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Examining the Factor Structure of Objective Health Literacy and Numeracy Scales: Large-Scale Cross-Sectional Study

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Abstract

Background: Scales for measuring health literacy and numeracy have been broadly classified into performance-based (objective) and self-reported (subjective) scales. Both types of scales have been widely used in research and practice; however, they are not always consistent and may assess different latent constructs. Furthermore, an increasing number of objective measures have been developed, and it is unclear how many latent factors should be assumed.

Objective: This study aimed to examine the psychometric properties and factor structure of items assessing objective health literacy across multiple scales and to clarify which aspects of objective health literacy would be correlated with subjective measures, as well as health behaviors and lifestyles.

Methods: A total of 5 objective scales (72 items in total) were administered to Japanese-speaking adults (N=16,097; women: 7722/16,097, 48%; mean age 54.89, SD 16.46 years). The analyzed scales included items assessing the numeracy, comprehension, and application of health information, some of which were contextualized for specific diseases, such as diabetes and cancer. Participants' responses were submitted to exploratory factor analysis, and individual factor scores were calculated to test correlations with subjective health literacy, health behavior, and lifestyle.

Results: Exploratory factor analysis identified 3 factors, which were interpreted as conceptual knowledge, numeracy, and synthesis. The conceptual knowledge factor consisted of items about medical word comprehension. All numeracy items loaded onto the same factor, even when contextualized for different diseases. The synthesis factor was characterized by items assessing the ability to read and understand health-related information and make judgments on it using one's own knowledge. The identified factors showed high interfactor correlations (r values 0.53 - 0.64) and small-to-moderate correlations with subjective health literacy (r values 0.14 - 0.45). Additionally, each factor indicated small positive correlations with healthy diet and nutrition and lower substance use (r values 0.17 - 0.26).

Conclusions: Our findings suggest that scales of objective health literacy have at least three latent constructs (ie, conceptual knowledge, numeracy, and synthesis) and that disease specificity is not psychometrically prominent. Each factor has some overlap with subjective health literacy, but overall, subjective and objective health literacy should be interpreted as independent constructs, given the small-to-modest correlations.

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KEYWORDS

objective health literacy; objective health numeracy; health-related behaviors; exploratory factor analysis; confirmatory factor analysis

Introduction

Background

Health literacy plays a pivotal role in acquiring and maintaining healthy lifestyles, which help individuals prevent diseases and maintain their well-being [1]. Although the definition of health literacy varies across studies, the core concept refers to the

ability of an individual to obtain, process, understand, and use health information and services [2]. This conceptualization covers health numeracy, namely, applying numerical and quantitative reasoning skills to navigate a health care environment, access care, engage in treatment, and make informed health decisions [3]. Empirical studies have demonstrated that lower health literacy, including lower health

numeracy, is associated with lower autonomy and self-control in health behaviors as well as negative health outcomes, such as higher older adult mortality, increased emergency and inpatient facility use, lower medication compliance, and lower preventive service use [3,4].

Health literacy assessment has long been a research target, and hundreds of measures have been developed and published over the past 3 decades [5-8]. As Nguyen [6] noted, a typical assessment approach is to ask respondents to self-report about their experience on Likert scales (ie, subjective measurement), whereas it is also common to challenge individuals using standardized test stimuli to evaluate their underlying traits, knowledge, skills, and numeracy [9-12] (ie, objective measurement). For example, the Lipkus Numeracy Scale (henceforth, Lipkus) requires respondents to perform numeracy tests in general (eg, “Imagine that we rolled a fair, six-sided die 1,000 times. Out of 1,000 rolls, how many times do you think the die would come up even (2, 4, or 6)?”) [12]. Another typical approach is to assess word comprehension of health-related and medical terms [13]. It is also common to present responders with hypothetical scenarios or visual materials, such as nutrition labels [14,15] or maps of hospitals [16], to assess their ability to read, interpret, and process relevant information. Objective measures have been suggested to be suitable for estimating individual skills guiding actual health behavior [6]—an experimental study showed that individuals with high levels of objective (but not subjective) health literacy were able to critically evaluate health information on websites, which further helped them to choose an appropriate treatment option [17]. In addition, a prospective cohort study on patients with cardiovascular-related diseases showed that the lack of objective health literacy predicted poor refill adherence [18].

In contrast, most subjective measures ask respondents to self-report their perceptions and experiences of handling health information, typically using a Likert scale [6]. The 47-item European Health Literacy Survey Questionnaire (HLS-EU-Q47) [19] is one of the most widely used measures to assess individuals’ perceived abilities to access, understand, appraise, and apply health information (eg, “Finding information on symptoms of illnesses that concern you is...”; respondents indicate from very easy to very difficult) [19]. Another example is the Subjective Numeracy Scale (SNS), which assesses individuals’ beliefs about their skill in performing various mathematical operations (eg, “How good are you at working with fractions?”) and individuals’ preferences regarding the presentation of numerical information (eg, “When reading the newspaper, how helpful do you find tables and graphs that are parts of a story?”) [20]. Subjective measures typically assess individuals’ self-perceived ability to find and understand health-related information as well as their confidence in doing so [17]. Also, some measures cover a wider range of psychological (eg, motivation and self-efficacy) aspects of health literacy [21]. A study suggested that individuals with lower levels of subjective numeracy are less motivated and less confident in numeric tasks [22]. Furthermore, the European Health Literacy Survey showed that subjective (but not objective) health literacy is predictive of self-perceived health [23], which might suggest that subjective measures may be

more suited to studying perception and beliefs about health status and behavior.

The objective and subjective measures appeared to tap into the same latent construct, that is, the ability to process health information. However, Waters et al [24] suggested that these 2 types of measures assess conceptually related but psychometrically distinct constructs and that numeracy should be separated from general health literacy. Begoray and Kwan [25] found almost null correlations between objective (word recognition and reading comprehension) and subjective (self-reporting of skills to access and communicate health information) assessments. Marks et al [26] suggested that objective measures may reflect medication knowledge, whereas subjective measures may not. For the associations with health outcomes and behaviors, a systematic review [27] concluded that the evidence is mixed. Several studies observed no differences between performance-based and self-reported health literacy for the associations with relevant health outcomes (eg, diabetes, stroke, and hypertension), whereas others documented objective-subjective discrepancies (eg, for cancer screening use). Hirsh et al [28] noticed that the self-reported disease severity of rheumatoid arthritis was associated with subjective health literacy but not with objective health literacy, including the ability to read and pronounce medical terms.

The possibility that objective and subjective measures assess different constructs of health literacy may make it difficult for researchers and practitioners to determine which type (or both) to include in their assessment batteries. Another challenge when building an assessment battery for health literacy research is that an enormous number of measures have been developed; thus far, there is no clear guidance on which to use and when [8]. Recently, we conducted an exploratory factor analysis of 219 items across 11 subjective measures (encompassing 45 subscales), indicating that dimension reduction was effective, as the items were well explained by 7 latent factors [29].

Objectives

In this study, we aimed to expand these findings to objective health literacy measures; namely, we conducted an exploratory factor analysis on 5 performance-based measures of health literacy and numeracy (see the *Methods* section for the selection criteria of the analyzed scales), including general and disease-specific (ie, chronic pain, cancer, and diabetes) scales. Through the analyses, we explored how many and what factors would emerge. In addition to the number of factors identified, we were also interested in whether disease-specific items would be recognized as independent factors or factors that reflect common skills and performances regardless of target diseases. Simultaneously, the identified factors were tested for their correlations with lifestyle and health status, as well as subjective health literacy and numeracy, to explore the consistencies and inconsistencies (or validity) with perceived health literacy and behaviors.

Methods

Data

Data from a larger longitudinal survey on the health behaviors, psychological characteristics, and lifestyles of Japanese-speaking adults (aged >18 y living in Japan) were used. We used quota sampling to represent the population distribution for age and gender in Japan, and thus, we did not use a survey weight in the analysis. The overarching project (still ongoing) is a 3-year longitudinal study that includes multiple waves with different focuses: wave 1 (N=20,573; early 2023) for physical activity (PA) and psychological characteristics [30] and for mobile health technology use [31], wave 2 (conducted in 2023; 6 mo after wave 1) for changes in PA and digital health behaviors [32], and wave 3 (conducted in early 2024) for health literacy and lifestyle. Wave 3 included both subjective and objective health literacy scales; the psychometric properties of the subjective scales have been reported elsewhere [26]. This study used the wave 3 data (N=16,097; women: 7722/16,097, 48%; mean age 54.89, SD 16.46 years), of which 87% (14,064/16,097) participated in wave 1. As the dropout rate was high, an additional sample of 2033 participants was recruited at wave 3. This addition was for the overarching project but not for this study specifically. Although we could not use quotas in this extra sampling due to the time pressure that we had, we found that the age and gender distributions were similar to those of the general population, so we included this additional sample in the analysis. This study focused exclusively on objective scales. We used data from 5 objective health literacy (or numeracy) scales together with the validation measures of subjective health literacy, health behavior, and lifestyle (refer to the *Measures* section).

Ethical Considerations

Participants were paid for online panels recruited by a survey firm. Interested individuals followed a link to the survey site, and on the top page, they received study information (written) and provided informed consent to proceed to individual questionnaire pages. Each participant was assigned a study ID, which was used as the key in merging their responses across different waves. No personal information was obtained throughout the study. The study was approved by the Ethics

Committee of the National Institute of Advanced Industrial Science and Technology (approval ID: 2022 - 1279).

Measures

Objective Health Literacy and Numeracy Scales

We selected the scales for inclusion in this study following published reviews (eg, [8,33,34], including Tavousi et al [8], the latest review on health literacy scales over the past 3 decades when the study was conceptualized, and Nakadai et al [34], a narrative review of the scales available in Japanese). Among the scales listed, we included those that met the following criteria: the scale was available in English or Japanese and could be implemented on a static online survey (ie, did not require audiovisual materials or in-person interactions), and specific instructions and items were available from published articles, supporting materials, or personal correspondence with the authors of the scales. This selection process resulted in four objective health literacy or numeracy scales: the Lipkus [12,35], Newest Vital Sign (NVS) scale [14,15], Functional Health Literacy Scale for Young Adults (funHLS) [13], and Cancer Health Literacy Test (CHLT) scale [16]. An additional database search (Google Scholar and PubMed) identified the Diabetes Health Numeracy (DHN) scale [36], which was eligible for this study. Table 1 summarizes the characteristics of each included scale; most objective health literacy scales are not Likert type. For example, the funHLS presented medical stem terms (eg, caries) and asked participants to indicate the most relevant words for each stem term among 3 response options (eg, virus, bacteria, and fungus). Across the scales, each response was binary coded to represent 1 (correct) and 0 (incorrect), and the total score was calculated for each scale, with higher values indicating higher levels of objective health literacy or numeracy. It should be noted that the current analyses included translated versions of the scales, and responses to some of the items were potentially affected by cultural differences. For example, the NVS and CHLT included items assessing comprehension of food nutrition and prescription medication labels. These stimuli were modified to be familiar to Japanese respondents—particularly for the NVS, the translation and adjustment were conducted rigorously in accordance with the established cross-cultural adaptation guidelines [37,38].

Table . Overview of the objective health literacy and numeracy scales.

Scale name (abbreviation)	Items, n (Cronbach α)	Test format	Description
Lipkus Numeracy Scale (Lipkus) [12,35]	10 (0.79)	Numeric response questions	Measures the ability to understand and use numeric information, particularly for probability: (eg, “Imagine that we rolled a fair, six-sided die 1,000 times. Of 1,000 rolls, how many times do you think the die would come up even (2, 4, or 6)”)?
Newest Vital Sign (NVS) scale [14,15]	6 (0.63)	Numeric response questions and open-ended questions	Measures comprehension, numeracy, and application and evaluation skills. Responders are presented with a nutrition label of ice cream, from which they are required to extract necessary information for calculation (eg, “If you eat the entire container, how many calories will you eat?”) and evaluation (eg, “Pretend that you are allergic to the following substances: penicillin, peanuts, latex gloves, and bee stings. Is it safe for you to eat this ice cream?”)
Functional Health Literacy Scale for Young Adults (funHLS) [13]	19 (0.93)	Multiple choice questions	Measures knowledge and comprehension of health-related and medical terms. Responders are presented with stem words, for each of which they are asked to indicate the most relevant among 3 response options (eg, stem=caries: response options=virus, bacteria, and fungus).
Diabetes Health Numeracy (DHN) scale [36]	7 (0.85)	Multiple choice questions	Measures numeracy skills, contextualized for diabetes (eg, “If you walk for about 30 minutes you can burn 100 calories. If you want to burn 150 calories, how long do you have to walk?”). Several items tap into interpretation skills (eg, “read a table about diagnostic criteria for diabetes and indicate the stage of an example patient”).
Cancer Health Literacy Test scale (CHLT) [16]	30 (0.85)	Multiple choice questions	Measures knowledge (eg, “Which is the highest in calories and protein? – French fries, cheeseburger, hard-boiled egg”), comprehension skills (eg, “In people who develop oral cancers, 25% of these cases occur in the tongue. Oral cancer occurs in the tongue...”), and their synthesis, contextualized for cancer.

Subjective Health Literacy Scale

The HLS-EU-Q47 [19,39] was used to assess subjective health literacy. The HLS-EU-Q47 and other self-report scales (see below) were used as validation measures to test for correlations with objective health literacy measures. The HLS-EU-Q47 measures 4 information-processing competencies (ie, how easy it is to access, understand, appraise, and apply health information) for 3 health-relevant domains (ie, health care, disease prevention, and health promotion). Participants indicated how applicable each item was to them using a 4-point scale (1=very easy and 4=very difficult). For ease of interpretation,

each item was reverse scored, with higher values indicating higher health literacy levels, and the total score was normalized to a range between 0 and 50 using the following formula: $(\text{mean}-1) \times (50/3)$. This scale has shown good reliability in the current data (Cronbach $\alpha=0.97$).

Subjective Health Numeracy Scale

The SNS was used to assess subjective health numeracy levels [20]. The SNS measures one's perceived ability to perform mathematical tasks (eg, How good are you at working with fractions?) and preferences for the use of numerical (vs prose) information (eg, When reading the newspaper, how helpful do

you find tables and graphs that are parts of a story?). Participants indicated how applicable each item was to them using a 4-point scale (1=not good at all, not helpful at all; 4=very good, very helpful). This scale has shown good reliability in the current data (Cronbach $\alpha=0.75$).

Physical Activity

The International Physical Activity Questionnaire Short Form [40,41] was used to assess PA levels. Respondents were asked to indicate the number of days and minutes per day spent walking, engaging in moderate-intensity activities, and engaging in vigorous-intensity activities. We did not use sedentary time for the current analyses. The weighted sum of the reported durations was calculated across the 3 activity categories, representing the total PA in the form of metabolic equivalents (METs hours per week). According to the Ministry of Health, Labour and Welfare in Japan, the recommended amount is 23 METs hours per week or higher for adults aged <65 years and 10 METs hours per week for older people [42].

Quality of Life and Health State

Quality of life (QoL) and health status were assessed using the 5-level EuroQol 5-Dimension (EQ-5D) version [43]. Participants indicated their health status by selecting the most appropriate statement (ie, no problems to extreme problems) for the following five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Participants' responses were combined into a 5-digit code, which was then converted into a numerical QoL score. The QoL score ranges from -0.025 to 1, where a negative value signifies a condition worse than death, 0 represents a state equivalent to death, and 1 denotes the highest possible health utility. At the end of the EQ-5D questions, participants were asked to rate their health status using a visual analog scale, ranging from 0 to 100, with 0 representing the worst health condition they could imagine and 100 representing the best health condition they could imagine.

Health-Related Lifestyles

The Short Multidimensional Inventory Lifestyle Evaluation (SMILE; [44]) consists of 45 items covering seven domains of health-related lifestyles: diet and nutrition, substance use, PA, strategies to deal with stress, sleep pattern, social support, and environmental exposure. Items asking about the use of illegal drugs (ie, items 10 and 11) were excluded to adhere to the ethics standards of the administering survey firm, and the remaining 43 items were used in the survey. Participants rated each item on a 4-point scale (1=always and 4=not at all). Summed scores were calculated for each domain, whereas items were reverse scored (with higher values indicating healthier lifestyles). The global score (sum of the 7 domains) demonstrated good internal consistency in the current data (Cronbach $\alpha=0.88$).

Statistical Analysis

An exploratory factor analysis was conducted on the 5 objective health literacy and numeracy scales. We excluded from the analysis (1) an item (funHLS12) exhibiting high correlations with other items (r values 0.72 - 0.80) and (2) 5 items to which >90% of participants responded correctly (ie, items 2, 4, 14, and 27 of the CHLT and item 5 of the Lipkus). The final dataset consisted of 66 items. As each item was binary scored (correct vs incorrect), polychoric correlations were calculated and used in factor analysis. The number of factors was determined based on the reduction in eigenvalues (ie, a scree plot), as well as on the interpretability of the identified factors. Exploratory factor analysis was conducted on randomly sampled 70% of the data ($n=11,268$), and the remaining 30% ($n=4829$) was used for confirmatory factor analysis as testing data. Before factor analyses, each dataset was tested with the Kaiser-Meyer-Olkin sampling adequacy measure (≥ 0.8 ; Kaiser 1970; [45]) and Bartlett sphericity test ($P \leq .05$; [46]). Confirmatory factor analysis was conducted with maximum likelihood estimation to replicate the factor structure obtained in the exploratory factor analysis. Our focus was on the goodness of fit of the model to the data, evaluated by the following indices: chi-square [47], comparative fit index [48], root mean square error of approximation [47,49], and the standardized root mean square residual [47]. For each factor, items with factor loadings of 0.40 or greater (a commonly used threshold for identifying meaningful loadings; eg, see [50]) were interpreted and were used to calculate a factor score (as the mean of raw item scores). For each factor, items with factor loadings of 0.40 or greater were interpreted and were used to calculate a factor score (as the mean of raw item scores). These factor scores were tested for correlations with validation measures (ie, subjective health literacy and numeracy scales, PA, QoL, health status, and health-related lifestyles). All analyses were performed using R (version 4.3.3; R Foundation for Statistical Computing). The *factanal* function was used for the exploratory factor analysis, and the *cfa* function of the *lavaan* package [51] was used for the confirmatory factor analysis.

Results

Descriptive Information

Table 2 presents the descriptive statistics. For the objective measures, the mean scores were comparable to those reported in previous studies—for example, in the general Japanese population (Lipkus, mean 9.6) [35], an Italian population-based sample (NVS, mean 4.1) [52], and a sample from the United States (CHLT, mean 22.3) [16]. The total score on the HLS-EU-Q47 was slightly higher than that reported among Japanese people (mean 25.3) but lower than that reported among Europeans in the literature (mean 33.8) [39].

Table . Descriptive statistics (n=16,097).

Variable	Values
Age (y), mean (SD)	54.89 (16.46)
Gender (women), n (%)	7722 (48)
Objective health literacy and numeracy scales, mean (SD)	
Lipkus ^a	7.80 (2.34)
NVS ^b	3.50 (1.69)
funHLS ^c	14.14 (5.21)
DHN ^d	5.38 (2.09)
CHLT ^e	24.67 (4.89)
Subjective health literacy and numeracy scales, mean (SD)	
HLS-EU-Q47 ^f	28.23 (8.07)
SNS ^g	3.24 (0.67)

^aLipkus: Lipkus Numeracy Scale.

^bNVS: Newest Vital Sign scale.

^cfunHLS: Functional Health Literacy Scale for Young Adults.

^dDHN: Diabetes Health Numeracy scale.

^eCHLT: Cancer Health Literacy Test scale.

^fHLS-EU-Q47: 47-item European Health Literacy Survey Questionnaire. A general health literacy index score comprising all items was standardized on a metric between 0 and 50, using the following formula: $(\text{mean} - 1) \times (50/3)$.

^gSNS: Subjective Numeracy Scale.

Exploratory Factor Analysis

The factor analysis performed on 66 items across 5 scales revealed eigenvalues of 16.43, 3.09, 1.93, and 1.59 for the 1- to 4-factor solutions. The reduction in the eigenvalue supported the 3-factor solution, with explained variances of 0.16, 0.15, and 0.10 for the 3 factors (total explained variance: 0.41).

Additionally, the 3-factor solution had good interpretability; the factor loadings are visualized in [Figure 1](#), which confirms that no items had double or triple loadings. The exact factor loadings for each item are listed in Table S1 in [Multimedia Appendix 1](#). [Table 3](#) summarizes the characteristics of each factor.

Figure 1. Items' factor loadings on each factor. CHLT: Cancer Health Literacy Test scale; DHN: Diabetes Health Numeracy scale; FA: factor; funHLS: Functional Health Literacy Scale for Young Adults; Lipkus: Lipkus Numeracy Scale; NVS: Newest Vital Sign scale.

