* value
Sociostructural-level variables		
Individuals could make an appointment to receive COVID-19 vaccination during the study period		
No	N/A[b]	N/A
Yes	N/A	N/A
There was a shortage of COVID-19 vaccines in the city where the participants were living during the study period		
No	N/A[b]	N/A
Yes	N/A	N/A
Participants belonged to priority groups that would receive COVID-19 vaccination in their cities during the study period		
No	N/A[b]	N/A
Yes	N/A	N/A
Individual-level variables		
Positive Attitude Scale score	1.11 (1.09-1.12)	<.001
Negative Attitude Scale score	0.96 (0.94-0.97)	<.001
Perceived Subjective Norm Scale score	1.53 (1.46-1.61)	<.001
Perceived Behavioral Control Scale score	1.13 (1.11-1.14)	<.001
Interpersonal-level variables		
Advice from doctors regarding COVID-19 vaccination	1.99 (1.65-2.40)	<.001
Advice from CBO[c] staff regarding COVID-19 vaccination	1.89 (1.51-2.36)	<.001
Advice from friends and/or family members regarding COVID-19 vaccination	3.22 (1.93-5.35)	<.001
Advice from other PLWHA regarding COVID-19 vaccination	2.38 (1.85-3.08)	<.001
Overall opinion regarding COVID-19 vaccination for PLWHA on the internet and social media	1.59 (1.31-1.94)	<.001

[a]aOR: adjusted odds ratio; odds ratios were obtained by fitting a single logistic regression model involving an independent variable of interest and all background variables listed in Tables 1 and 2 with *P*<.05 in univariate analysis.

[b]Univariate analyses of these variables yielded *P*>.05, so multivariate analyses were not conducted.

[c]CBO: community-based organization.

Testing the Mediation Effects of Perceptions on the Association Between Interpersonal-Level Variables and Willingness to Receive COVID-19 Vaccination

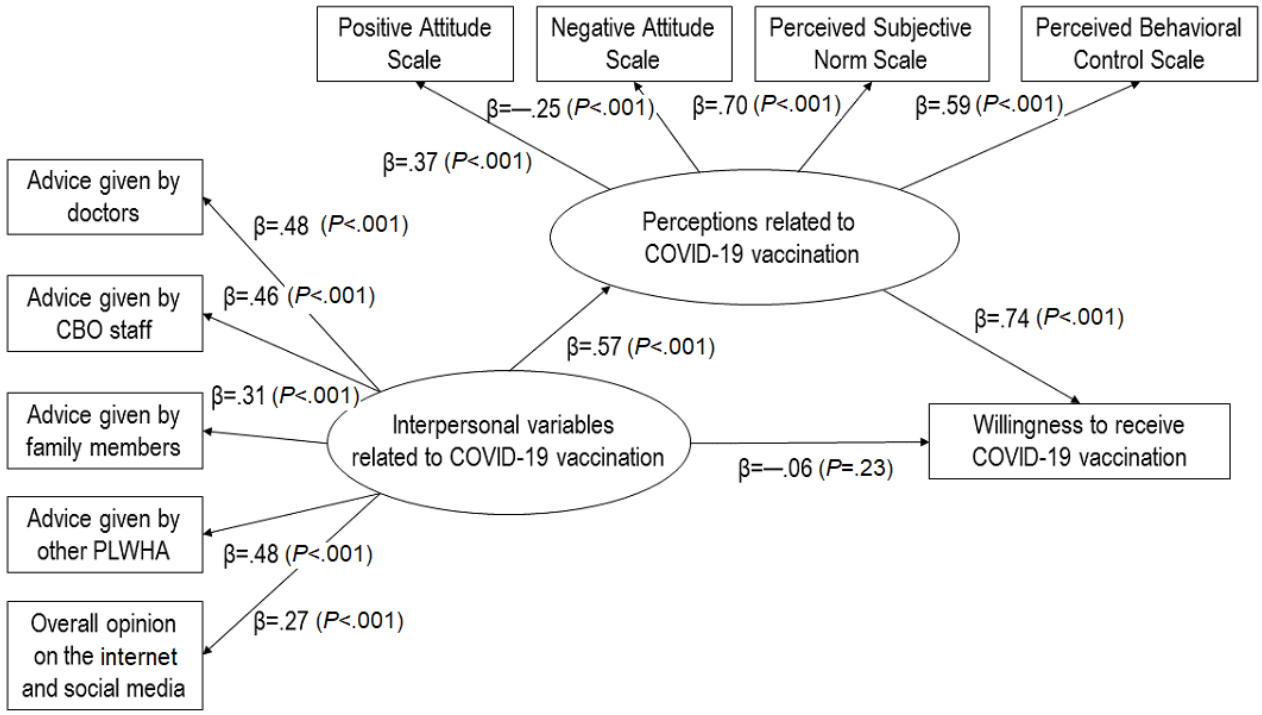
Model Testing

Confirmative factor analysis showed that perceptions fit the data well (CFI=0.98, TLI=0.90, and RMSEA=0.08). All the factor loadings were significant at $P<.001$, with β ranging from .23 to .73. The interpersonal-level variables also fit the data well (CFI=0.98, TLI=0.97, and RMSEA=0.02). All the factor loadings were significant at $P<.001$, with standardized coefficients ranging from .27 to .50. The hypothesized mediation model showed good fit to the data (CFI=0.96, TLI=0.94, and RMSEA=0.03).

Path Coefficients

Path analysis showed that interpersonal-level variables were positively associated with perceptions (B=4.72, β=.57, $P<.001$), while their association with willingness to receive COVID-19 vaccination was nonsignificant (B=–0.28, β=–.06, $P=.23$). Perceptions were positively associated with willingness to receive COVID-19 vaccination (B=0.43, β=.74, $P<.001$; Figure 5).

Figure 5. Mediation model with path coefficients. CBO: community-based organization; PLWHA: people living with HIV and AIDS.



Mediation Effects

Bootstrap analysis showed that interpersonal-level variables (B=2.01, 95% CI 1.67-2.53; β=.43, 95% CI .37-.51; $P<.001$) were indirectly associated with willingness to receive COVID-19 vaccination via perceptions. Perceptions fully mediated the association between interpersonal-level variables and willingness to receive COVID-19 vaccination.

Discussion

Principal Findings

We found that willingness to receive COVID-19 vaccination among PLWHA is essential in the scale-up of COVID-19 vaccination among this group. The finding represents the latest estimate of willingness to receive COVID-19 vaccination among PLWHA in China and can be used to project future vaccine uptake in this group. We extended the existing literature by conducting this study in multiple cities in different geographic regions of China, with a large sample size, and examined the multiple-level factors that correlated with willingness to receive the vaccine.

We found that the level of willingness among our participants was relatively low (<60%). This level was lower than that of PLWHA in France and the United States as well as the general population in most parts of the world [19] and China (70%-90%) [26,27]. Since there is a gap between willingness and actual uptake, COVID-19 vaccination coverage among PLWHA would be even lower without effective interventions [32]. The above findings revealed COVID-19 vaccination hesitancy and highlighted a strong need to promote COVID-19 vaccination among PLWHA.

This study examined associated factors at all three levels suggested by the socioecological model; the findings could inform tailored interventions promoting COVID-19 vaccination among PLWHA. This was the first study to demonstrate that the individual-level variables (ie, perceptions related to COVID-19 vaccination) and interpersonal-level variables (ie, advice from others and information exposure on the internet and social media) were determinants of willingness among PLWHA. The findings extended the application of the socioecological model. More importantly, this study examined the potential mechanism of the associations between

interpersonal interactions and willingness to receive COVID-19 vaccination. The results suggest that exposure to advice and information supporting PLWHA in receiving COVID-19 vaccination might enhance perceptions favoring COVID-19 vaccination, which, in turn, may increase their willingness to receive such vaccination. The significant mediation effect supported the mechanism proposed by the social learning theory [33].

This study also had numerous practical implications for developing tailored vaccination strategies for PLWHA. First, more attention should be given to PLWHA who are transgender persons, with chronic conditions, and who have severe AIDS-related symptoms, as these subgroups reported lower willingness. Transgender people are often marginalized, encountering difficulties to access health care services [34]. Future programs targeting PLWHA should consider including transgender-friendly vaccination services. Having AIDS-related symptoms was also associated with lower willingness. Since official opinions in China stated that the effectiveness of COVID-19 vaccination was lower for people with immunodeficiency [18], PLWHA might think that they may not benefit from COVID-19 vaccination. Health communication messages should clearly state that it is recommended that PLWHA receive COVID-19 vaccination if their chronic conditions are stable, regardless of AIDS-related symptoms.