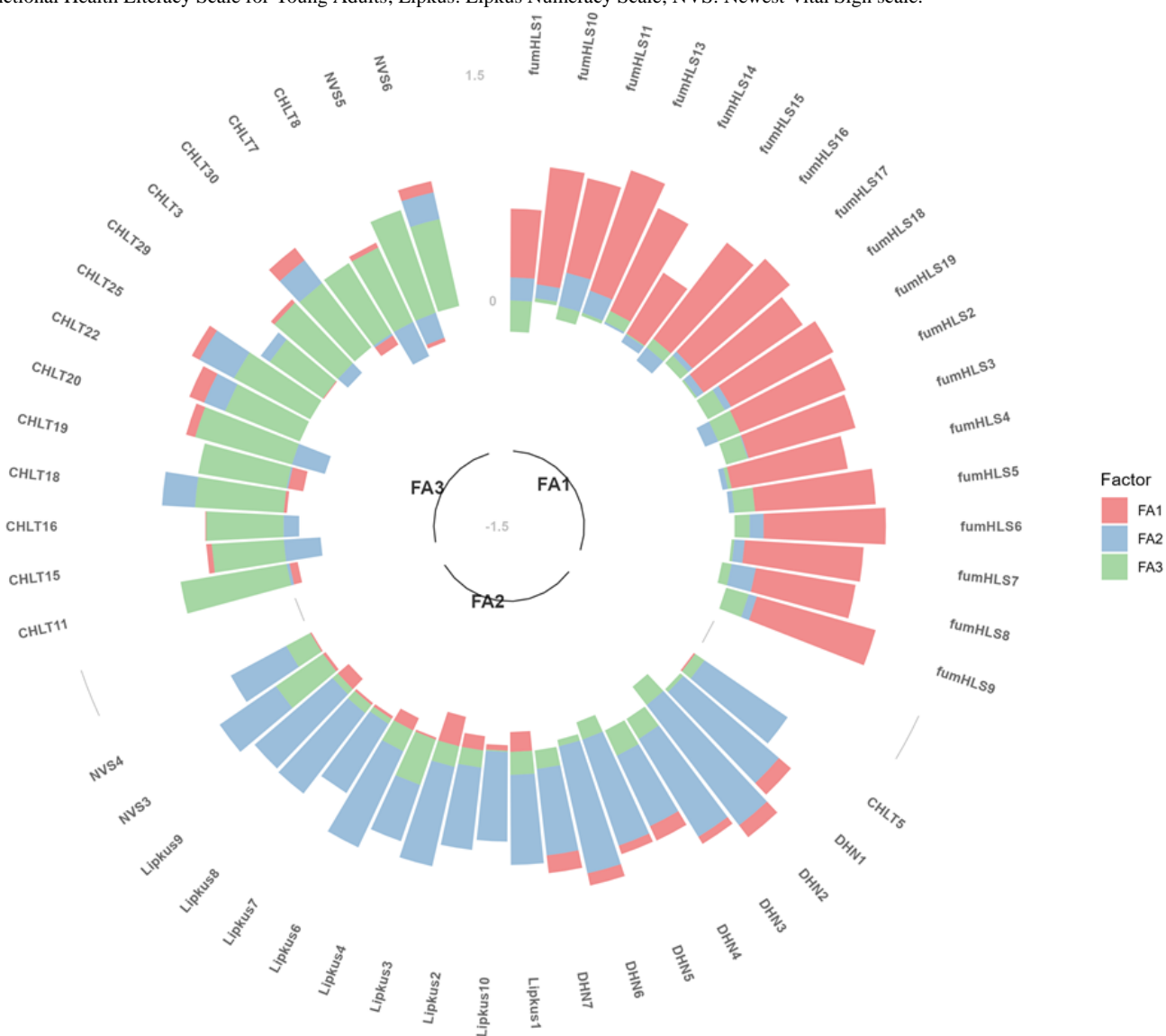


Table . Interpretations of identified factors.

Factor ^a and item with a factor loading of 0.40 or higher	Example item
FA1 (conceptual knowledge)	
funHLS ^b (items 1 - 11 and 13 - 19)	funHLS 6: “Indicate the most relevant word for <i>Vitamin C</i> . Response options: <i>Vegetables, Fat, Grain, and I Don’t know.</i> ”
FA2 (numeracy)	
Lipkus ^c (items 1 - 4, 6 - 10)	Lipkus 6: “If Person A’s risk of getting a disease is 1% in ten years, and person B’s risk is double that of A’s, what is B’s risk?”
NVS ^d (items 3 and 4)	NVS 3: “Your doctor advises you to reduce the amount of saturated fat in your diet. You usually have 42 g of saturated fat each day, which includes 1 serving of ice cream. If you stop eating ice cream, how many grams of saturated fat would you be consuming each day?”
DHN ^e (items 1 - 7)	DHN 2: “A male diabetic patient weighs 80 kilograms (kg). The doctor advised this patient to lose 10% of his weight. How much weight does this patient need to lose?”
CHLT ^f (item 5)	CHLT 5: “In people who develop oral cancers, 25% of these cases occur in the tongue. Oral cancer occurs in the tongue...”
FA3 (synthesis)	
NVS (items 5 and 6)	NVS 5: “Pretend that you are allergic to the following substances: Penicillin, peanuts, latex gloves, and bee stings. Is it safe for you to eat this ice cream?”
CHLT (items 3, 7 - 8, 11, 15 - 16, 18 - 20, 22, 25, and 29 - 30)	CHLT 18: “An appointment card says not to eat or drink anything 9 hours prior to the appointment. Sally has an appointment at 11:15 a.m. on Friday. What time should she stop eating or drinking?”

^aThe means and SDs of each item as well as their factor loadings are provided in the supplementary materials in [Multimedia Appendix 1](#).

^bfunHLS: Functional Health Literacy Scale for Young Adults.

^cLipkus: Lipkus scale.

^dNVS: Newest Vital Sign scale.

^eDHN: Diabetes Health Numeracy scale.

^fCHLT: Cancer Health Literacy Test scale.

Factor 1 (FA1) consisted exclusively of items from the funHLS, which asked participants to indicate the word most relevant to a stem (medical) word. Items from the funHLS assess word comprehension and knowledge about diseases and symptoms that young adults often experience, as well as nutrition, diet, and human biology. All items of the funHLS showed loadings of >0.40 on FA1. Although the funHLS items covered a range of topics (eg, caries, depression, and BMI), most items loaded on the same factor, and items from other scales were not included in FA1. This factor could be interpreted as a conceptual knowledge of health-related and medical terms in general (ie, not limited to a particular disease or health condition); however, it is still possible that the factor may reflect the unique test format, as the other scales require binary (true-false) responses or numeric responses, for example, to calculate a probability or health risk.

Factor 2 (FA2) included items from 4 of the 5 analyzed scales (ie, Lipkus, NVS, DHN, and CHLT), representing performance-based health numeracy in general (eg, “Imagine that we rolled a fair, six-sided die 1,000 times. Out of 1,000 rolls, how many times do you think the die would come up even (2, 4, or 6)?”). These 4 scales target different populations—Lipkus was designed for the general population, whereas the other 3 were contextualized for particular diseases and health conditions (DHN for diabetes and CHLT for cancer). The test format also differed across the 4 scales; the CHLT used multiple-choice questions, whereas the NVS and DHN included numeric response questions. These results suggest that the items assessing performance-based numeracy correlate well with each other, regardless of heterogeneity in the target diseases and test format.

Factor 3 (FA3) included items from 2 scales, the NVS and CHLT, which assess the ability to process and synthesize

health-related information. For example, item 5 of the NVS concerns abstract reasoning, integrating reading, comprehending, and interpreting skills as applied to material with health content [15]. Respondents were presented with a hypothetical nutrition label of ice cream and asked to judge whether the ice cream would be safe if the respondents were allergic to the indicated substances. Similarly, many of the items loaded onto FA3 required respondents to comprehend and synthesize the presented information (eg, the nutrition label) to make the correct response. Items from the CHLT are contextualized in a daily cancer patient routine at a clinic (eg, instructions for the use of medicines and reading a floor map of a hospital), assessing respondents' knowledge, numeracy, navigation, and synthesis [16]. Therefore, compared to FA1 (word comprehension and knowledge) and FA2 (numeracy), FA3 is distinguished in that it broadly measures higher order skills that require the synthesis of multiple skills (eg, reading, comprehension, and interpretation) to apply in a daily health context.

Confirmatory Factor Analysis

The testing dataset was found suitable for factor analysis: Kaiser-Meyer-Olkin=0.98 and the Bartlett Test of Sphericity, $P \leq .001$. We built a confirmatory factor analysis model with the 3 factors identified through exploratory factor analysis. This model showed an excellent fit to the testing data, $\chi^2_{1271}=7015.7$,

comparative fit index=0.97, root mean square error of approximation=0.03, and standardized root mean square residual=0.05, which reassures that the analyzed scales can be reduced to the 3 factors.

Correlation Analysis

The 3 identified factors were tested for their correlations with subjective health literacy and numeracy, as well as with health status and lifestyle (Table 4). Each correlation was interpreted for magnitude but not for statistical significance, given the large sample size of the analyzed dataset. The Cohen guideline was used, with $r=0.10$, 0.30 , and 0.50 being interpreted as small, moderate, and large effects, respectively [53,54]. FA1 to FA3 showed large interfactor correlations. However, these factors showed small-to-moderate correlations with the HLS-EU-Q47 (subjective health literacy), SNS (subjective numeracy), and SMILE (subscales of diet, nutrition, and substance use). Moreover, FA1 and FA2 showed small correlations with SMILE sleep and social support (r values $0.10 - 0.13$). None of the factors showed interpretable size correlations with the International Physical Activity Questionnaire Short Form (total PA) or EQ-5D (QoL and subjective health) scores. The 2 subjective measures, the HLS-EU-Q47 and SNS, presented stronger correlations with the SMILE subscales, except for substance use, than FA1 to FA3.

Table . Correlations between each factor and comprehensive health status.

	Values, mean (SD)	FA1 ^a	FA2 ^b	FA3 ^c	HLS-EU ^d	SNS ^e
FA1	0.74 (0.27)	— ^f	—	—	—	—
FA2	0.75 (0.24)	0.63	—	—	—	—
FA3	0.80 (0.19)	0.53	0.64	—	—	—
HLS-EU-Q47	28.23 (8.07)	0.24	0.19	0.14	—	—
SNS	3.24 (0.67)	0.33	0.45	0.32	—	—
Total physical activity (METs ^g hours per week)	34.20 (55.21)	−0.00	−0.02	−0.05	0.09	0.06
EQ-5D ^h quality of life	0.82 (0.14)	−0.01	0.03	0.02	0.10	0.07
EQ-5D health status	76.17 (17.59)	0.05	0.06	0.02	0.18	0.12
SMILE ⁱ diet	2.88 (0.49)	0.26	0.24	0.19	0.33	0.27
SMILE substance use	3.29 (0.82)	0.21	0.17	0.20	0.08	0.07
SMILE physical activity	2.29 (0.62)	0.05	0.05	−0.02	0.24	0.19
SMILE stress management	2.40 (0.48)	0.11	0.09	0.02	0.32	0.21
SMILE sleep	2.77 (0.58)	0.10	0.11	0.05	0.23	0.17
SMILE social support	2.59 (0.63)	0.13	0.11	0.06	0.31	0.23
SMILE environment	2.44 (0.53)	0.04	0.03	−0.02	0.16	0.13

^aFA1: factor 1 (conceptual knowledge).^bFA2: factor 2 (numeracy).^cFA3: factor 3 (synthesis).^dHLS-EU-Q47: 47-item European Health Literacy Survey Questionnaire. A general health literacy index score comprising all items was standardized on a metric between 0 and 50, using the following formula: $(\text{mean} - 1) \times (50/3)$.^eSNS: Subjective Numeracy Scale.^fNot available.^gMET: metabolic equivalent.^hEQ-5L: EuroQol 5-dimension.ⁱSMILE: Short Multidimensional Inventory Lifestyle Evaluation.

Discussion

Principal Findings

This study examined the factor structure of the multiobjective health literacy and numeracy scales among Japanese-speaking adults. Specifically, we explored how many factors would emerge in the pool of 72 items extracted from 5 scales, with or without being contextualized for specific diseases. The exploratory factor analysis indicated that the items could be categorized into three factors: performance-based conceptual knowledge (FA1), numeracy (FA2), and synthesis (FA3).

Most funHLS items loaded on FA1, assessing the conceptual knowledge of health-related and medical terms. FA2 consisted of items from 4 scales targeting people with different health

conditions and diseases that typically assess their ability to perform mathematical calculations. The NVS and CHLT items not included in FA1 were identified as FA3, which required the synthesis of multiple skills to handle health information, such as reading, knowledge, navigation, and interpretation skills, to provide a correct response. A correlation analysis indicated that all factors had weak correlations with subjective health literacy, moderate correlations with subjective health numeracy, and weak correlations with lifestyle (eg, diet, nutrition, and substance use). Lifestyles concerning sleep and social support demonstrated small correlations only with FA1 and FA2 but not with FA3.

In line with Altin et al [9] and Wu et al [55], we observed small-to-moderate correlations between the 3 factors and the

subjective scales (ie, HLS-EU-Q47 and SNS). Furthermore, the 3 identified factors were highly correlated with each other, yet were recognized as independent factors. These findings echo Waters et al's [24] argument—health literacy and numeracy are related but distinct constructs, each of which can be psychometrically divided into performance-based (objective) and self-reported (subjective) constructs. Another important point is that our analysis did not identify disease-specific factors, although we included cancer- and diabetes-specific items in the item pool. Therefore, it is plausible to assume that the 3 identified factors—conceptual knowledge, numeracy, and synthesis—form a common basis for processing health information in general. Health literacy covers a range of skills from basic to advanced levels. Basic skills include reading and writing (ie, literacy), which allow individuals to function effectively in everyday situations. These skills serve as a foundation for more advanced ones, for example, extracting information, deriving meaning from different sources of communication, and applying new information to changing circumstances [1]. We assume a similar hierarchical structure for the identified 3 factors, which may explain the interfactor correlations; that is, synthesis represents higher order skills that require more basic ones, such as numeracy and knowledge, along with other cognitive and literacy skills (eg, reading, comprehension, and interpretation).

Regarding the associations with health behaviors and lifestyles, each factor presented small correlations with diet and substance use but not with PA. Some overlaps were noticed at the item content level; for example, the NVS includes items about caloric calculation as well as reading and interpreting a nutrition label, whereas the SMILE asks how often respondents eat high-calorie sweet or fatty foods and how frequently they check the food ingredient labels. A similar association was found in patients with diabetes; performance-based numeracy is positively correlated with a healthy diet [56]. These findings suggest that skills and abilities assessed by objective measures underlie perceived health behaviors (eg, individuals are able to read and interpret ingredient labels and check them regularly when shopping for food). However, the size of the correlations was modest, and the results should be interpreted carefully, particularly for the practical significance.

Compared with objective measures, subjective measures demonstrated overall larger correlations with health behaviors and lifestyles. The conceptual knowledge and numeracy factors (FA1 and FA2) had small correlations with sleep and social support of the SMILE (r values 0.11 - 0.13) but subjective health literacy (HLS-EU-Q47) and numeracy (SNS) presented slightly larger correlations with sleep and nutrition (r values 0.17 - 0.33) as well as with other subscales (eg, PA, $r=0.24$; stress management, $r=0.33$). Higher levels of objective health literacy are thought to be associated with an inclination to behave in a manner that is beneficial to one's own and others' health (eg, choosing beneficial treatments for a disease) [17]. However, subjective health literacy may share even larger variance with the perception of health behaviors; that is, how people perceive their ability to process health information may overlap with how they believe to behave in a context where their health matters. It is too early to conclude that subjective

measures are more suited for studying health behaviors based only on the correlations found in this study. Instead, it is fair to argue that objective and subjective measures reflect different psychological processes, and further research is warranted to clarify which type (or both) of health literacy measure is associated with actual health behaviors that can be assessed using sensors and devices, such as accelerometers for PA.

Limitations

This study has several methodological limitations. First, the item pool was neither exhaustive nor comprehensive. Importantly, we did not include Test of Functional Health Literacy in Adults (TOFHLA) [10] and Rapid Estimate of Adult Literacy in Medicine (REALM) [11], which are the most widely used objective measures, because of language and cultural differences (all materials had to be in the Japanese language) and technical limitations of the survey platform (audio-visual recording could not be implemented). Both tools are closely bound to the English language (or even to the culture and health care system of the country where the scales were developed). For example, the REALM evaluates whether respondents pronounce medical terms correctly, and the TOFHLA assesses the ability to read and understand health-related materials contextualized in the US health care system. Yet, our analyses covered the scales and items conceptually overlapping with the REALM and TOFHLA; the funHLS is a word recognition test for medical terms, the CHLT and NVS assess reading comprehension of texts and tables, and the Lipkus evaluates numerical ability. However, we acknowledge that the exact items of the REALM and TOFHLA were not included here, and this may affect the interpretation of the results, particularly for the generalizability of the study findings. Furthermore, it is highly likely that the results of the factor analysis and subsequent analyses might differ if the item pool were expanded. Second, the exploratory factor analysis showed that the 3-factor structure explained less than half of the total item variance. A possible explanation is that measurement invariance might not be assumed in subgroups of participants as the data covered a diverse range of people in terms of demographics and other psychosocial variables. Different factor structures could be found across participants with different backgrounds, which should be clarified in future research. Third, participants were recruited using quota sampling to match the known population distribution in Japan for age and gender. Quota sampling is useful to ensure broad coverage of different groups and to prevent overrepresentation of a particular group in data. However, this approach is known to be vulnerable to sampling bias within a subgroup, which could be addressed by the use of self-weighted sampling if the cost of random sampling does not matter. Fourth, diagnostic information on physical or mental disorders was not collected. Testing patients with a particular disease or disorder was out of our focus, as we set a community sample as our target population. Health literacy is essential in maintaining one's health and preventing future diseases. However, it is important to widen the focus to include patient care and disease management, for which health literacy and assessments are highly relevant. Fifth, convenient self-reporting tools were used to assess PA and lifestyle habits. Health behaviors can be assessed using wearable devices and e-diaries

(eg, food recordings), which may allow for a more reliable estimation of healthy lifestyles [57]. It was technically impossible for us to use device- or sensor-based assessments, given the sample size of this study, but objective assessment tools could be considered when a focused sample is the research target.

Conclusions

Despite these limitations, our findings contribute to the psychometric evidence base of objective health literacy and numeracy scales. The results of the exploratory factor analysis identified 3 factors—conceptual knowledge, numeracy, and synthesis—among 66 items from 5 scales, independent of disease specificity and different contextualizations of the items. These 3 factors showed marginal correlations with subjective measures of health literacy and numeracy, highlighting the distinction between performance-based and self-reported assessment approaches [58]. Researchers and practitioners should be aware that self-report measures do not always reflect the skills and abilities reflected in performance on tests assessing conceptual knowledge, numeracy, and more integrated information processing skills. In other words, both subjective

and objective measures should be considered if one wishes to assess different aspects of health literacy. In general, subjective measures are easier to administer and less cognitively demanding [6,7]; also, these measures are more suitable for assessing meta-cognitive, emotional, or motivational aspects of health literacy rather than knowledge and numeracy [22,27]. However, self-reported measures are vulnerable to social desirability and other biases owing to health beliefs [20], which may reduce the accuracy of assessing health information skills [9]. In contrast, objective measures are less affected by response biases [6,17] but may feel like examinations and evoke a sense of shame and stigma. This aspect is particularly relevant for individuals feeling uncomfortable with examinations and not confident in their skills (eg, test anxiety). Also, objective measures often cover a limited, highly contextualized range of skills [6]. Given these advantages and disadvantages, it is not readily possible to uniformly determine the best measures to assess health literacy. It is important for individual researchers to be aware of what aspects of health literacy they want to assess, which then helps them select appropriate scales and items in line with their objectives.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: KT

Data curation: KT, TO

Formal analysis: CM

Methodology: CM, KT, NK

Project administration: K Kimura

Supervision: KT

Writing – original draft: CM

Writing – reviewing & editing: KT, TO, NK, K Katahira, K Kimura

All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

The means and SDs of each item as well as their factor loadings.

[[XLSX File, 19 KB](#) - [publichealth_v12i1e71701_app1.xlsx](#)]

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Abbreviations

CHLT: Cancer Health Literacy Test

DHN: Diabetes Health Numeracy

EQ-5D: EuroQol 5-Dimension

funHLS: Functional Health Literacy Scale for Young Adults

HLS-EU-Q47: 47-item European Health Literacy Survey Questionnaire

Lipkus: Lipkus Numeracy Scale

MET: metabolic equivalent

NVS: Newest Vital Sign

PA: physical activity

QoL: quality of life

REALM: Rapid Estimate of Adult Literacy in Medicine

SMILE: Short Multidimensional Inventory Lifestyle Evaluation

SNS: Subjective Numeracy Scale

TOFHLA: Test of Functional Health Literacy in Adults

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Original Paper

Establishing One Health Surveillance Platform for Electronic Integrated Disease Surveillance and Response in Malawi: Action Design Research Study

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Abstract

Background: Facing the threats of emerging and reemerging health issues requires One Health surveillance systems to provide information for integrated responses. Malawi started enhancing the electronic integrated disease surveillance and response (eIDSR) system in 2015, progressing with the aim of developing a One Health Surveillance Platform (OHSP) using District Health Information Software 2 (DHIS2) as its technical backbone, thereby supporting the COVID-19 pandemic response more resiliently and impacting the integrated disease surveillance and response (IDSR) performance. Digital solutions are critical components of One Health surveillance; however, evidence of the successful establishment and implementation of adaptive digital One Health surveillance systems is scarce.

Objective: This study aims to report on the establishment of the OHSP in Malawi and how an adaptive digital health solution contributed to strengthening and impacting the country's eIDSR during the COVID-19 pandemic and beyond the pandemic.

Methods: The establishment of Malawi's OHSP was based on the action design research methodology with a transdisciplinary approach. The core team reflected the multiple iterative processes of building the OHSP and formalized its impact on IDSR reporting quality.

Results: The OHSP core team conducted multiple iterative cycles to build the platform, leveraging lessons from previous eIDSR pilots, reusing digital health infrastructure, and developing DHIS2 digital solutions in 2019, right before the COVID-19 pandemic. The initial establishment was to cover 48.3% (14/29) of the country's health districts. Pivoting from the initial plan as the COVID-19 pandemic emerged, the core team swiftly adapted the OHSP to scale up nationwide and assisted the health system in responding to the pandemic. The pandemic shock resulted in a national scale-up of the OHSP and impacted the national weekly IDSR reporting quality from nonexistence in 2015 to 97.8% and 74.5% for completeness and timeliness, respectively, in 2024.

Conclusions: The establishment of the OHSP significantly bolstered the surveillance function for weekly IDSR reporting. Government leadership and good coordination were key to success. Continuous capacity building, enhancement of community-level surveillance with digital innovations, adaptable technical infrastructure, and a reuse strategy can provide long-term sustainability for One Health surveillance. Malawi's experience may apply to other countries with demonstrated value of resilient, government-led digital health interventions. Future efforts should focus on improving interoperability with other One Health domains and investing in infrastructure upgrades with local leadership and domestic funding to prepare for future emergencies.

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KEYWORDS

adaptive digital health system; DHIS2; District Health Information Software; eIDSR; IDSR; integrated disease surveillance and response; One Health surveillance; One Health; pandemic preparedness

Introduction

Emerging and reemerging health threats, coupled with the complexity of modern health systems, underscore the need for an integrated approach to health surveillance and response, known as the One Health approach [1-3]. Leveraging the One Health approach, the One Health surveillance system emphasizes intersectoral and multidisciplinary collaboration and integrated surveillance of human, animal, and environmental health, which offers promising avenues for strengthening public health management and pandemic preparedness [2,3]. The recent COVID-19 pandemic highlights the critical need to adopt and realize the One Health approach-aided surveillance systems to foster the health system's resilience and reduce disease risks [1,3]. However, given the broad scope of One Health, a proper implementation model for examining the One Health surveillance system and resilient health systems has yet to be fully developed [1,4].

In strengthening health system resilience, surveillance is essential for enhancing the health system's governance function during the shock onset, alert, and impact management stage [5]. Considering health system resilience and recent COVID-19 pandemic experience, effective information and communication systems and digital technologies-empowered surveillance can aid health authorities in responding more resiliently [5-7]. The "One Health surveillance system" is considered a collaborative surveillance system that provides the systematic collection, validation, analysis, and interpretation of data, and dissemination of information collected from humans, animals, and the environment to inform decisions for more effective, evidence-based health interventions [2,8]. By linking surveillance data across different sectors and applying a transdisciplinary approach, One Health surveillance can help different health-related actors address the full spectrum of disease and outbreak detection, emergency preparedness, response, management, and global health security and health system resilience [2,4].

However, establishing, realizing, and implementing a functional One Health surveillance system has proven challenging, with findings showing that the absence of a clear vision for the future of One Health is a barrier to interdisciplinary collaboration and that siloed approaches by different sectors restrict the ability of professionals to work collaboratively across disciplines [9,10]. At the policy level, political will and legal basis are essential for integrating surveillance systems yet remain difficult to attain

the collaborative goal [2,8,10]. At the institutional level, establishing a formal governance body with representatives from each sector could assist in overcoming long-standing barriers of privacy and distrust, where sociopolitical factors were considered as organizational attributes contributing to establishing a One Health surveillance system [2,8-10]. At the operational level, technical barriers highlight that the requirements for a successful One Health surveillance system should include understanding disease transmission and the importance of domain experts' knowledge as scientific support, as well as technical mechanisms to support collaboration [2,10].

Malawi adopted the integrated disease surveillance and response (IDSR) system as its national surveillance system for human health and recognized the need for improvements through advanced information technologies [11]. The latest IDSR technical guidelines highlight the importance of using electronic and digital tools to strengthen its function, known as electronic integrated disease surveillance and response (eIDSR) [12]. Countries are urged to implement electronic tools with an interoperable approach to fortify the eIDSR system and information-sharing platforms between various health units to expedite data transmission and enable a swift response to public health threats [12].

In 2014, the Ministry of Health (MoH) sought to enhance the nation's health emergency preparedness plan and piloted an in-house-developed eIDSR system for the first time [13]. After the World Bank-funded eIDSR pilot project, the Public Health Institute of Malawi (PHIM) of the MoH carried out another pilot by using SMS text message technology—Argus—to aid periodic eIDSR reporting [14]. However, these 2 pilots could not be sustained and scaled up. Meanwhile, Malawi recognized the importance of adopting a One Health approach and leveraging digital tools for surveillance by strengthening the eIDSR system as a starting point for the human health domain in the country [11,15,16].

After Cyclone Idai in 2019, the postdisaster needs assessment revealed the urgent need for strengthening and sustaining epidemiological surveillance and emergency preparedness for overall health system resilience [17]. As Malawi has responded continuously to numerous health disasters, including floods, droughts, and disease outbreaks, the idea of the One Health Surveillance Platform (OHSP) originated amidst the pilots of eIDSR, a successful response to an animal-originated anthrax outbreak and the postdisaster period learning [18]. As a result, the MoH chose the District Health Information Software 2

(DHIS2), a technology that has been used for Malawi's health management information system (HMIS) with a successful nationwide scale-up [16,19], as the technical backbone to establish the OHSP.

Health system resilience is the ability of the system to prepare for and respond to sudden shocks and everyday challenges, and its capacity to absorb deteriorations, adapt, and transform to cope with them [5,20]. It requires strong leadership, political will, a collaborative and coordinated governance structure, and robust surveillance systems to detect shocks and their impact in a timely manner [5,6]. In response to the emerging challenges posed by the COVID-19 pandemic, the MoH decided to accelerate the speed of the establishment of the OHSP to accommodate emerging needs. Malawi was able to use the OHSP as one of the digital health innovations, thereby bouncing forward resiliently during the COVID-19 pandemic [21]. This study aims to report on the establishment of OHSP in Malawi and how an adaptive digital health solution contributed to strengthening and impacting the country's eIDSR during the COVID-19 pandemic and beyond the pandemic.

Methods

Overview

The establishment of Malawi's OHSP for eIDSR started in 2015 based on the action design research (ADR) methodology [22] with the initial intention to strengthen the country's IDSR system. The ADR method has four stages: (1) problem formulation; (2) building, intervention, and evaluation (BIE); (3) reflection and learning; and (4) formalization of learning [22]. We chose this method to ensure that practical insights, stakeholder feedback, and emerging needs were continually incorporated into the platform's development.

Context of the Public Health Surveillance System in Malawi

Malawi is a landlocked country situated in southeastern Africa with a population of almost 16 million. It borders Tanzania, Zambia, and Mozambique [23]. Administratively, the country is divided into 3 regions—northern, central, and southern—with further demarcation into 5 zones, 29 health districts, and 4 major cities. The epidemiology department of the PHIM within the MoH is the main custodian of the IDSR system.

Malawi adopted the IDSR strategy in 2002, and the third edition technical guidelines were published in May 2014 with incremental notifiable diseases and health conditions to fulfill the International Health Regulations (IHR) 2005 and public health needs [24]. Malawi conducted a nationwide assessment of the IDSR system in 2017 [11] and found that the IDSR system showed relatively good completeness but poor timeliness of monthly reports nationwide and zero weekly reports. The use of IT to overcome challenges and improve the surveillance system to have better timeliness for IDSR reporting was proposed [11]. Ever since the assessment, PHIM has been

working on strengthening the nation's IDSR system activities with electronic and digital solutions, and later on added the One Health surveillance vision after successfully responding to a hippopotamus' original anthrax outbreak in 2019 [18].

Research Materials and Analysis Methods

Our analysis centered around various documents, including policies, meeting minutes from focus group meetings and key informant interviews, field notes, technical documentation, and digital health products used during the establishment of the OHSP. The OHSP is a digital health innovation accelerated during the COVID-19 pandemic for resilient responses [21] and was sustained for eIDSR functions beyond the pandemic. We summarize the findings from the current establishment to fill the existing knowledge gaps in the implementation of the digitalized OHSP. The impact of the OHSP digital health innovations on the weekly IDSR reporting quality was analyzed using 2024 weekly IDSR reporting quality data with the built-in function of the Reporting Rate Summary in the DHIS2, using the same approach as applied in the previous study [11].

Reflection and Learning Analytic Tool for OSHP and Impact on IDSR System

In order to rigorously reflect on how the OHSP establishment, and the use in responding to the COVID-19 pandemic resiliently, an analytic tool against the resilience framework was synthesized from the available literature, covering the One Health surveillance systems establishment, attributes of engineering resilient information systems for emergency response, strengthening health systems resilience, and known challenges of implementing DHIS2 [2,5,6,9,10,25,26]. Based on the synthesized findings, we first defined the following five analysis domains: (1) One Health surveillance characteristics, (2) addressing known DHIS2 challenges, (3) health system resilience phases, (4) health system resilience attributes, and (5) health system resilience tools [2,5,6,25]. We then identified thematic areas [2,5,6,25,26] and their corresponding establishment level of a One Health surveillance system, namely policy, institutional, and operational levels, based on Bordier et al [2]. Key attributes and challenges were identified from the reviewed literature [1,2,5,6,9,10,25-28]. We selected the relevant strategies and principles applied to the thematic areas and finally selected attributes for our analysis. The high-level analytic tool is shown in Table 1, and the indicators are detailed in Multimedia Appendix 1 [1,2,5,6,9,10,25,26].

In the One Health surveillance characteristics domains, we focused on analyzing the One Health surveillance-related policies, legal instruments, governance, and leadership in Malawi, reflecting on the known characteristics of setting up and sustaining a One Health surveillance at the policy and institutional levels [2,9,10]. We further analyzed the stakeholders' engagement processes and strategy for data integration and the technical infrastructure of the OHSP to see if it fulfills the One Health surveillance needs at the operational level [2,9].

Table 1. High-level analytic tool for health system resilience reflection and learning of the One Health Surveillance Platform establishment.

Domain	Thematic area	Establishment levels	Attributes and challenges
One Health surveillance characteristic	<ul style="list-style-type: none"> Policy and governance Sustainability Data integration Technical infrastructure 	<ul style="list-style-type: none"> Policy level Institutional level Operational level 	<ul style="list-style-type: none"> Policies, legal and operational framework Funding and scalability Data exchange across domains Hardware, software, and communication infrastructures
Addressing known DHIS2 ^a implementation challenges	<ul style="list-style-type: none"> Political, cultural, social, and structural infrastructure Appropriate data Workforce Education and training 	<ul style="list-style-type: none"> Institutional level Operational level 	<ul style="list-style-type: none"> Political challenges Stability Integrity of the health system or fragmentation Structural infrastructure Sufficient and qualified data Data quality Adequate technical support Comprehensive training programs
Health system resilience phases	<ul style="list-style-type: none"> Anticipation Preparation 	<ul style="list-style-type: none"> Policy level Institutional level Operational level 	<ul style="list-style-type: none"> Early detection and risk analysis Scenario planning Resource mobilization
Health system resilience attributes	<ul style="list-style-type: none"> Stakeholder Ecosystem Awareness Adaptive resilience Robustness 	<ul style="list-style-type: none"> Policy level Institutional level Operational level 	<ul style="list-style-type: none"> Stakeholder engagement Sectoral interaction Situation awareness Operational environment Adaptive structures Interoperability Coping strategies Withstanding challenges Capacity to handle increased demand Mobilization of essential resources
Health system resilience tools	<ul style="list-style-type: none"> Institutionalization 	<ul style="list-style-type: none"> Policy level Institutional level Operational level 	<ul style="list-style-type: none"> Capacity building System and infrastructure enhancement

^aDHIS2: District Health Information Software 2.

Since the DHIS2 was chosen as the backbone technology for the OHSP, we applied the Addressing Known DHIS2 Implementation Challenges domain for analysis [25]. Among the 11 themes, we selected 4 relevant themes, focusing on analyzing the infrastructure issues, the data pipeline, and the workforce to provide technical support, as well as education and training to implement the OHSP, and synthesized the rest in other domains.

For the health system resilience phases and attributes, adaptive resilience was selected to assess the ability of the OHSP and development team to swiftly adjust to immediate challenges with flexibility while continuously evolving and improving based on past experiences and new information. Resilient digital health systems should be designed to adapt and maintain functionality, as well as enable smooth recovery and reintegration amid changing circumstances to accommodate new requirements, emerging threats, or evolving user needs. The practice of adaptability includes integrating new business requirements and new technologies, scaling up or down as

necessary, and supporting interoperability with other systems [1,9,27,28].

Finally, since the OHSP is now institutionalized in Malawi and clearly stated in Malawi's Health Sector Strategic Plan III 2023-2030 (HSSP III) [29], we applied the same reporting quality indicators, completeness, and timeliness, to assess the OHSP's preliminary impact on weekly IDSR reporting at the national level [11]. Completeness was measured using the number of actual reports received against the number of expected reports from health facilities according to the health system level. At the same time, the timeliness of reporting was calculated based on the proportion of health facilities submitting surveillance reports on time to the district, with a national target of 80% for both indicators [11].

Ethical Considerations

This study was approved by the Malawi National Health Science Research Committee with approval number 16/4/1563 and the Regional Ethics Committee, Regionale Komiteer For Medisinsk

Of Helsefaglig Forskningsetikk sør-øst, with approval number 2015/2441/REK sør-øst A for its ethical conduct as part of the first author's PhD study. The establishment of the OHSP was conducted under the supervision of the MoH to strengthen the country's surveillance system in accordance with the relevant guidelines and regulations. All key informants were informed and obtained their verbal consent to provide information. The policies for analysis are publicly available. The meeting minutes from focus group meetings and key informant interviews, and field notes are kept safely by the first author and restricted access unless approval is obtained from the MoH. PHIM and the Digital Health Division of the MoH keep the technical documentation and digital health products. No compensation or reimbursement was provided to the meeting participants and key informants.

Results

The observable implementation activities and outputs, including the establishment, implementation, and experience of the OHSP with the COVID-19 pandemic shock, and the post-COVID-19 pandemic impact on the IDSR reporting, are presented in this section based on the ADR method.

Constitution of the OHSP Development Team

At the beginning of the study, the first author, TSJW, fulfilled his roles as an ADR researcher and practitioner in his capacity and was deeply immersed in the country's digital health development context. He facilitated the constitution of the OHSP core team with the MoH leadership. The OHSP core team (n=12) comprises 2 government officials responsible for the nation's IDSR system, 3 epidemiology unit and institution leaders at the PHIM, 5 digital health and IT staff from the Digital Health Division and Information Communication Technology Division of the MoH, a coordination officer, and a technical advisor. TSJW, the first author and technical advisor who was involved in the 2017 IDSR performance assessment, executed eIDSR pilots and provided technical inputs and guidance on developing the OHSP throughout the BIE stages. The extended OHSP development team consists of government technical officers from different sectors, in their role as the IHR focal person in the respective departments. The OHSP core team inherited technical officers supported by partners and sustained the institutional memories within the government from the previous eIDSR pilot projects by integrating them into the OHSP core team, and started working on establishing the OHSP technical solutions in 2019.

Problem Formulation Stage

The establishment of the OHSP to support the eIDSR function was inspired by surveillance practices in the country and international recommendations, aligning with the third edition of the IHR 2005. The initial problems of the IDSR system were identified, highlighting the lack of technological solutions for weekly IDSR reporting. In order to tackle this problem, the first author, TSJW, continuously engaged the MoH and development partners to strengthen the IDSR system with 2 eIDSR pilots conducted from 2015 to 2018.

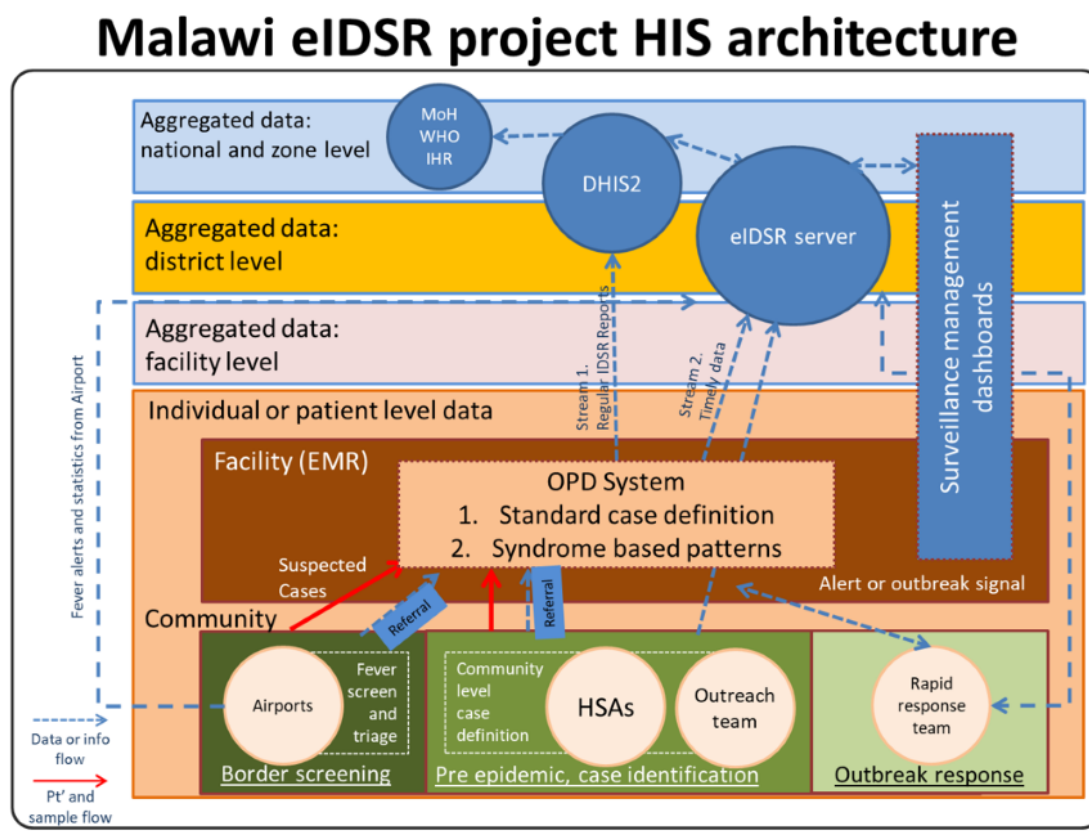
The World Bank supported the first pilot for the post-Ebola era with the aim of developing and implementing an eIDSR system at all levels of the health system in 2015. The following three main activities were conducted: (1) development of a comprehensive eIDSR system architecture and system logical design, (2) software development, and (3) system deployment and field support. During the first eIDSR pilot, we managed to develop the architecture design, establish a border health fever screening system, and develop the IDSR immediate notifiable disease reporting and syndromic reporting automated functions in the outpatient module of a partner-funded electronic medical record system (EMRS). The eIDSR architecture design used the organizational architecture level to guide respective information product developments and information flow; at the same time, the dashboard was designed to enable monitoring of the diseases and syndromic patterns of the outpatient visits together with a geographic information system and global health news Really Simple Syndication feeds function, as shown in Figure 1.