Second, modifying perceptions related to COVID-19 vaccination is potentially useful in health promotion, as they were significantly associated with willingness in the expected directions. It is useful to increase positive attitudes toward COVID-19 vaccination, as this was a facilitator. Health communication messages should emphasize the physical and psychological benefits of COVID-19 vaccination. About half of the participants had concerns related to side effects, exposing PLWHA's identities, and potential interactions between COVID-19 vaccines and HIV and ART. Having more concerns was associated with lower willingness. Testimonials on positive experiences shared by vaccinated PLWHA might be useful in reducing their concerns related to side effects and privacy. Health communication messages should also emphasize that there is no evidence showing that ART and COVID-19 vaccination would have negative impacts on each other [35]. Less than 40% of the participants perceived that medical professionals, CBO staff, family members, and friends would support them in taking up COVID-19 vaccination. Such perception was also a facilitator. Future programs should consider involving the significant others of PLWHA in order to create a subjective norm favoring COVID-19 vaccination uptake. It is also useful to enhance perceived behavioral control, as this was another facilitator. There is much room for improvement. Facilitating PLWHA in forming a plan to receive COVID-19 vaccination may be helpful for improving perceived behavioral control.

Third, the significant mediation effect of perceptions on the association between interpersonal-level variables and willingness to receive COVID-19 vaccination suggested that future programs should involve clinical doctors, CBO staff, friends and/or family members, and peers of PLWHA to give supportive advice. Health authorities should also disseminate clear recommendations for PLWHA to receive COVID-19 vaccination through official online channels, which are considered influential and credible sources by Chinese people [36]. These strategies may be useful to modify PLWHA's perceptions and, in turn, increase their willingness to receive COVID-19 vaccination.

This study also had some limitations. First, policies and guidelines related to COVID-19 vaccination are changing rapidly. Our findings are most applicable to the early phase of COVID-19 vaccination implementation in China. Second, participants were recruited in large Chinese cities. Generalizations to PLWHA living in smaller cities or counties in China should be made cautiously. Third, we were not able to collect information from PLWHA who refused to participate in the study. PLWHA who refused to complete the survey may have different characteristics from the participants. Selection bias existed. Fourth, most items and scales used in this study were self-constructed based on those used in the general population. The internal validity of these scales was acceptable. However, external validation data were seldom available. Fifth, it was a limitation that we did not ask whether participants anticipated or had experienced challenges in making an appointment to receive the COVID-19 vaccine. The procedures to make an appointment are easy. Most Chinese people did not encounter difficulties when they were using the appointment system. We believe that the impact of anticipated and experienced challenges in making an appointment on PLWHA's willingness to receive COVID-19 vaccination was limited. Sixth, we did not study PLWHA's preferences for different types of COVID-19 vaccines. Although inactivated vaccines were the only available COVID-19 vaccines in China during the study period, it is worthwhile to look at their preferences for other types of vaccines (eg, mRNA or adenovirus vector vaccines) [37]. Moreover, the selection of the time frame for the history of other vaccinations (ie, past 3 years) was arbitrary. Furthermore, causality could not be established, as this was a cross-sectional study.

Conclusions

In sum, PLWHA in China reported a relatively low willingness to receive COVID-19 vaccination compared to PLWHA in other countries and the general population in most parts of the world. Perceptions related to COVID-19 vaccination and interpersonal-level variables, such as receiving advice from others or information exposure through the internet and social media, were determinants of willingness. Information exposure on the internet and social media and interpersonal communications with doctors, CBO staff, friends, family members, and other PLWHA may be major sources of influence on PLWHA's perceptions and willingness to receive COVID-19 vaccination. The study findings could be used to design tailored interventions with the aims of improving vaccination coverage and reduce risks of COVID-19 among PLWHA.

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Authors' Contributions

WT, ZW, and JX were responsible for the conceptualization of the study. HZQ, WT, and JX were responsible for the methodology of the study. XH, MY, GF, GL, LL, JY, YQ, and JZ were responsible for data curation. ZW and HJ were responsible for the formal analysis. XH, MY, GF, GL, LL, JY, YQ, JZ, XZ, XJ, GC, and JX were responsible for project administration and for securing resources. JX was responsible for supervision. ZW, HJ, and JX were responsible for writing and preparing the original draft of the paper. HZQ, WT, ZW, and JX were responsible for writing, reviewing, and editing the paper. JX was responsible for funding acquisition. All authors have read and agreed to submission of the manuscript. XH, MY, GF, GL, LL, JY, YQ, and JZ contributed equally as first authors; WT, ZW, and JX contributed equally as corresponding authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Frequency distribution of items measuring individual-level and interpersonal-level variables.
[DOCX File , 20 KB - publichealth_v7i10e31125_app1.docx]

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Abbreviations

aOR: adjusted odds ratio
ART: antiretroviral therapy
CBO: community-based organization
CFI: comparative fit index
mRNA: messenger RNA
PLWHA: people living with HIV and AIDS
RMSEA: root mean square error of approximation
TLI: Tucker-Lewis index
WHO: World Health Organization

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