The following two main problems were identified based on the eIDSR pilot implementation results:

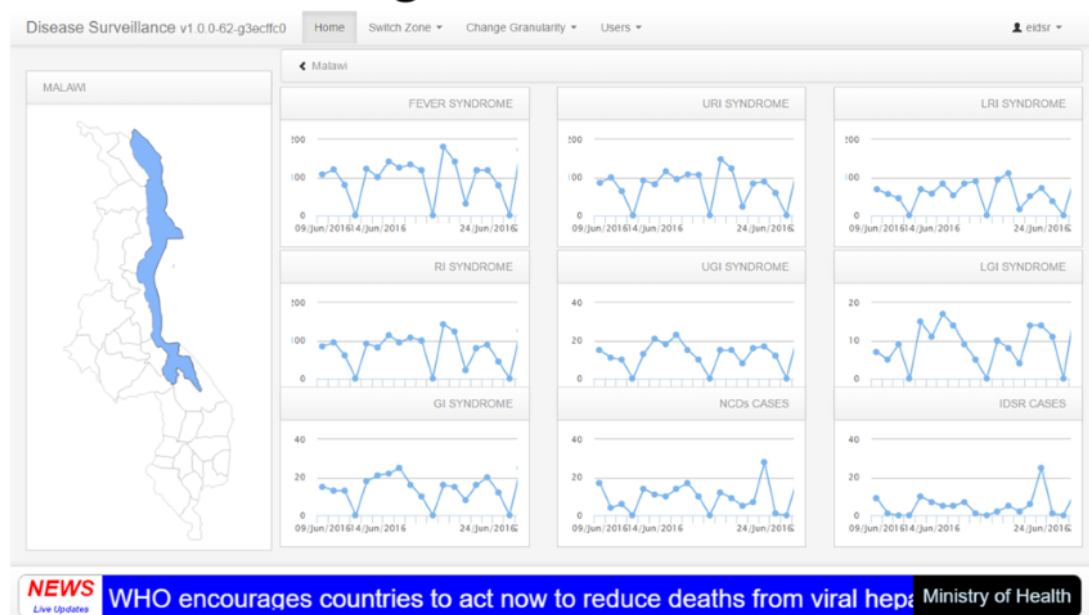
1. Sustainability: most of the project team members were dismissed after the project, leaving a minimal capacity within the MoH to maintain the developed systems. The management dashboard and eIDSR central database were designed in-house without the full transition of the source codes to the ministry, and the eIDSR functions in the EMRS were removed after the pilot due to a lack of funding for continuous support.
2. Technical infrastructure: the eIDSR pilot at the facility level was implemented in 59 health facilities with EMRS; however, it covered only 3.2% (59/1849) of the total public health facilities in the country at that time. By the time the pilot ended, the eIDSR pilot also did not cover the whole country for the needed periodic IDSR reporting (weekly and monthly) and community-level case detection.

In order to continue the eIDSR enhancement, the MoH obtained support from the United Nations International Children's Emergency Fund (UNICEF) to pilot the World Health Organization (WHO) Argus solution and facilitate system integration for the country in mid-2017. The UNICEF support was to address the need for a timely weekly IDSR report using the technology. The solution was built and deployed to 220 health care workers for weekly IDSR reporting. However, sustainability and technical infrastructure challenges remained, with no subsequent financial resources and inadequate coverage of the facilities. During the pilot, an additional need was identified to have interoperability between the WHO-Argus solution and the nation's HMIS, which uses DHIS2 technology. The 2 pilots provided lessons for the subsequent establishment of the OHSP. The prevention of the hippopotamus' original anthrax outbreak in late 2018 inspired the MoH to decide to build a suitable digital system to accommodate the One Health surveillance needs and serve the eIDSR functions with the DHIS2 as the technological backbone support.

Figure 1. Preliminary electronic integrated disease surveillance and response (eIDSR) architecture and dashboard concept of the pilot in 2015. DHIS2: District Health Information Software 2; EMR: electronic medical record; HSA: health surveillance assistant; IHR: International Health Regulations; MoH: Ministry of Health; OPD: outpatient department, Pt': patient; WHO: World Health Organization.



eIDSR management dashboard – v1.0.0



BIE Cycles

Pre-COVID-19 Pandemic BIE Cycle

The OHSP establishment formally started in September 2019. Based on the pilot experience, the OHSP core team identified sustainability and technical infrastructure as the 2 key problems

to be addressed in the forthcoming OHSP. In addition, previous core team members studied IDSR implementation gaps and community-level surveillance barriers in relation to technology for timely reporting; inadequate training, limited resources, and health-seeking behaviors affecting surveillance capability were also taken into consideration when the team started the OHSP establishment, as summarized in [Textbox 1](#).

Textbox 1. Problems identified from the Malawi electronic integrated disease surveillance and response (IDSR) pilots and previous studies during 2015-2019.

Sustainability

- Organizational sustainability
 - Lack of coordination leading to duplication of efforts
 - Lack of engagement from key personnel
 - Unavailability of key Ministry of Health (MoH) staff
 - Coordination issues for systems deployment
 - Conflicting project schedules with some implementing partners
- Human resource sustainability
 - User non-compliance with system usage
 - Technical staff were dismissed without a full transition
 - Inadequate technical personnel in the MoH to continue the development and maintenance
- Financial sustainability
 - Unforeseen communication expenses
 - Cash flow issues are delaying hardware procurement
 - Lack of financial resources for scale-up and sustainability

Technical Infrastructure

- Incomplete functionality for the full IDSR system needs, including the community-level surveillance
- Low coverage of the solution
- Extended power outages are affecting deployment
- Connectivity issues affecting system functionality
- Labor-intensive setup process for the terminal device (smartphone)
- Congestion and delivery failures of the SMS service

The OHSP core team initiated the BIE stage to address organizational sustainability issues by reviewing the organizational structure across One Health domains, government documents, and literature to inform the design of the OHSP organizational architecture to accommodate One Health surveillance's needs and the IDSR weekly electronic reporting function. Addressing the coordination and leadership issue was the first step. The core team conducted technical meetings with MoH leadership and learned that the One Health task force was formed during the anthrax response. Through these iterative meetings, we transparently communicated the governance concerns and affirmed that the ownership and leadership of the OHSP belong to PHIM within the MoH. PHIM's leadership then led the core team to further engage with stakeholders to

contribute to the architecture design of the OHSP. The OHSP core team began engaging with the animal and environmental sectors, with the animal health domain, represented by the Ministry of Agriculture, being fully consulted. While for the environmental domain, due to its vast fields, the team decided to engage further in the next phase of the OHSP implementation after the consultation with relevant stakeholders.

The core team developed a high-level business process architecture of the OHSP (Figure 2), and aligned information flows based on the identified organizational units, surveillance personnel, and studied data collection tools. The hierarchy of the surveillance units is similar across domains but still shows differences at the subnational level across the 3 One Health domains, as listed in Table 2.

Figure 2. High-level business process architecture of the One Health Surveillance Platform in Malawi, 2019. AFRO: World Health Organization Regional Office for Africa; AHSA: animal health surveillance assistant; AWF: African Wildlife Foundation; BH: border health; CAHW: community animal health worker; CDC: Centers for Disease Control and Prevention; CHW: community health worker; FAO: Food and Agriculture Organization; IDSR: integrated disease surveillance and response; ILO: International Labour Organization; IPCC: Intergovernmental Panel on Climate Change; IUCN: International Union for Conservation of Nature; UNEP: United Nations Environment Programme; WFF: World Wildlife Fund; WHO: World Health Organization; WMO: World Meteorological Organization; WOA: World Organisation for Animal Health.

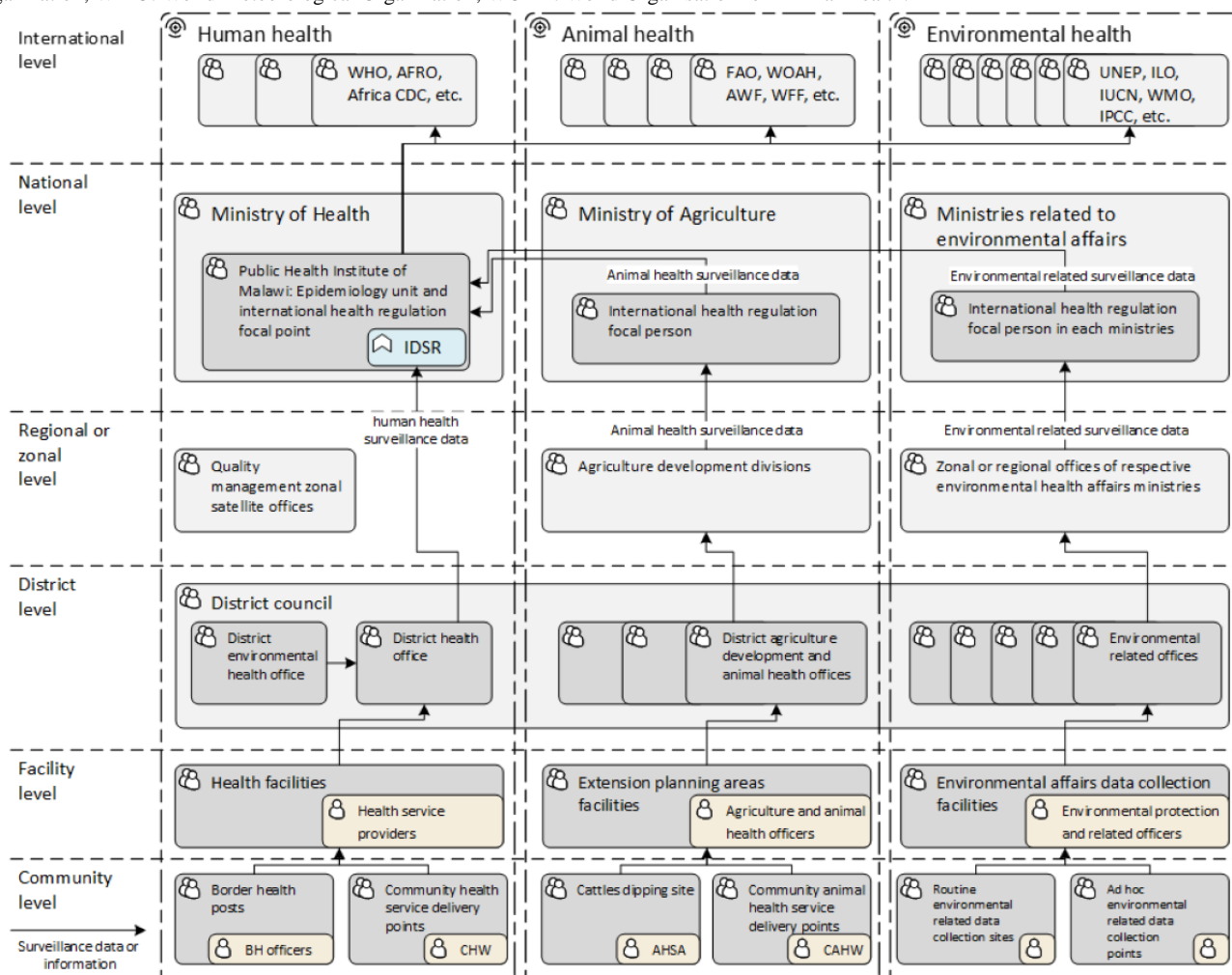


Table 2. Organizational units mapping between the 3 One Health domains in the context of Malawi.

Administrative level	Human health	Animal health	Environmental health
National level	<ul style="list-style-type: none"> Ministry of Health 	<ul style="list-style-type: none"> Ministry of Agriculture 	<ul style="list-style-type: none"> Ministries of Water and Sanitation, Natural Resources and Climate Change, Mining, Labour, and Land
Subnational level: region, zone, or division	<ul style="list-style-type: none"> 3 regions, 5 health zones 	<ul style="list-style-type: none"> 8 agricultural development divisions 	<ul style="list-style-type: none"> Different from each ministry
District level	<ul style="list-style-type: none"> 29 health districts with district health offices 	<ul style="list-style-type: none"> 28 administrative districts with district agricultural development offices 	<ul style="list-style-type: none"> 28 administrative districts
Facility level	<ul style="list-style-type: none"> Central hospitals District hospitals Rural and community hospitals Health centers 	<ul style="list-style-type: none"> Extension planning areas and sections where agriculture extension development officers work 	<ul style="list-style-type: none"> Different from each ministry
Community level	<ul style="list-style-type: none"> Health post Village clinic Outreach clinic Village health committees (operated by community health workers) 	<ul style="list-style-type: none"> Area development committees Village development committees (operated by animal health surveillance assistants) 	<ul style="list-style-type: none"> Different from each ministry

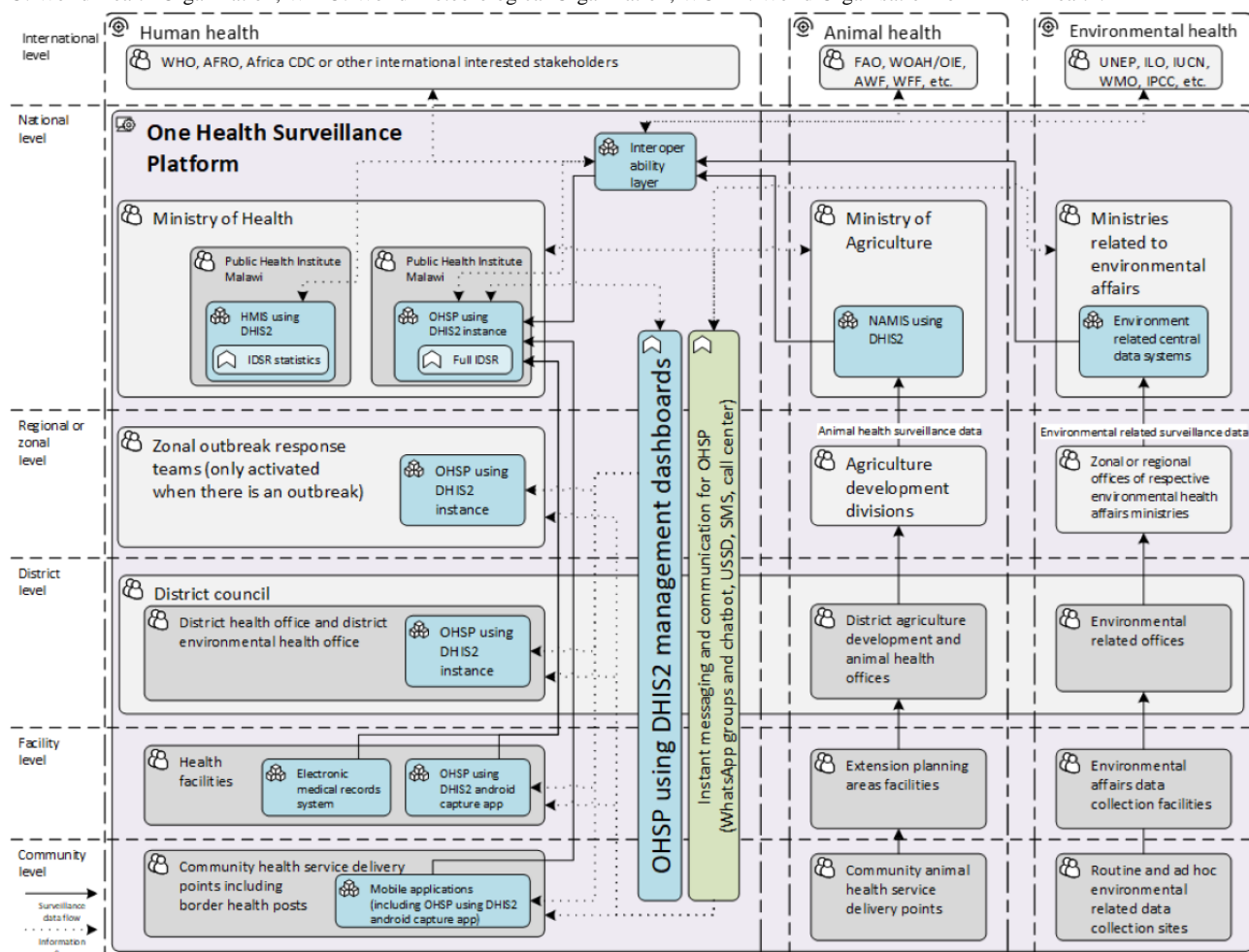
Upon stakeholder engagement, we noticed that only the human health surveillance system had standardized reporting and data collection tools using IDSR technical guidelines. Animal health surveillance has a reporting structure, but the standardized reporting forms and tools have yet to be updated and made available. Environmental health surveillance encompasses an even larger degree of complexity, including climate change, weather forecasts, air and water quality monitoring, waste management, pollution incident surveillance, occupational hazards, and risk surveillance.

After the high-level business process architecture was developed, the core team focused on establishing the main data repository to enable facility-level periodic IDSR reporting and to prepare for integrating animal and environmental health surveillance data pipelines in the next phase. The core team developed a strategy to mobilize future surveillance-related investment for human resource retention and to continue the enhancement of the OHSP to anchor and align the One Health surveillance architecture and existing solutions. At the beginning of the OHSP establishment, UNICEF supported the initial OHSP development and committed to initial implementation covering 48.3% (14/29) of the country's health districts.

Once the high-level OHSP architectures were designed, the core team started working on the technical infrastructure for the establishment of the OHSP. Technical factors were considered to favor collaboration and integration of data from different domains, including DHIS2, as an existing national DHIS2-enabled digital health infrastructure used in HMIS, and an interoperability layer (IL), as an existing national information exchange infrastructure, to address these needs.

The core team started the development of the OHSP in November 2019. In terms of roles, the technical staff were responsible for software development and deployment. The first author worked as a technical advisor serving leading and mediating functions in the communication between different stakeholders, including the requirements and limitations from different disciplines to the technical staff. Using a transdisciplinary approach, he translated the business process, information flow, and available tools into programmable technical requirements for developers. After the technical execution, the core team designed the technical architecture for the OHSP, as shown in [Figure 3](#).

Figure 3. Technical architecture of the One Health Surveillance Platform (OHSP) after the transdisciplinary translation from public health needs to programmable digital health solutions in Malawi, 2019. AFRO: World Health Organization Regional Office for Africa; AWF: African Wildlife Foundation; CDC: Centers for Disease Control and Prevention; DHIS2: District Health Information Software 2; FAO: Food and Agriculture Organization; HMIS: health management information system; IDSR: integrated disease surveillance and response; ILO: International Labour Organization; IPCC: Intergovernmental Panel on Climate Change; IUCN: International Union for Conservation of Nature; NAMIS: National Agriculture Management Information System; UNEP: United Nations Environment Programme; USSD: unstructured supplementary service data; WFF: World Wildlife Fund; WHO: World Health Organization; WMO: World Meteorological Organization; WOA: World Organisation for Animal Health.



Based on the architectural design, the core team technical staff applied the Agile method, executing Scrum sprints to build the OHSP digital products. An instant messaging and communication collaboration mechanism was established and included in the OHSP. The One Health forum WhatsApp group was created for all IHR focal persons from different ministries to collaborate on health emergency preparedness and responses for real-time communications during the 2018-2019 anthrax outbreak response and was managed by the MoH. The functional One Health forum WhatsApp served as one of the digital solutions in the OHSP, providing alerts to the group members. Similar WhatsApp groups have existed to facilitate IDSR coordination and collaboration since 2018. The experts in the One Health forum WhatsApp group anticipated that COVID-19 would become a great threat to the nation's public health in mid-January 2020. The signal was provided to the core team for the team to focus on leveraging available infrastructure resources and reusing technologies from previous eIDSR pilots to develop the following three DHIS2-related digital products: (1) a national DHIS2 instance for the OHSP, (2) a DHIS2 Android Capture app for OHSP, and (3) an interoperability mediator between HMIS and OHSP.

The primary focus during January 2020 was setting up the national DHIS2 instance, especially the metadata design for weekly, monthly, and quarterly IDSR reporting. The core team paid attention to building the OHSP with integration and interoperability infrastructure, especially in relation to the HMIS. The IDSR periodic report and case-based surveillance form were standardized to provide appropriate data and replicated on the OHSP to match those in the HMIS to maintain data integrity. The integration was done by first matching the data element IDs, including the data field IDs and the dataset IDs. The organizational unit IDs were mapped and aligned with national standards using a master health facility registry. The team cloned existing facility mappings and data element mapping identification from the existing HMIS instance and registered the OHSP as a client in the nation's IL so that it could recognize the OHSP instance as a source for data exchange.

Technical solutions were applied to ensure graceful degradation and seamless reintegration, including the DHIS2 features of PostgreSQL (PostgreSQL Global Development Group) performance tuning to improve query performance and scalability. The MoH-owned Proxmox (Proxmox Server

Solutions GmbH) cluster was created to tolerate server downtime without affecting user access through multiple web servers. Load balancing within Nginx (F5 Inc) was configured to distribute load evenly across server instances and to detect any unavailable instances and reroute traffic as needed. The core team applied the “sticky sessions” solution of the DHIS2 to help maintain user session continuity by routing requests from the same client to the same server. The core team configured daily data backups of the OHSP to ensure data restoration capabilities. Fire and water safety controls and a continuous power backup supply at the national digital health server room were applied for the OHSP to operate continuously with minimal downtime. For security, the OHSP DHIS2-related products used password protection and controlled access.

In February 2020, the team concentrated on ensuring HMIS-OHSP interoperability. When building the interoperability, an initial script was created to directly transfer the IDSR data from the HMIS instance into the OHSP. However, when running the script, there was a time-out due to the huge payload that was being sent from HMIS to OHSP; hence, the team decided to use the IL for chunking functionality. Process-wide, the IDSR periodic reporting process was not standardized; some facilities reported in HMIS, while some reported in the OHSP. The MoH leadership addressed the issue by disseminating an internal memo to regulate all surveillance data to be entered in OHSP. The core upgraded the HMIS and OHSP instance, so the payload was channeled through the IL to use the chunking of the payload when sending it from the OHSP to the HMIS.

Simultaneously, the team worked on the integration and user interface design of the DHIS2 Android Capture app to interact with the OHSP instance for data collection and reporting. Also, the team worked on obtaining additional public IP addresses with the government domain for OHSP to facilitate Secure Sockets Layer acquisition and deployment of the solutions through the internet. By March 2020, OHSP was tested by PHIM and was fully ready for implementation to support Malawi's surveillance and response needs.

During the COVID-19 Pandemic BIE Cycle

Right before the core team was ready to deploy the OHSP products, new requests emerged as the country faced the impending threats from the COVID-19 pandemic. According to the original plan, the first release of the OHSP products was to facilitate timely IDSR periodic aggregated data reports. However, with the emergency, the MoH and the national COVID-19 response team at the emergency operation center raised requests and digital health solutions needs, which required additional functions, integration, and interoperability between the OHSP products and other digital health solutions.

The COVID-19 response emergency operation center was formed according to the Africa Centres for Disease Control and Prevention recommendations in April 2020. The first author, TSJW, was appointed acting manager at the COVID-19 emergency operation center that same month, supporting response activities while continuing to serve on the core team for OHSP development. The core team responded to the requests raised and prioritized them according to the consensus and

guidance from the government by leveraging available digital solutions and the IL. The case-based surveillance form of the IDSR system in OHSP was harmonized and standardized with various stakeholders' expectations and updated with COVID-19 conditions in May 2020. Additional forms for border health declaration and contact tracing were developed and added to the OHSP during May-June 2020. The validation rules for mandatory data entry were programmed in the OHSP to ensure data quality at the same time. After the new features of OHSP products were developed, they were included in the new national emergency preparedness and response plans to support the response from May 2020.

The core team applied the agreed strategy to mobilize resources for the national scale-up of OHSP instead of only implementing it in 14 districts when funders and partners showed interest in investment resources for pandemic response. Through the government leadership and collaboration mechanism, multiple funders accepted the advocacy at the beginning of the COVID-19 pandemic, and the core team secured access to additional technical infrastructure resources, especially the server, terminal devices (tablets), and reverse billing approach of connectivity, for deploying the OHSP products countrywide since June 2020. However, the team was unable to mobilize adequate resources for comprehensive redundancy and backup servers of OHSP DHIS2-related products till the end of the pandemic in May 2024.

During the national rollout, all partners followed the MoH leadership to provide standardized training, follow-up supervision, and refresher training. A training program for OHSP products users was designed and implemented comprehensively with user manuals, standardized presentations, a deployment checklist, and detailed schedules, covering computer literacy from the beginner level. A centralized digital health helpdesk at the Digital Health Division was established to provide support to OHSP users. The core team members received further education and training for their DHIS2-related capacity building through online and in-person participation in DHIS2 academies from 2021 to 2023.

A national OHSP enhancement plan was developed to institutionalize OHSP, and a dedicated technical working group was established to facilitate One Health surveillance and regular updates and the One Health bulletin at PHIM in 2023. A comprehensive capacity-building plan and a system infrastructure enhancement plan of OHSP were developed to integrate animal health and environmental health data pipelines in 2024. After the deployment, the OHSP core team has constantly collected the needs and feedback from relevant stakeholders through the established collaboration mechanism. Since then, the OHSP digital products have been sustained and continue to be used for IDSR reporting to date.

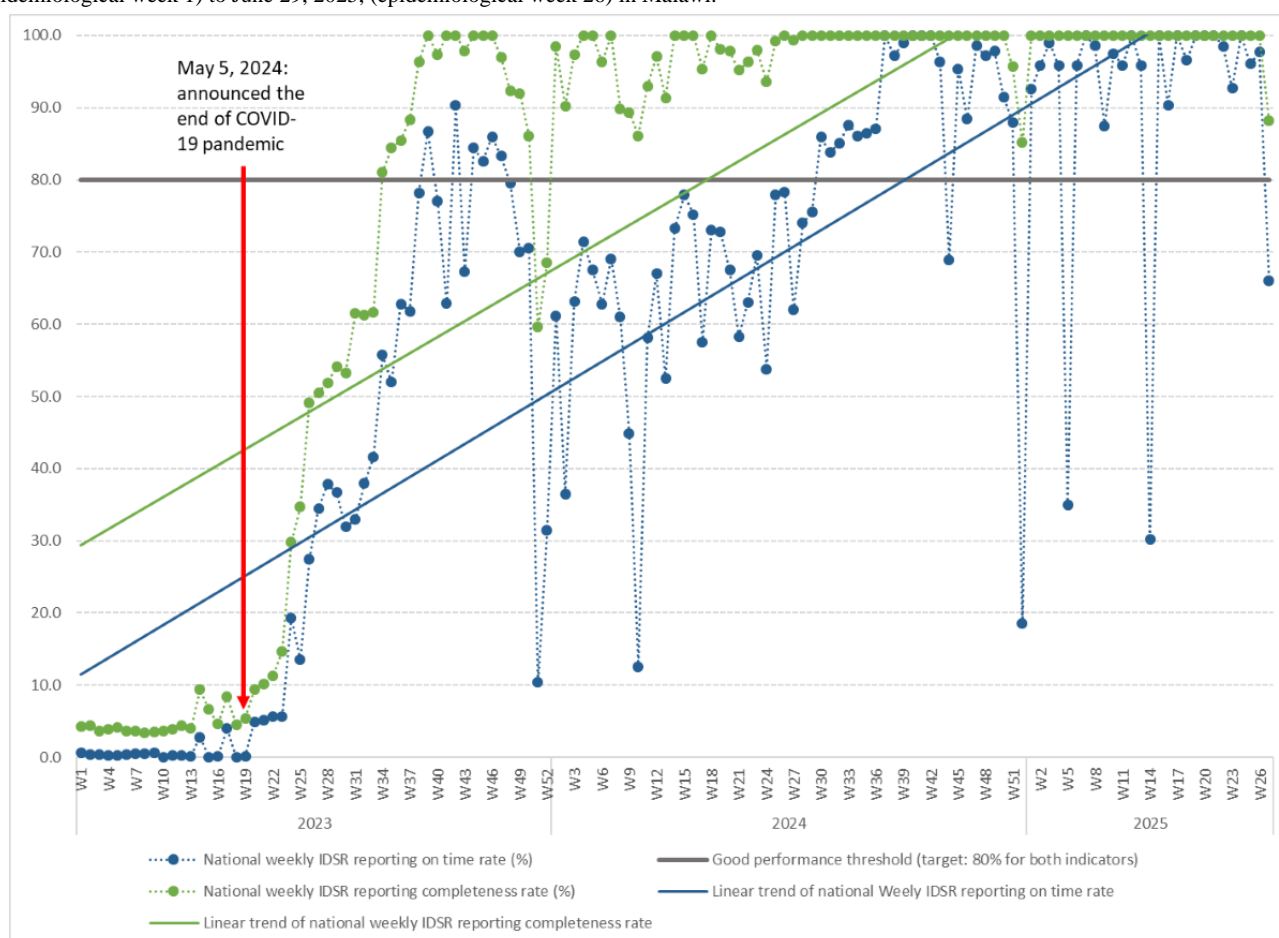
Post-COVID-19 Pandemic OHSP's Impact on IDSR Reporting

The OHSP became the main digital data repository for all IDSR surveillance periodic reports after the pandemic. The interoperability mediator is functioning with the MoH as the custodian, ready for reuse and tapping into other One Health surveillance domains' data. The One Health forum WhatsApp

group is still functioning to facilitate the ongoing One Health surveillance activities. The completeness and timeliness of IDSR periodic reports' data quality indicators were defined according to the national guideline and configured in the OHSP's national DHIS2 instance. The MoH continuously provides appropriate feedback on data quality issues through the dashboards, bulletins, and WhatsApp groups to reporting facilities to ensure data quality, with the OHSP core team maintained within the

MoH governance structure. The OHSP dashboards developed provide functionality to monitor the epidemiological patterns of notifiable diseases routinely for outbreak detection. As a result, the weekly IDSR reporting transformed from nonexistence in 2015 to a state where the nation reached 97.8% and 74.5% reporting quality for completeness and timeliness, respectively, in 2024. The secular trends and weekly IDSR reporting rate quality are illustrated in Figure 4.

Figure 4. The integrated disease surveillance and response (IDSR) weekly reports completeness and timeliness indicators from January 2, 2023, (epidemiological week 1) to June 29, 2025, (epidemiological week 26) in Malawi.



Discussion

Summary of Main Findings

This study aims to report on the establishment of the OHSP in Malawi and how an adaptive digital health solution contributed to strengthening and impacting the country's IDSR system during the COVID-19 pandemic and beyond the pandemic. Our findings show that Malawi successfully established a government-led digital tools-aided OHSP right before the COVID-19 pandemic, building on the ongoing effort and further strengthening the country's IDSR system. The OHSP was built corresponding to the characteristics of One Health surveillance systems across policy, institutional, and operational levels [1,2]. Amid the COVID-19 pandemic, the MoH evidently used the OHSP to mitigate the spread and impact of the pandemic [21], and the weekly IDSR reporting improved significantly after the pandemic, from zero reporting in 2015 [11] to 97.8%

completeness and 74.5% timeliness by 2024, while PHIM is currently undertaking a full impact assessment of the OHSP.

Findings from this study indicate that the alignment of the national health policies and the establishment of a formal coordination body with government leadership were essential to the One Health surveillance governance. The government-owned and government-led strategy was useful for communicating with all potential funders to invest in the OHSP and align with the government's direction.

The developed holistic OHSP architecture guided the data and information integration design, especially on organizational units and reporting tools standardization. The mapping of the corresponding organizational units with the human health system hierarchy at each administrative level for animal and environmental domains, and having standardized data elements, was a complex task. Considering the complexity, the OHSP core team sensitized all stakeholders engaged in helping with the proper mapping of the units and understanding of the

importance of the data standards for future One Health surveillance data exchange and interoperability.

The reuse of the eIDSR pilots' hardware and available digital solutions provided adequate hardware, software, and communication infrastructure for the initial establishment of the OHSP and accelerated in responding to the COVID-19 pandemic needs. Several known DHIS2 implementation challenges were addressed during the establishment of the OHSP. The OHSP anticipation and adaptive resilience abilities were observed in the study. A detailed discussion, comparison, and contrast of findings with existing literature is followed.

Interpretations and Implications of Lessons Learnt

One Health Surveillance Characteristics

Our findings were reflected based on four thematic areas using the analytic tool developed (Table 1) under the One Health surveillance characteristics domain, corresponding to the policy, institutional, and operations levels according to the One Health surveillance framework developed by Bordier et al [2].

Policy and Governance at the Policy and Institutional Levels

As known challenges, robust policy frameworks and governance structures are essential factors toward a successfully integrated One Health surveillance system [2,8-10]. The third edition of the IHR 2005 [30] was the main international legal instrument used to justify the One Health surveillance initiative in Malawi. The Joint External Evaluation conducted in Malawi in 2019 highlights the importance of operationalizing and strengthening the One Health platform, improving surveillance systems, and enhancing the data-sharing platform [15], providing an operational framework for Malawi to take action.

The Public Health Act (1948) [31] and the Control and Diseases of Animals Act (1967) [32] provide legal frameworks for disease surveillance, reporting, and control in both human and animal health sectors in Malawi. The Environment Management Act (2017) [33] complements the One Health approach by promoting environmental protection, monitoring, reporting, and public participation in decision-making processes. Malawi's health sector policy, especially the HSSP III [34], highlights the adoption of the One Health approach and OHSP, particularly in areas of antimicrobial resistance and climate change, echoing the One Health surveillance focuses found by Bordier et al [2] and Malawi's emerging needs [17]. At present, the OHSP is institutionalized at PHIM in Malawi to strengthen the IDSR reporting quality, avoiding potential abandonment of the digital health initiative after the COVID-19 temporary use [29]. The developed OHSP enhancement plan and HSSP III [34] guide the gradual integration of different One Health domain data pipelines using the OHSP digital tools. These are useful legal instruments that solidify the government-led coordination mechanism at the policy and institutional level, as advocated in relevant literature [2,5,6], and may be applied in other settings.

Concerning the governance and operation of collaborative surveillance across different sectors, the political will is essential in establishing a One Health surveillance system and may foster

its success [2,9,10,35]. Our findings clearly indicated that Malawi showed strong political will, solidified soon after the successful anthrax outbreak response, and gained momentum from the resilient response to the COVID-19 pandemic. The 2 instances affirmed the leadership role of PHIM and strengthened the commitment of the government to take the same One Health approach for future health emergencies. As advocated, government-owned and led digital health interventions offer an opportunity to strengthen health systems and attain health-related goals on the continent [36]. The reinforced government commitment to OHSP's development had effectively reduced the creation of "silos" in the health surveillance system. Political will and leadership are the two key enabling factors contributing to the sustainable operation of the One Health surveillance system, echoing the findings from Vietnam and Australia's experience [10,35]. Coordinated implementation with government leadership maintained continuity and OHSP ownership, further ensuring financial and organizational sustainability in Malawi at the institutional level [2,26].

Sustainability for All Levels

The affirmation of the One Health leadership, established coordination mechanisms, and policy alignment secured the organizational sustainability of Malawi's One Health surveillance initiatives, reflecting the advocacies from others [2,9,10]. The government officials at the forefront led the implementation and delivery of the OHSP digital products to avoid district and facility health care workers conceiving the OHSP as an external system. This approach further reduced operational costs and silo creation, ensuring long-term sustainability as argued by academics in the same field [2,8,10,35]. Meanwhile, the reuse of technology strategy with open-source digital solutions, such as the global DHIS2 and Open Health Information Exchange communities [25,37], provides technical advancement and long-term software sustainability, coupled with the ongoing maintenance by the core team, making the OHSP a resilient information system [26].

Concerning financial sustainability, the strategy of advocating and lobbying for surveillance-related investment to anchor and align the One Health surveillance architecture was a useful approach for the OHSP to scale up nationwide, with the COVID-19 pandemic providing the MoH with an opportunity to align and direct partners' investment to support it. Government ownership and leadership of the OHSP avoid the potential interruption, silos, or hiccup of funding availability, responding to the challenges observed and concepts reported before [2,5,9,10,35]. The OHSP, as a government system, with or without external financial support, requires all civil servants to commit to making it work.

Data Integration at the Operational Level

Most of the One Health surveillance systems in action are focused on zoonotic diseases [38,39] for data to be integrated with human surveillance. The established OHSP can swiftly connect with animal and environmental health surveillance data with its adaptability. In fact, the recent development of the National Agriculture Management Information System (NAMIS) in Malawi also uses the same DHIS2 technology to support the

Ministry of Agriculture in improving livestock production, enhancing herd health, and addressing transboundary animal diseases [40]. The OHSP can provide its affordance to interoperate with NAMIS for surveillance needs. Environmental health, by the nature of its vast domain, has more work to do. Therefore, the OHSP enhancement plan focuses on climate change in alignment with HSSP III can be supported by the same DHIS2 solutions [41]. However, as per our findings, the standardization of organizational units to cover all One Health surveillance domains will be a key issue that needs to be addressed, ideally using a similar master facility registry for animal and environmental surveillance sites.

Technical Infrastructure Reuse at the Operational Level

The functional OHSP, as an effective information system, addressed Malawi's Joint External Evaluation report issues and lack of weekly IDSR reporting by operationalizing and strengthening the One Health platform [11,15]. The high-level architecture, inspired by the concept of the integrated health information system architecture [42] and its alignment with IDSR processes, supported the design of OHSP and the strategy to reuse the existing infrastructure. Although the collaboration with stakeholders during the COVID-19 pandemic secured adequate technical infrastructure for the nationwide OHSP scale-up; however, the current collaborative modalities and technical support mechanisms are still limited in the human health domain, similar to other settings' One Health surveillance progress [38,43,44], where investment will be needed in other domains.

Digital health tools have proven instrumental in improving resilience and maintaining essential health services during crises [21]. However, the challenges noted in the infrastructure, particularly the lack of comprehensive redundancy and the limitations of the server room, point to the need for continuous investment, as highlighted by engineering resilience [26], to have a robust technical infrastructure to ensure OHSP's scalability and reliability.

Corresponded to Known DHIS2 Implementation Challenges

Findings were mainly reflected and compared with Dehnavieh et al [25].

Political, Cultural, Social, and Structural Infrastructure

The legal instruments, MoH's leadership, and institutionalization of the OHSP at PHIM addressed known politically related challenges [25]. However, as discussed earlier, sustaining stable financing for technical infrastructure remains a challenge.

Appropriate Data—Quality and Standards

The standardized IDSR data collected through the OHSP—including updates and additions introduced during the COVID-19 pandemic—along with validation rules for mandatory data entry, defined data quality indicators, data quality monitoring dashboards, and a weekly epidemiological bulletin ensured appropriate surveillance data supplies. These results directly addressed the challenges identified in Dehnavieh et al [2,25].

Workforce and Capacity Building

Malawi has a relatively adequate workforce for the development and implementation of OHSP DHIS2-related products, as evidenced by the constitution of the core team consisting of government officials and technical support officers from partner organizations who programmed the DHIS2 solutions locally. The OHSP enhancement plan, capacity-building plan, and online DHIS2 academies [45] addressed the human resource challenges [25].

Health System Resilience—Anticipation and Adaptive Resilience

Concerning the health system resilience, Malawi's health emergency awareness capacity was enhanced through real-time communication using WhatsApp groups for timely information sharing and decision-making. The use of such a digital solution with the One Health approach corresponds to the Riyadh Declaration to improve preparedness and response to future pandemics [46]. However, although the MoH manages these WhatsApp groups, risks remain for intentional information leakage by group members.

The adaptability of the OHSP was evident in the rapid response to COVID-19, with adjustments made to the system based on emerging needs. This finding echoes the recent organizational resilience studies during COVID-19 about adaptation, innovation, capabilities, and the use of new technology [47]. The Agile software development method, a skilled and committed core team, and affordable digital tools made the success possible.

The result demonstrated that Malawi's OHSP is a resilient system with high adaptability that supports the surveillance goals during the COVID-19 pandemic [21]. The OHSP core team consistently managed to build effective governance with strong government leadership to provide clear policy directions, which are essential for building resilient health systems [1,4]. The government's strong leadership in the establishment of the OHSP paved the way for OHSP digital health solutions to be developed with resilience and rapidly scaled nationwide, echoing conclusions on Africa's digital transformation [36].

Remaining Gaps and Future Directions

The OHSP addressed some identified barriers to support the IDSR system [11]; however, the current functionality has yet to address the community-level surveillance gaps fully [48]. Event-based surveillance (EBS) is one of the recommended surveillance methods to support community-level surveillance, as stated in the recent IDSR technical guidelines [12]. Other countries' EBS implementation experiences and practices encountered some challenges, including the trade-off between sensitivity and specificity, low awareness of EBS, and inadequate infrastructure [49,50]. The role of middle-layer actors in participating in community-level surveillance, community engagement, and additional digital solutions should be considered as the OHSP is enhanced to support the EBS in the country, not only for human health but also animal, including wild and domestic, and the surrounding environment as a whole [1,48,50]. Engagement with stakeholders using existing coordination mechanisms and applying the participatory

approach should be encouraged for future OHSP enhancement [35]. Despite Malawi managing to address the OHSP establishment challenges through strategic planning and implementation, continuous capacity building, training, supervision, and retaining skilled personnel for the OHSP to be resilient still exist in Malawi with constrained resources, similar to the challenges that Tanzania encountered trying to establish a similar platform [51]. Mobilizing and lobbying resources to fully operationalize the OHSP enhancement plan, with highlighting multisectoral benefits as argued by Fasina et al [44], is the recommended direction.

Limitations

Our study focused on the establishment experience of the OHSP in Malawi; despite its impact on the weekly IDSR reporting quality, its further use, linkage to other One Health domains, and its impact on the overall One Health surveillance are limited. Regarding the health system resilience, although the frameworks were developed [5,6], they are limited to emergency management and health care systems, with none specifically for One Health surveillance systems [26,52,53]. The synthesis analytic tool we developed for the OHSP establishment analysis can be used in similar settings for assessing the One Health surveillance system, despite the fact that our analysis was limited

to the One Health surveillance system establishment stage; further use of the tool is encouraged.

Conclusions

The success of Malawi's OHSP establishment highlights the importance of government leadership and coordination in ensuring financial and organizational sustainability. Key findings informed the need for continuous capacity building, adaptable technical infrastructure, and enhanced community-level surveillance in the long run.

As global health systems continue to face emerging threats to respective contexts, Malawi's experience demonstrates that a well-integrated, government-led digital OHSP can enhance resilience and preparedness to these health challenges. Amid the dynamic of the global development policy changes and complex human-animal-environmental interactions, findings from this study can be applied to broader audiences to enhance their surveillance and health systems in combating the pandemics to come.

Future investments, with emphasis on local leadership and domestic financial resources, in interoperability, infrastructure, and community engagement, will be essential for maximizing the impact of OHSP and similar initiatives worldwide.

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The authors declare that Grammarly was used as a machine tool to suggest language improvement within the language. No other generative AI tools were used in this manuscript.

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Data Availability

All meeting minutes and internal notes are available upon request. The One Health Surveillance Platform-related source codes and documentation, for public access according to the Ministry of Health regulations, are available in the following GitHub repositories: (1) Ministry of Health of Malawi in production services GitHub repository [54] and (2) Ministry of Health of Malawi Project-Based GitHub repository [55].

Conflicts of Interest

None declared.

Multimedia Appendix 1

Detailed analytic tool for health system resilience reflection and learning of the One Health Surveillance Platform establishment. [[XLSX File \(Microsoft Excel File\)](#), 26 KB - [publichealth_v12i1e72029_app1.xlsx](#)]

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Abbreviations

ADR: action design research
BIE: building, intervention, and evaluation
DHIS2: District Health Information Software 2
EBS: event-based surveillance
eIDSR: electronic integrated disease surveillance and response
EMRS: electronic medical record system
HMIS: health management information system
HSSP III: Health Sector Strategic Plan 2023-2030
IDSR: integrated disease surveillance and response
IHR: International Health Regulations
IL: interoperability layer
MoH: Ministry of Health
NAMIS: National Agriculture Management Information System
OHSP: One Health Surveillance Platform
PHIM: Public Health Institute of Malawi
UNICEF: United Nations International Children's Emergency Fund
WHO: World Health Organization

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Interactive Digital Visualization Counseling for Lifestyle Change in Patients at Risk of Cardiovascular Diseases: Randomized Controlled Trial

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Abstract

Background: Cardiovascular disease (CVD) remains the leading cause of death. Primary prevention relies heavily on health risk assessments and lifestyle changes, which can reduce long-term risk and mortality. Digital health offers an accessible and cost-effective approach to support prevention, enabling data sharing and visualization of key indicators such as blood pressure and glucose fluctuations. These visual insights may help patients better understand the effects of lifestyle changes and enhance communication with health care providers.

Objective: This research aims to evaluate whether the use of CVD risk visualization (Petal-X) and continuous glucose monitoring (CGM), alone or in combination, is associated with lifestyle changes and the perception of person-centered care (PCC) among patients at increased risk of CVD.

Methods: We conducted a 4-arm, single-blind, 2×2 factorial randomized controlled feasibility trial in primary care. A total of 119 participants were enrolled, of whom 101 completed the 6-month follow-up. Participants were randomized to 1 of 4 arms: (1) Petal-X CVD risk visualization+CGM; (2) CGM only; (3) Petal-X only; or (4) standard care with routine lifestyle counseling and no digital tools. CGM was used for 10 days in the CGM arms. Since this was a feasibility trial, no formal sample size calculation was performed. Primary outcomes are healthy lifestyle (Health Lifestyle and Personal Control Questionnaire [HLPCQ]) and perception of PCC (Person-Centered Practice Inventory—Service User [PCPI-SU]), and secondary outcomes (Systematic Coronary Risk Evaluation 2 [SCORE2], anthropometrics, and biological age) were assessed at baseline and 6 months. Descriptive statistics and Kruskal-Wallis tests (K independent samples) were used for analyses.

Results: At baseline, mean SCORE2 values ranged from 3.84 (SD 2.08) in intervention group 3 to 4.87 (SD 2.61) in intervention group 1, with the control group having a mean value of 4.53 (SD 3.63). Regarding the assessment of a healthy lifestyle, the domain of daily routine had the highest baseline scores across all groups (eg, mean 19.24, SD 5.87 in intervention group 1), and these scores improved by the final evaluation, although there were no statistically significant differences ($P=.42$) in changes between the groups. The perception of PCC was rated highest across all groups in the domain of shared decision-making, with no statistically significant differences ($P=.26$) between the groups. Results indicated improvements in healthy lifestyle habits, but the impact of interventions on perceived changes remained insignificant.

Conclusions: Healthy lifestyle and perceived PCC scores improved, although no statistically significant between-group differences were found. Risk visualization appears to be a key tool for increasing CVD awareness and strengthening patient involvement in care planning. Longer interventions with larger samples are needed to clarify these effects and optimize digital tools for lifestyle change.

Trial Registration: ClinicalTrials.gov NCT06226948; <https://clinicaltrials.gov/study/NCT06226948>

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KEYWORDS

biological age; cardiovascular disease; CGM; healthy lifestyle; Petal-X; RCT; visualization; continuous glucose monitoring; randomized controlled trial

Introduction

Chronic diseases are long-lasting and usually progressive in nature and not transmissible between people. They represent a major global health burden, both in terms of mortality and health care costs. There are 4 main types of chronic disease: cardiovascular disease (CVD), cancer, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma), and diabetes. These chronic diseases are responsible for most deaths worldwide [1,2]. Importantly, these diseases share common modifiable lifestyle risk factors such as poor diet, physical inactivity, tobacco use, and harmful alcohol consumption [2-4]. In 2021, they were estimated to cause 20.5 million deaths, approximately a third of deaths worldwide, which affected more than half a billion people [5-8]. The prevalence of CVD is rising due to increases in obesity, hypertension, type 2 diabetes mellitus, and physical inactivity [5,9-12]. Given that unhealthy lifestyles are estimated to contribute to around 60% of chronic disease risk [3,5,13,14], managing behavioral and environmental risk factors remains one of the most effective approaches to alleviating the burden of CVDs. Targeted lifestyle interventions have been shown to reduce CVD incidence and related mortality over the long term [15,16]. According to Visseren et al [17], lifestyle improvement should be the first line of intervention, including dietary changes (eg, reducing salt, saturated fats, and alcohol) and physical activity. The guidelines divide patients into risk categories so that prevention can be targeted. The groups are: I-very high risk of CVD (>40% in the next 10 y), II-high risk of CVD (20% - 40% in the next 10 y), III-moderate risk of CVD (10% - 20% in the next 10 y), IV-low risk of CVD (<10% in the next 10 y) [18]. However, many individuals at risk for CVD do not understand their personal risk or the potential benefits of lifestyle change. Moreover, they may underestimate the consequences of inaction, which underscores the importance of interventions that enhance awareness and promote sustained behavioral change [19-21].

In this context, digital health has emerged as a promising tool. Technological innovations are increasingly being used to deliver scalable interventions aimed at improving health behaviors [22]. Smartphones, which are now owned by approximately 6.9 billion people worldwide (86% of the global population), have become a platform for delivering digital health interventions [23]. Evidence suggests that digital health applications can support lifestyle change, improve glycemic control [24,25], lower blood pressure (BP) [26], and even reduce hospitalizations when integrated into cardiac rehabilitation programs [27,28]. Digital technologies also offer new ways of presenting health information in an engaging and understandable way. Visual representations of risk (graphs, dendrograms, and interactive charts) can improve patients' understanding of their condition and motivate behavior change [8,29-31]. As noted by Visseren et al [17], absolute risk and risk reduction are more easily understood when presented visually, rather than numerically.

Advanced tools such as decision support systems and continuous glucose monitoring (CGM) devices provide real-time, personalized insights into patient health. These technologies support prevention and treatment by integrating clinical data with evidence-based knowledge to enable personalized interventions [32]. For example, CGM systems not only help reduce the risk of hypoglycemia and hyperglycemia but also encourage behavior change by providing instant feedback on glucose levels [33-35]. However, the successful implementation of digital health tools depends on both patient engagement and health literacy [36]. Without the ability to understand and act on digital information, even the most advanced tools may have a limited effect. This is where person-centered care (PCC) becomes crucial. By involving patients as active partners in their own care and decisions, PCC has been shown to enhance outcomes across a range of conditions [37,38]. Research focuses on how risk for CVD can be effectively visualized using digital health tools, with a particular focus on CGM and its role in supporting lifestyle change. In line with the principles of PCC, the aim is to understand how these technologies can promote greater patient engagement and ultimately contribute to improved CVD outcomes. Simultaneously, the research recognizes the need for high-quality evaluations of the tools and visualization strategies used in clinical settings.

Methods

The research used a quantitative, multiarm design with data collected through validated questionnaires and direct participant measurements to comprehensively assess behavioral changes as well as subjective and objective health outcomes.

Study Design and Research Protocol

A quantitative research design was used to obtain measurable and generalizable data, which were collected using a combination of validated questionnaires and direct participant measurements, allowing a comprehensive assessment of both subjective experiences and objective health indicators. The trial followed a 4-arm 2×2 factorial design, and the research protocol was registered at ClinicalTrials.gov (NCT06226948). The primary objective was to compare changes in lifestyle behaviors across these 4 arms and to explore whether the combined use of CVD risk visualization and real-time CGM (intervention group 1) leads to greater improvements than standard care. Standard care consisted of routine clinical management at the primary care level, including regular check-ups with a family physician or nurse, brief lifestyle counseling (on diet, physical activity, smoking, and alcohol use) according to national guidelines, and access to general educational materials on CVD prevention. No additional digital tools or enhanced monitoring were provided to the control group.

The secondary objective was to compare changes in estimated CVD risk (SCORE2 [Systematic Coronary Risk Evaluation 2]) across the 4 groups. Additionally, we aimed to determine which lifestyle domains changed in patients at risk of CVD following

exposure to CVD risk visualization, real-time CGM, or their combination.

Type of Study

This research was designed as a single-blind, 4-arm randomized controlled trial (RCT) and was conducted from May to December 2024. Participants were informed only about the intervention they received and were not informed about the full set of study arms or the interventions delivered in other groups (limited disclosure). This RCT was designed as a pragmatic feasibility study embedded in routine primary care. A formal sample size or power calculation was not performed, as this study was designed as a pragmatic feasibility trial. The primary aim was to evaluate feasibility, usability, and behavioral trends rather than to test definitive effectiveness. Therefore, the sample size was determined based on practical feasibility considerations, including the number of eligible patients available in primary care and the logistical capacity for conducting clinical and laboratory assessments. As a result, the study may have been underpowered to detect statistically significant between-group differences.

Participants were randomly assigned to 4 study arms:

- Intervention group 1: Petal-X CVD risk visualization+CGM
- Intervention group 2: CGM only
- Intervention group 3: Petal-X visualization only
- Control group: standard care

Participants were randomized in a 1:1:1:1 ratio into 4 arms using a computer-generated allocation sequence (RAND function in Microsoft Excel). The randomization sequence was generated by the study researcher. The same researcher enrolled participants and assigned them to the trial arms according to the generated sequence. Given the pragmatic feasibility design, formal allocation concealment procedures were not implemented; the enrolling researcher was aware of the upcoming assignment. Participants without a compatible smartphone were randomized only between the 2 non-CGM arms (Petal-X only vs standard care).

The study followed the intention-to-treat principle, whereby all participants were analyzed within the groups to which they were originally assigned, regardless of whether they completed the intervention [39]. This approach preserved the integrity of randomization and reduced bias.

The trial and its reporting were in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 flowchart and the CONSORT extension for pilot and feasibility RCTs (see *Results*), and the corresponding checklist has been completed and submitted ([Checklist 1](#)).

Assessment Instrument

The primary outcomes (healthy lifestyle and perception of PCC) were assessed using 2 validated instruments: the Health Lifestyle and Personal Control Questionnaire (HLPCQ) and the Person-Centered Practice Inventory—Service User (PCPI-SU).

The following validated instruments were used in the research.

The HLPCQ [40] was used to assess lifestyle and perceived personal control. The questionnaire included demographic data

(sex, age, marital status, number of children, smoking status, and education and employment status) and anthropometric measures (body weight and height). The HLPCQ consists of 26 items grouped into 5 domains. We used a validated Slovenian version of the questionnaire [41]. In the Slovenian validation study conducted among 666 adults at risk of CVD, the total scale showed good internal consistency (Cronbach $\alpha=0.85$), with subscale α coefficients ranging from 0.59 to 0.88, indicating acceptable to good reliability [41]. In the present feasibility trial, we therefore relied on these previously established psychometric properties and did not repeat internal consistency testing (eg, Cronbach α) in our sample. The main aim of this questionnaire was to identify and quantify lifestyle patterns that reflect lifestyle change as reflected in stress levels and internal control over health. All domains were significantly positively related to each other, suggesting that people who adopt healthy eating habits and avoid harmful diets also follow a daily routine of activities, engage in organized exercise, seek social support, and take care of their mental health. Higher scores indicate a better lifestyle.

The PCPI-SU [42] was used to assess perceptions of PCC. It consists of 20 items and is designed to capture individuals' views on their perceptions of PCC. It covers 5 domains: working with the patient's beliefs and values (4 items), shared decision making (5 items), genuine collaboration (4 items), compassionate presence (3 items), and holistic action (4 items). The questionnaire was a 5-point Likert scale. Higher scores indicated better perceptions of PCC. In a Slovenian study among 426 adults with noncommunicable diseases, the PCPI-SU demonstrated good internal consistency, with Cronbach $\alpha=0.82$ for the total scale [43]. Consistent with our feasibility design and to avoid redundancy, we did not recalculate Cronbach α in the current sample and relied on these existing reliability estimates.

Participants were shown the Petal-X visualization [44] using a graphical tool that illustrated their current level of CVD risk in a visual representation. This tool was based on the SCORE2 prognostic model [45], which calculates an individual's 10-year risk of developing CVD. We then modified the parameters to reflect target values and used the visualization again to show how an individual's risk could potentially be reduced through lifestyle changes and adherence to the guidelines provided. The code of the Petal-X dashboard is publicly available on GitHub [46], and the English version of the dashboard as a web application is available on the internet [47]. The dashboard was developed using the Observable framework, with the Petal-X visualization [44] implemented using the Observable Plot system [48]. Petal-X was developed using a human-centered design process with iterative prototyping and expert review to ensure clarity and interpretability of the risk visualization [44]. In addition, the underlying surrogate model of SCORE2 was quantitatively validated and demonstrated high fidelity to the original SCORE2 equations, and a controlled experiment with 88 health care students showed that Petal-X supported more accurate interpretation of modifiable risk factor contributions than standard SCORE2 graphical score charts, without reducing perceived transparency, trust, or intention to use the tool [44]. Based on this prior evidence, we considered Petal-X to be of

sufficient quality and validity for use as an intervention tool in this feasibility trial. It is based on the validated SCORE2 prognostic model.

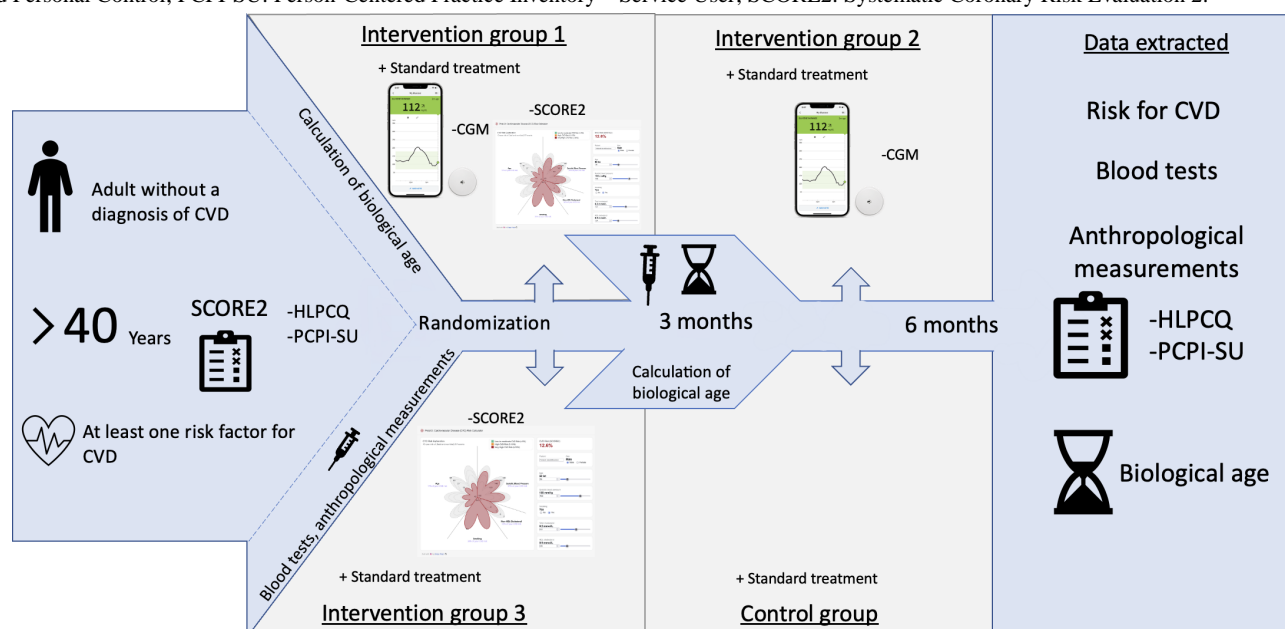
Biological age is calculated from plasma GlycanAge analysis [49] and is based on the algorithm developed by Levine et al [50], which incorporates 9 blood biomarkers most strongly associated with mortality: mean corpuscular volume, C-reactive protein, albumin, blood glucose, alkaline phosphatase, red cell distribution width, creatinine, lymphocyte percentage, and chronological age; CGM data is collected using the Dexcom system G7 [51], allowing for real-time monitoring of blood glucose levels.

Description of the Research Process

All participants who met the inclusion criteria completed the HLPQC and the PCPI-SU at baseline and at the 6-month follow-up, and were also assessed for CVD risk using the SCORE2 prognostic model, incorporating the following

variables: age, sex, systolic BP, total cholesterol, high-density lipoprotein (HDL) cholesterol, and smoking status. Venous blood samples were collected at baseline and at 6 months to determine standard biochemical markers (including lipid profile and fasting glucose) and to calculate phenotypic and glycated biological age, with an additional blood sample taken at 3 months for biological age assessment only. The risk assessment using SCORE2 was repeated after 6 months to evaluate potential changes. Additionally, biological age was calculated at 3 and 6 months as a more precise indicator of lifestyle changes compared to chronological age. Two models were used: the model by Levine et al [50], based on blood biomarkers, and GlycanAge, based on glycan analysis, as defined by Lauc and Primorac [49]. Participants were allocated to the following 3 different intervention groups and 1 control group according to the quantitative research design, with the groups differing according to the type of intervention they received during treatment (Figure 1).

Figure 1. Intervention groups and research process. CGM: continuous glucose monitoring; CVD: cardiovascular disease; HLPQC: Healthy Lifestyle and Personal Control; PCPI-SU: Person-Centered Practice Inventory—Service User; SCORE2: Systematic Coronary Risk Evaluation 2.



Intervention group 1 received both CGM for 10 days and the Petal-X CVD risk visualization tool [44]. Petal-X allowed for a visual presentation of the participant's current risk and an interactive simulation of how lifestyle changes could improve the risk profile.

Intervention group 2 used CGM for 10 days, without using the Petal-X CVD risk visualization tool.

Intervention group 3 received only the Petal-X risk visualization.

The control group received standard care without additional intervention and did not receive any of the digital interventions (Petal-X or CGM) after study completion, as the trial did not include a delayed-intervention phase.

At baseline and after 6 months, all participants underwent anthropometric and blood measurements, completed the HLPQC and PCPI-SU questionnaires, and received updated CVD risk (SCORE2) and biological age assessments. These data allowed

for comparisons between groups and evaluation of changes in lifestyle and CVD. The 6-month duration was selected based on previous studies demonstrating meaningful changes in health behaviors within this period [52,53]. Adverse events and device-related issues (eg, CGM-related problems) were monitored throughout the study. No serious adverse events were reported.

Study Sample

Recruitment was open to individuals across Slovenia, but the promotional campaign and study implementation were concentrated in a Community Health Center in central Slovenia. Purposive sampling was used, and inclusion criteria included adults being 40 years or older with no previous diagnosis of CVD but with at least one of the following risk factors: elevated BP (systolic >140 mmHg), elevated fasting glucose (>6.1 mmol/L), abnormal lipid levels (total cholesterol >5 mmol/L, HDL <1.4 mmol/L for men and <1.6 mmol/L for women,

low-density lipoprotein >3.5 mmol/L, triglycerides >1.7 mmol/L), or BMI >30 .

Preexisting CVD, being younger than 40 years, and the absence of risk factors were the exclusion criteria. The sample was selected using purposive sampling. In total, 119 participants were included at baseline: 30 in intervention group 1 (CGM and Petal-X), 24 in intervention group 2 (CGM only), 33 in intervention group 3 (Petal-X only), and 32 in the control group. At follow-up, 101 participants remained: 27 in intervention group 1, 22 in intervention group 2, 26 in intervention group 3, and 26 in the control group. Dropout reasons included newly diagnosed health conditions, inability to attend follow-up appointments, or personal commitments.

Statistical Analysis

Descriptive statistics (means and SDs for continuous variables and absolute and relative frequencies for categorical variables) were used to characterize the sample and summarize outcome measures. Group differences in categorical baseline characteristics (eg, gender, smoking status, and education) were analyzed using chi-square tests. All statistical analyses adhered to the intention-to-treat principle. IBM SPSS Statistics 29.0 was used for all analyses, and statistical significance was set at $P \leq .05$.

For Hypothesis 1, differences in lifestyle change across the 4 randomized groups were analyzed using the Kruskal–Wallis test, with the HLPCQ total score as the dependent variable. For Hypothesis 2, changes in cardiovascular risk across the 4 groups were analyzed with SCORE2 as the dependent variable, also using the Kruskal–Wallis test, due to nonnormal distributions and modest cell sizes. HLPCQ and PCPI-SU scores were treated as continuous variables using their total scale scores.

Spearman's rank correlation coefficients were calculated to explore associations between healthy lifestyle (HLPCQ) and perceived PCC (PCPI-SU) [54].

To reduce detection and analysis bias, outcome data were handled using coded group labels during data cleaning and analysis, and laboratory assessments were performed according to standard procedures without reference to group allocation.

Ethical Considerations

All data collection and intervention procedures were conducted at a community health center in Central Slovenia. The research

was carried out by a researcher under the supervision of an associate professor and a physician.

Participants underwent venous blood sampling at baseline, 3 months, and 6 months. Appointment invitations included a brief personalized summary of test results, which served to further motivate participants. The study was single-blind at the participant level: participants were informed only about procedures in their allocated arm and were not informed about the full set of study arms. Due to the pragmatic implementation, study personnel were not blinded.

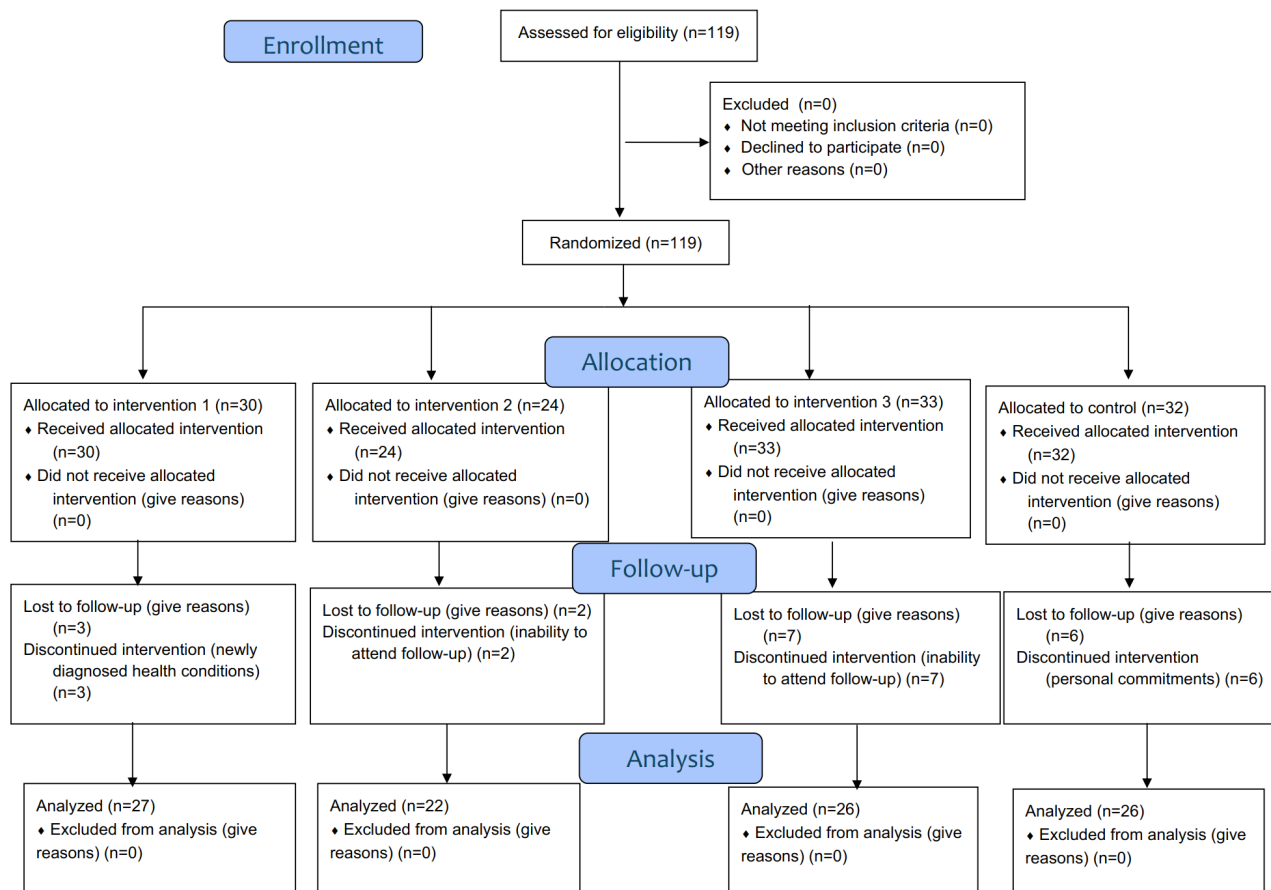
The study was approved by the Ethics Committee for Nursing Research at the Faculty of Health Sciences, University of Maribor (Approval No. 02/7K-2023), and the National Medical Ethics Committee of the Republic of Slovenia (Approval No. 0120-217/2023/4). We have also registered the research protocol in clinical trials (ClinicalTrials.gov NCT06226948) [55]. All participants were informed that their data would be used exclusively for research purposes.

Participants received written and verbal information about the study and provided written informed consent before any study procedures. Participation was voluntary, and participants could withdraw at any time without consequences for their usual care. To protect privacy and confidentiality, each participant was assigned a unique study identification code; identifiable information was stored separately from research data and was accessible only to authorized study personnel. Data were handled in accordance with applicable data protection regulations (eg, General Data Protection Regulation) and institutional policies, and were stored on password-protected systems with restricted access; only anonymized or aggregated data were used for analysis and reporting. No financial compensation was provided for participation.

Results

Participant Enrollment

Figure 2 presents the CONSORT participant flow diagram. In total, 119 participants were enrolled and randomized into 4 arms, and 101 participants completed the 6-month follow-up; dropouts were mainly due to newly diagnosed health conditions, inability to attend follow-up appointments, or personal commitments.

Figure 2. The CONSORT (Consolidated Standards of Reporting Trials) 2010 flowchart.

Demographic Characteristics

Of the 119 participants, 71% (n=85) were women and 29% (n=34) were men. At the start of the study, most participants were married (n=56, 47%) and had children (n=107, 90%). Most participants had specialization in a professional higher education program, completed a university program or a master's degree (second degree; n=43, 36%), and were employed (n=110, 92%). Most participants did not smoke (n=82, 69%).

Table 1 shows the basic demographic characteristics of all intervention groups and the control group at baseline. The only demographic variable that differed significantly between the groups was educational level ($\chi^2_{15}=37.15$; $P=.001$). Participants

in Intervention group 1 (13/30, 43.3%) and Intervention group 3 (15/33, 45.5%) more frequently reported holding a master's degree compared with the control group (6/32, 18.8%). No other demographic characteristics differed significantly across groups, including gender ($\chi^2_3=3.15$; $P=.37$), age ($H_3=3.13$; $P=.37$), marital status ($\chi^2_{12}=9.22$; $P=.68$), having children ($\chi^2_3=0.71$; $P=.87$), number of children ($H_3=0.94$; $P=.82$), employment ($\chi^2_6=7.62$, $P=.27$), smoking status ($\chi^2_6=2.08$; $P=.91$), and number of cigarettes smoked ($H_3=3.18$; $P=.36$). Any differences in the study were due to the interventions in the intervention groups and the level of education in the context of demographic characteristics.

Table . Descriptive characteristics of participants.

	Intervention group 1	Intervention group 2	Intervention group 3	Control group	<i>P</i> value
Gender, n (%)					.37
Man	9 (30)	9 (37.50)	6 (18.18)	11 (34.38)	
Woman	21 (70)	15 (62.50)	27 (81.82)	21 (65.63)	
Nonbinary	0 (0)	0 (0)	0 (0)	0 (0)	
Age (years), mean (SD)	51.87 (7.22)	48.50 (7.02)	50.33 (7.14)	49.84 (8.44)	.37
Marital status, n (%)					.68
Married	15 (50)	9 (37.50)	16 (48.48)	16 (50)	
Extramarital community	11 (36.67)	10 (41.67)	8 (24.24)	12 (37.50)	
Single	4 (13.33)	5 (20.83)	6 (18.18)	3 (9.38)	
Widower	0 (0)	0 (0)	2 (6.06)	1 (3.13)	
Other	0 (0)	0 (0)	1 (3.03)	0 (0)	
Having children, n (%)					.87
Yes	28 (93.33)	21 (87.50)	29 (87.88)	29 (90.63)	
No	2 (6.67)	3 (12.50)	4 (12.12)	3 (9.38)	
Number of children, mean (SD)	1.70 (0.84)	2.00 (1.22)	1.76 (1.03)	1.78 (1.01)	.82
Educational level, n (%)					.001
No education	0 (0)	0 (0)	0 (0)	0 (0)	
Primary education	1 (3.33)	0 (0)	0 (0)	0 (0)	
Secondary school education	8 (26.67)	7 (29.17)	2 (6.06)	13 (40.63)	
Higher university education	4 (13.33)	7 (29.17)	16 (48.48)	13 (40.63)	
Master's degree	13 (43.33)	9 (37.50)	15 (45.45)	6 (18.75)	
PhD	4 (13.33)	0 (0)	0 (0)	0 (0)	
Other	0 (0)	1 (4.17)	0 (0)	0 (0)	
Employment, n (%)					.27
Yes	28 (93.33)	22 (91.67)	32 (96.97)	28 (87.50)	
No	2 (6.67)	0 (0)	1 (3.03)	1 (3.13)	
Retired	0 (0)	2 (8.33)	0 (0)	3 (9.38)	
Other	0 (0)	0 (0)	0 (0)	0 (0)	
Smoking status, n (%)					.91
Yes	6 (20)	5 (20.83)	8 (24.24)	8 (25)	
No	20 (66.67)	18 (75)	23 (69.70)	21 (65.63)	
Stop smoking	4 (13.33)	1 (4.17)	2 (6.06)	3 (9.38)	
Number of cigarettes, mean (SD)	15 (6.32)	9.80 (5.26)	11.50 (5.63)	9.75 (5.63)	.37

Evaluation of the Measurements of the Participants in the Main Research

Intervention group 1 had the highest mean SCORE2 at baseline (4.87, SD 2.61), followed by the control group (4.53, SD 3.63) and intervention group 2 (4.08, SD 2.42), while intervention

group 3 had the lowest score (3.84, SD 2.08). This indicates that intervention group 3 had the most favorable CVD risk profile at baseline, as lower scores reflect lower risk. Intervention group 1 had the highest mean total cholesterol value at baseline (5.93, SD 1.10), while intervention group 2 had the lowest mean value (4.82, SD 1.51). Intervention group

3 had the highest mean HDL value, with a final value of 1.62 (SD 0.34), while intervention group 2 had the lowest mean value, with a baseline value of 1.28 (SD 0.31).

The highest mean systolic BP was measured in intervention group 1, with a baseline value of 129.23 mmHg (SD 16.76), while the lowest mean was in intervention group 3, with a final value of 119.69 (SD 11.58).

There were no statistically significant differences between groups in SCORE2 ($H_3=3.269$; $P=.35$), total cholesterol

($H_3=2.402$; $P=.49$), HDL ($H_3=2.93$; $P=.40$), systolic BP ($H_3=3.346$; $P=.34$), diastolic BP ($H_3=2.588$; $P=.46$), heart rate ($H_3=2.170$; $P=.54$), BMI ($H_3=4.066$; $P=.25$), phenotypic biological age ($H_3=2.708$; $P=.44$) and glycated biological age ($H_3=0.261$; $P=.97$). Statistical analysis showed no significant differences between groups. This means that the groups compared with respect to SCORE2, total cholesterol, HDL, BP, heart rate, BMI, phenotypic biological age, and glycated biological age were like each other. The baseline and final values for all measurements are presented in Table 2.

Table . Participant measurements by randomized groups.

	Intervention group 1, mean (SD)	Intervention group 2, mean (SD)	Intervention group 3, mean (SD)	Control group, mean (SD)	Change in <i>P</i> value (SD)
SCORE2 ^a					.35
Baseline value	4.87 (2.61)	4.08 (2.42)	3.84 (2.08)	4.53 (3.63)	
Final value	4.06 (2.71)	3.53 (2.02)	3.17 (1.99)	4.36 (3.27)	
Total cholesterol					.49
Baseline value	5.93 (1.10)	5.09 (0.66)	5.68 (0.93)	5.28 (1.12)	
Final value	5.10 (2.26)	4.82 (1.51)	5.43 (0.99)	5.44 (1.07)	
HDL ^b					.02
Baseline value	1.43 (0.28)	1.28 (0.31)	1.61 (0.33)	1.33 (0.32)	
Final value	1.42 (0.31)	1.34 (0.31)	1.62 (0.34)	1.38 (0.32)	
Systolic blood pressure					.34
Baseline value	129.23 (16.76)	124.17 (14.21)	122.36 (13.32)	123.38 (17.09)	
Final value	128.26 (10.88)	121.36 (14.98)	119.69 (11.58)	124.77 (12.58)	
Diastolic blood pressure					.46
Baseline value	84.73 (8.73)	82.54 (11.92)	78.48 (9.86)	82.38 (10.93)	
Final value	78.93 (9.14)	77.18 (9.51)	75.35 (7.70)	78.19 (7.99)	
Heart rate					.54
Baseline value	76.07 (12.53)	73.79 (13.08)	72.15 (9.90)	71.66 (11.62)	
Final value	72.11 (8.38)	71.36 (12.69)	71.81 (9.33)	71.31 (9.70)	
BMI					.25
Baseline value	26.35 (4.19)	26.83 (4.50)	25.16 (4.03)	28.01 (5.64)	
Final value	26.48 (4.21)	26.55 (4.22)	24.48 (3.97)	27.65 (5.11)	
Phenotypic biological age					.44
Baseline value	46.82 (7.89)	43.30 (7.53)	43.90 (7.01)	43.34 (9.38)	
Final value	43.07 (14.02)	40.64 (11.36)	36.35 (16.98)	40.44 (16.43)	
Glycan biological age					.68
Baseline value	56.73 (16.17)	48.71 (21.73)	54.33 (16.08)	51.72 (18.31)	
Value after 3 mo	57.39 (16.53)	53.23 (20.79)	54.74 (16.00)	49.37 (19.8)	
Final value	56.04 (18.73)	51.86 (20.95)	54.96 (17.09)	53.50 (15.76)	

^aSCORE2: Systematic Coronary Risk Evaluation 2.

^bHDL: high-density lipoprotein cholesterol.

Based on the analyses of the data, we found that there were no significant differences in lifestyle changes between participants in the intervention groups and those in the control group.

Healthy Lifestyle Assessment: HLPCQ

In all 3 intervention groups and the control group, the domain with the highest baseline score was daily routine. The mean scores for this domain were 19.24 (SD 5.87), 19.17 (SD 3.59), 19.93 (SD 5.18), and 17.61 (SD 5.82) for the first, second, and third intervention groups and the control group, respectively. However, the lowest-rated domain in all groups was organized exercise. The mean scores were 4.27 (SD 1.87), 4.00 (SD 1.78), 4.55 (SD 2.08), and 4.09 (SD 1.69).

At the end point, the highest and lowest rated domains remained unchanged but increased, indicating an improvement in HLPCQ scores. The mean scores for the highest-rated domain, Daily Routine, were: 21.27 (SD 4.94) for the intervention group 1; 21.50 (SD 4.30) for the intervention group 2; 21.25 (SD 3.90) for the intervention group 3; and 19.80 (SD 4.85) for the control group. However, organized exercise was the lowest rated domain

in all groups. The mean scores were 5.31 (SD 1.67) in the first intervention group, 4.36 (SD 1.94) in the second intervention group, 4.54 (SD 2.00) in the third intervention group, and 4.88 (SD 2.01) in the control group.

Missing data were minimal across variables, with no missing values for healthy dietary choices at baseline (n=0), and only isolated cases for dietary harm avoidance (n=1), daily routine (n=3), organized physical activity (n=1), and social and mental balance (n=2); the highest number of missing values occurred in the total HLPCQ scores, with up to 5 in 1 group at final measurement.

There were no statistically significant differences in change in HLPCQ scores between groups ($H_3=2.801$; $P=.42$). Thus, the Kruskal–Wallis test showed that group had no significant effect on the change in HLPCQ (Table 3).

Table . Baseline and final HLPCQ^a scores by randomized group.

HLPCQ	Intervention group 1, mean (SD)	Intervention group 2, mean (SD)	Intervention group 3, mean (SD)	Control group, mean (SD)
Healthy dietary choices				
Baseline value	15.93 (3.50)	14.79 (2.30)	16.94 (2.57)	15.25 (3.44)
Final value	17.72 (4.08)	16.64 (3.55)	18.28 (3.39)	16.42 (2.80)
Dietary harm avoidance				
Baseline value	10.40 (2.39)	10.52 (2.25)	11.31 (2.15)	10.28 (2.73)
Final value	11.08 (2.04)	10.32 (2.23)	11.88 (2.01)	10.46 (1.94)
Daily routine				
Baseline value	19.24 (5.87)	19.17 (3.59)	19.93 (5.18)	17.61 (5.82)
Final value	21.27 (4.94)	21.50 (4.30)	21.25 (3.90)	19.80 (4.85)
Organized physical activity				
Baseline value	4.27 (1.87)	4.00 (1.78)	4.55 (2.08)	4.09 (1.69)
Final value	5.31 (1.67)	4.36 (1.94)	4.54 (2.00)	4.88 (2.01)
Social and mental balance				
Baseline value	14.10 (2.51)	13.92 (2.54)	14.36 (2.36)	13.53 (3.29)
Final value	14.36 (2.04)	14.45 (2.82)	13.88 (3.05)	13.96 (2.73)
HLPCQ total				
Baseline value	64.17 (12.54)	63 (7.53)	66.76 (8.91)	60.58 (12.96)
Final value	69.50 (10.34)	67.27 (8.56)	68.90 (7.78)	65.72 (10.18)

^aHLPCQ: Healthy Lifestyle and Personal Control Questionnaire.

The Kruskal–Wallis test ($H_3=2.801$; $P=.42$) revealed no statistically significant differences between the groups regarding changes in HLPCQ. However, the control group showed the most significant improvement in terms of a healthy lifestyle.

Perception of Person-Centered Care: PCPI-SU

At baseline, the highest-rated domain in all 3 intervention groups and the control group was sharing decision-making. The mean scores were 19.57 (SD 4.68) in the first intervention group, 18.00 (SD 4.64) in the second intervention group, 19.39 (SD 4.96) in the third intervention group, and 18.78 (SD 5.08) in

the control group. However, engaging authentically was the lowest scoring domain in all groups, with average scores of 11.00 (SD 2.85) in the first intervention group, 10.29 (SD 2.48) in the second intervention group, 11.00 (SD 3.01) in the third intervention group, and 10.31 (SD 2.79) in the control group.

The domains that were highest and lowest rated at the final perception remained unchanged. The average domain scores for sharing decision-making in the first intervention group were 19.77 (SD 4.61), in the second intervention group 20.86 (SD 4.16), in the third intervention group 19.27 (SD 5.80), and in the control group 19.35 (SD 4.91). The lowest-rated domain

was being sympathetically present in all groups. The average scores were 10.96 (SD 2.57) in the first intervention group, 11.55 (SD 2.99) in the second intervention group, 11.42 (SD 3.24) in the third intervention group, and 11.20 (SD 3.16) in the control group.

Missing data were low across variables, with no missing values for several baseline and final measurements. Occasional missing

data were observed for working with the person’s beliefs and values (n=1), sharing decision-making (n=1), engaging authentically (n=3), being sympathetically present (n=1), and working holistically (n=2). The highest number of missing values occurred in the total PCPI-SU scores, with 3 at baseline and 2 at the final measurement (Table 4).

Table . The perception of PCPI-SU^a and components at the start and end of the study by the groups that were randomly selected.

	Intervention group 1, mean (SD)	Intervention group 2, mean (SD)	Intervention group 3, mean (SD)	Control group, mean (SD)
Working with the person’s beliefs and values				
Baseline value	15.43 (3.99)	14.00 (3.84)	15.15 (3.83)	14.44 (4.26)
Final value	15.23 (3.93)	15.27 (4.24)	14.88 (4.08)	15.35 (3.98)
Sharing decision-making				
Baseline value	19.57 (4.68)	18.00 (4.64)	19.39 (4.6)	18.78 (5.08)
Final value	19.77 (4.61)	20.86 (4.16)	19.27 (5.80)	19.35 (4.91)
Engaging authentically				
Baseline value	14.69 (3.41)	14.17 (3.24)	14.33 (3.37)	13.66 (3.64)
Final value	14.84 (3.14)	15.59 (3.26)	14.65 (3.50)	14.40 (3.69)
Being sympathetically present				
Baseline value	11.00 (2.85)	10.29 (2.48)	11.00 (3.01)	10.31 (2.79)
Final value	10.96 (2.57)	11.55 (2.99)	11.42 (3.24)	11.20 (3.16)
Working holistically				
Baseline value	14.55 (3.93)	13.61 (4.24)	14.42 (3.87)	13.87 (4.40)
Final value	14.23 (3.86)	15.00 (4.08)	15.50 (4.35)	14.77 (4.22)
PCPI-SU total				
Baseline value	75.64 (17.82)	70.13 (15.98)	76.70 (14.98)	71.17 (18.53)
Final value	74.92 (16.16)	79.19 (17.12)	75.73 (19.02)	73.54 (18.23)

^aPCPI-SU: Person-Centered Practice Inventory—Service User.

This indicates that there are no significant differences between the groups in terms of changes in PCPI-SU. This is consistent with the results of the Kruskal–Wallis test, which showed no statistically significant differences ($H_3=4.056$; $P=.26$). However, it shows that there was a difference in the change in the second intervention group, in which the CGM was worn. Based on this, it can be concluded that the intervention in the second group had an impact on improving the perception of PCC.

Discussion

Effectiveness of Risk Visualization and Glucose Monitoring in Reducing CVD Risk

The overall trend for the SCORE2 risk showed a decrease in CVD for all participants over the 6-month period. This suggests that participants showed some improvement in their risk profile regardless of the type of intervention. The group that was exposed to risk visualization through the Petal-X tool as part of the intervention showed the most improvement. When comparing all 3 intervention groups with the control group more

explicitly, a clear pattern emerges. The group receiving combined CVD risk visualization and CGM showed the largest numerical reduction in SCORE2, followed by the group receiving visualization only, while the CGM-only group demonstrated a smaller improvement. The control group also exhibited a reduction in SCORE2, but the magnitude of change was consistently lower than in the visualization-based intervention groups. Although these differences did not reach statistical significance, the direction and relative size of the effects suggest that visual risk communication may have stronger motivational value than glucose monitoring alone, and that combining visualization with CGM may provide additional reinforcement. This highlights the potential value of visual feedback in supporting risk awareness and self-regulation. The findings are consistent with previous research indicating that traditional CVD factors, such as elevated BP, high cholesterol levels, and smoking, remain important in predicting future CVD events [56,57]. Despite the use of different methodologies and assessment tools in different studies, the consistency in core risk factors supports the reliability of tools such as SCORE2 for estimating individual risk. In the present study, the use of a

validated prognostic model (SCORE2), combined with robust data collection from the Slovenian population, provided a solid foundation for evaluating risk trends.

Unlike other research designs, such as the focus group methods used by Vivek Dhukaram et al [58] or the large-scale registry analyses conducted in the Taiwanese study using the National Health Insurance Research Database [59], our approach provides clinically relevant insights into how risk evolves in real-world conditions. Furthermore, physician-led evaluations based on European guidelines, as demonstrated in the study by Dudas et al [60], continue to be a fundamental aspect of CVD risk management. Our findings support these approaches by integrating a PCC component through visualization, which may enhance patient engagement and understanding of personal risk. In line with international evidence [57,61], this study confirms that identifying at-risk individuals early on through structured risk assessments enables more precise preventive interventions. Visualizing risk, particularly when paired with ongoing monitoring or tailored counseling, may further encourage behavioral changes and reduce the long-term burden of CVD. The results of the CVD risk assessment allow for early identification of at-risk individuals, which may contribute to more targeted preventive interventions and a reduction of the burden of CVD in the population, and these findings are also consistent with the reviewed literature [56,57,61]. It is important to interpret the results within the context of this feasibility trial. The absence of statistical significance may be related to the modest sample size, baseline variability, and the short duration of exposure to the interventions. These factors limit the ability to detect smaller but potentially meaningful behavioral changes. Therefore, the results should be interpreted as preliminary indicators of trends rather than definitive effect estimates.

Evaluating and Modifying Lifestyle Behaviors in CVD Risk Patients Through Visualization and Glucose Monitoring

Assessment of lifestyle using the HLPCQ revealed improvements in multiple domains, particularly among participants who received CVD risk visualization and CGM. These tools were most effective in promoting healthy dietary choices and enhancing daily routines, emphasizing the importance of combining risk awareness with real-time feedback [62]. Participants who received only visualization or only CGM also showed progress, though less consistently. Organized physical activity remained the weakest area across all groups, suggesting that general interventions may be insufficient to influence this behavior. Further research confirms the importance of routine, nutrition, and physical activity in improving quality of life and reducing the risk of disease [63–68]. Social and mental balance showed minimal change, which suggests that these aspects may be more resistant to digital or informational interventions and more dependent on the broader psychosocial context. The avoidance of dietary harm also decreased, particularly in groups without combined support. Older participants tended to report better organization of their lifestyle and healthier eating habits. This aligns with findings that age can positively influence adherence to preventive behaviors. Although no statistically significant differences were

found, there were meaningful behavioral shifts in groups with combined interventions. The HLPCQ proved to be a useful tool for detecting these changes, particularly given its ability to incorporate self-regulation and health-related behaviors. Its future use in primary care and epidemiological research appears promising. It is important to note that lifestyle change depends not only on information but also on health literacy, motivation, and contextual support [69]. Research from Sweden has emphasized the importance of valid methods for engaging communities in sustainable prevention efforts, particularly among populations with low health literacy or limited access to care [70]. Therefore, enhancing health literacy could be central to national strategies for preventing lifestyle-related conditions [71]. In conclusion, visualization and CGM can support behavioral changes in individuals at risk of CVD, particularly regarding dietary and routine habits. However, more targeted approaches are needed for physical activity and psychosocial domains, which remain less responsive.

Lifestyle Change Across Intervention and Control Groups

We tested the hypothesis that there would be significant differences in lifestyle change between groups, but this was not confirmed. The Kruskal–Wallis analysis revealed no statistically significant differences in HLPCQ score changes between the 4 study groups (3 intervention groups and the control group). The control group reported the greatest overall change in healthy lifestyle behavior, followed by smaller positive changes in all intervention groups. This suggests that the inclusion of new technologies, such as CVD risk visualization and CGM, did not result in statistically superior lifestyle improvements over 6 months. Nevertheless, the presence of positive trends in all intervention groups indicates a potential motivational effect of the interventions. A sustainable lifestyle change is a long-term process requiring continuity, reinforcement, and individual adaptation to have a lasting impact on quality of life and health-related well-being [17]. Based on other studies with similar intervention durations [17,53], we expected to detect measurable changes after 6 months. However, the short-term use of CGM and limited intervention exposure may have reduced the observable impact within the timeframe of our research.

Additionally, the Petal-X visualization of CVD risk was described as a concrete and motivating element that helped individuals recognize the necessary behavioral changes in their daily lives. These observations indicate that while measurable outcomes were modest, experiential factors may still play an important role in behavior change. Further research should explore longer intervention periods and enhanced support structures to evaluate the full potential of visual and self-monitoring tools in promoting healthy lifestyles. It is important to note that educational level differed significantly between the randomized groups at baseline. This imbalance is a common limitation in small feasibility samples, where randomization may not fully equalize sociodemographic characteristics. Since higher educational attainment is associated with better health literacy, greater engagement in preventive behaviors, and improved ability to interpret risk information, it is possible that educational level influenced participants'

responses to the interventions. Although we cannot determine the extent of this influence, it may have contributed to behavioral differences observed across groups. Future studies should include stratified randomization or larger sample sizes to minimize such baseline imbalances.

Determining Whether Person-Centered Care Is Associated With Lifestyle Change

A link between PCC and lifestyle change was demonstrated. The results of the correlation analysis revealed a weak, yet statistically significant, positive relationship between perceived PCC and healthy lifestyle behaviors, including self-regulation. The Spearman correlation coefficient showed that higher HLPCQ scores, reflecting healthier lifestyle patterns and greater personal control, were associated with higher perceptions of PCC. Although the correlation was weak, its statistical significance suggests that the association is unlikely to be due to chance. These findings show that improving lifestyle and self-management behaviors could lead to a more positive perception of care quality from the patient's perspective. Therefore, even minor improvements in perceived PCC could be meaningful, particularly when promoting long-term behavioral change and better health outcomes. Researchers emphasize the importance of health care professionals assessing individual risk, designing care plans that are tailored to patients' lifestyles and contexts, and implementing PCC approaches to positively influence health outcomes [72-76]. Furthermore, interventions targeting lifestyle changes have been shown to improve BP and lipid profile control, highlighting the effectiveness of PCC in managing risk factors and encouraging behavioral changes [77]. This evidence highlights the importance of tailoring health care delivery to patients' individual needs and preferences. PCC has the potential to improve patient satisfaction and may reduce CVD risk factors such as hypertension [78-80]. Therefore, integrating lifestyle-oriented PCC strategies into clinical practice should be considered a priority in both prevention and chronic care management.

These findings should be interpreted with caution, as the study may have been underpowered and the intervention period relatively short, both of which could have limited the ability to detect statistically significant effects. It is also important to consider potential clinical significance. Both the HLPCQ and PCPI-SU scores showed improvements across groups, including the control group. Although these changes were not statistically significant, small improvements in lifestyle behaviors or person-centeredness may still be clinically meaningful in a primary care setting. Behavior change is often gradual and incremental, and even minor positive shifts can contribute to long-term cardiovascular risk reduction when sustained over time.

Limitations

This study has several limitations. The lack of a double-blind design may have introduced bias, and participants may have perceived differences between the intervention groups, which could have influenced the outcomes. The sample included only individuals with an increased risk of CVD based on clinical markers, excluding those with behavioral risk factors. Variability

in digital literacy, particularly among older participants, may have affected uptake of the technology-supported interventions. Motivation fluctuated due to personal life events, and some technical issues with CGM devices occurred, but these were resolved. Although the lifestyle questionnaire had not been validated in Slovenia, the necessary cultural adaptations were made in line with WHO guidelines.

Additionally, the study was not sufficiently powered to detect small or moderate effects, as the sample size was limited and no formal power calculation was conducted prior to recruitment. This may have contributed to the absence of statistically significant findings despite observable clinical trends. The 6-month intervention period may have been too short to capture measurable changes in long-term lifestyle behaviors or CVD risk, which typically require sustained support and longer follow-up. This likely reduced the detectable impact of both visualization and CGM-based interventions. Consequently, the trial was not adequately powered to detect small or moderate between-group differences, and the absence of statistically significant findings should therefore be interpreted with caution.

Key Findings and Recommendations

Although the quantitative results did not confirm statistically significant improvements, participants in the intervention groups reported enhanced awareness, motivation, and engagement in their health management. Digital tools such as Petal-X, CGM, and biological age assessment supported PCC and encouraged meaningful lifestyle adjustments. These findings demonstrate the potential for integrating digital tools into preventive health care to improve understanding of CVD risk and promote behavior change. Future studies should include larger and more diverse samples, extend the follow-up period, and examine effects in specific subgroups. Strengthening digital literacy among health care professionals and patients will be essential for successful implementation. With better training and user-friendly tools, technologies such as Petal-X and CGM could provide substantial support for lifestyle change, ongoing risk monitoring, and more effective PCC.

Conclusions

This study makes a valuable contribution to the growing field of digital health, demonstrating the potential of combining risk visualization (Petal-X), CGM, and biological age assessment for the lifestyle-based prevention of CVD. While no clinically significant improvements were observed, the findings provide valuable insights into the feasibility, usability, and motivational impact of digital tools in PCC. Integrating such technologies could facilitate the early identification of risk, encourage patient engagement, and promote behavior change. These results emphasize the necessity of further longitudinal research and the development of digital infrastructure to facilitate lifestyle interventions within preventive health care in Slovenia. We also provided a detailed description of the standard care received by the control group to ensure transparency and comparability between intervention arms, in accordance with CONSORT recommendations.

This study highlights the potential of integrating digital tools such as Petal-X visualization, CGM, and biological age

assessment into preventive health care. While statistical significance was limited, participants reported increased awareness, motivation, and involvement in managing their health. These findings support the value of PCC approaches and the need for further research on long-term,

technology-supported lifestyle interventions. Expanding digital literacy and developing national guidelines for digital integration will be key to enhancing care quality and reducing CVD risk in the future.

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Responsibility for the final manuscript lies entirely with the authors. GAI tools are not listed as authors and do not bear responsibility for the final outcomes.

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Authors' Contributions

The research presented in this paper was a collaborative effort involving multiple authors who contributed to various aspects of the review. The review was conceived by GŠ, AS, ML, DM, and ZK-K. AS and GŠ structured the review, synthesized the evidence, drafted the manuscript, reviewed the manuscript, and completed the final version. GŠ, AS, ML, ZK-K, LG, and DM provided evidence and edits for the review and reviewed the full manuscript when completed. AS collected the data, while LG, GŠ, and AS performed the statistical analysis.

Conflicts of Interest

None declared.

Checklist 1

CONSORT-eHEALTH checklist (V 1.6.1).

[[PDF File, 314 KB](#) - [publichealth_v12i1e83488_app1.pdf](#)]

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Abbreviations

BP: blood pressure
CGM: continuous glucose monitoring
CONSORT: Consolidated Standards of Reporting Trials
CVD: cardiovascular disease
HDL: high-density lipoprotein
HLPCQ: Healthy Lifestyle and Personal Control Questionnaire
PCC: person-centered care
PCPI-SU: Person-Centered Practice Inventory—Service User
RCT: randomized controlled trial
SCORE2: Systematic Coronary Risk Evaluation 2

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Original Paper

Mediation Analysis of the Relationship Between Health Literacy and the French General Population's Opinions on Hepatitis B Vaccination: Representative Cross-Sectional Survey of the SLAVACO Project

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Abstract

Background: In France, reluctance toward hepatitis B vaccination remains high, despite the availability of a safe and effective vaccine to prevent this infection. To boost vaccination coverage, it is therefore essential to identify the factors that are likely to encourage a more favorable opinion of this vaccine. Health literacy (HL) is one such factor. It refers to the individual ability to access, understand, critically appraise, and apply health information to make informed decisions about health issues for oneself and for others.

Objective: This study explored the mechanisms through which HL might affect opinions about hepatitis B vaccination, both directly and indirectly, by relevant factors, including opinions about vaccination in general, trust in government health agencies, and trust in medical doctors.

Methods: The analysis used data from the SLAVACO-Wave 3 (Suivi Longitudinal des Attitudes à l'Égard d'un Vaccin Contre la COVID-19) survey, conducted in December 2021 among a representative sample of French adults (N=1932). Favorable and unfavorable opinions of hepatitis B vaccination were measured using a 5-point Likert scale, while HL was assessed using the HLS₁₉-Q12 questionnaire (12-item general health literacy questionnaire used in Health Literacy Survey 2019-2021). A structural equation model examined the relationship between HL and hepatitis B vaccination opinions, taking into account the potential mediating role of trust in the health care system (ie, government health agencies and medical doctors).

Results: Findings showed that individuals with a favorable opinion of hepatitis B vaccination (1437/1932, 74.4%) had a higher HL level than those with a negative or neutral opinion (62.6 vs 57.0, $P<.001$). The association between HL and hepatitis B vaccination opinions was fully mediated by trust in the health care system. The indirect effect of HL was estimated at 0.068 (95% CI 0.042-0.093), accounting for 52.4% (0.068/0.1297) of the total effect. This effect was particularly pronounced in people over 50 years (0.084, 95% CI 0.042-0.126, accounting for 0.084/0.1306, 64.3% of the total effect). Goodness-of-fit indicators were satisfactory.

Conclusions: Enhancing HL might positively influence hepatitis B vaccination opinions and uptake through greater trust in the health care system. From a public health perspective, strategies should go beyond providing clear information and access to vaccines and actively work to strengthen trust in health care institutions and professionals. National campaigns correcting misconceptions about hepatitis B vaccination could be complemented by targeted interventions for groups most likely to hold negative opinions. Repeating this survey in the post-COVID-19 context could also reveal different trends, given evolving public perceptions of vaccines and health authorities.

KEYWORDS

health literacy; hepatitis B vaccination; vaccine hesitancy; trust; SLAVACO survey; France

Introduction

Hepatitis B is a communicable infectious disease associated with an increased risk of cirrhosis and liver cancer [1]. In 2022, the World Health Organization (WHO) estimated that 254 million people were living with chronic hepatitis B infection and that approximately 1.1 million died as a result of the disease, mainly from cirrhosis or hepatocellular carcinoma [2]. Although safe and effective vaccines have been developed, 1.5 million new hepatitis B virus (HBV) infections occur annually worldwide [3,4]. The WHO aims to reduce the incidence of chronic hepatitis infection by 90% and the annual number of deaths due to chronic hepatitis by 65% before 2030 [5]. To achieve these targets, the organization's guidelines [6] include systematic treatment for people with chronic HBV infection, the prevention of perinatal and infant infection through vaccination, and catch-up vaccinations for both high-risk populations (eg, injection drug users, men who have sex with men, and sex workers) and health care professionals. As of 2023, hepatitis B vaccination for infants was mandatory in 190 countries, and global coverage was estimated at 83% [7].

Hepatitis B is slightly endemic in France; in 2016, the estimated prevalence in the general population in metropolitan France was 0.3% [8]. Although this prevalence may seem low in the European context—it is higher than in Germany (0.2%) but lower than in Southern and Eastern European countries, where it varies between 0.5% and 1.5% [9]—hepatitis B remains a major public health problem due to its chronic progression and severe complications. Moreover, the burden is marked by unequal distribution, with significant socioeconomic disparities disproportionately affecting the most vulnerable populations [10]. Its impact is also reflected in mortality; from 2005 to 2020, a total of 2133 deaths occurred in patients hospitalized for related complications (cirrhosis or hepatocellular carcinoma) in metropolitan France, representing a lethality rate of 6% [11]. Beyond morbidity and mortality, hepatitis B also generates substantial direct and indirect health care costs, particularly in the stages of cirrhosis or hepatocellular carcinoma [12]. To combat this infection, starting in the late 1980s, the French National Authority for Health recommended vaccination for individuals at high risk of exposure and for all newborns. Moreover, a catch-up program for children and adolescents younger than 15 years was implemented in 1995 [13]. In the context of the WHO's goal to eliminate viral hepatitis by 2030, primary vaccination became mandatory for all infants born on or after January 1, 2018 [14]. The French primary childhood immunization schedule recommends 3 doses: the first at 2 months of age, the second at 4 months, and a booster at 11 months [15]. Full immunization is considered complete once the 3-dose series has been administered. As the majority of HBV infections in France in adults occur through sexual transmission [16], vaccination is strongly encouraged for persons older than 18 years of age. The immunization schedule consists

of 3 doses, administered at 0, 1, and 6 months [15]. According to the 2021 LaboHEP survey, which was conducted among all public and private bioanalytical testing laboratories to estimate hepatitis screening activity, the rate of positive HBV diagnosis in metropolitan France was 54/100,000, representing a 10% increase compared to 2016 [17]. In addition, although hepatitis B vaccination coverage among infants has gradually increased over time, reaching over 90% for children aged 21 months since 2018 [18], it was below 50% among adolescents and adults in 2015 [19,20]; this reflects a clear generational gap in hepatitis B immunization.

Health Barometer surveys conducted between 2010 and 2023 show that in terms of vaccine hesitancy rankings in metropolitan France, the hepatitis B vaccine placed third after COVID-19 and influenza vaccines [21]. Despite this, no recent study has investigated the determinants of hesitancy over this vaccine. In the present analysis, we formulate the hypothesis that health literacy (HL), defined by Sørensen et al [22] as a concept “linked to literacy and that entails people's knowledge, motivation and competences to access, understand, appraise, and apply health information to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course,” might explain hepatitis B vaccine hesitancy in France. In general, higher HL is associated with greater vaccine acceptance and lower hesitancy [23]. This relationship may be influenced by the type of vaccine and the population studied. In the case of hepatitis B vaccination, controversies surrounding a potential link to demyelinating diseases [24] may contribute to differences or similarities compared to other vaccines. These specificities highlight that vaccine hesitancy is not uniform but rather a complex and multifactorial challenge to public health [25–27], frequently rooted as much in a lack of trust as in limited access to, and limited understanding of, vaccine-related information. Trust in the health care system—understood here as health agencies and medical doctors—is well-documented as a central determinant of vaccine acceptance [28,29]. However, it is often difficult to create strategies to build this trust. This gap highlights the relevance of exploring HL as a sustainable mediating lever to support trust [30]. Additionally, given that vaccine hesitancy does not necessarily regard specific vaccines but vaccination more broadly [31], any examination of opinions on a particular vaccine should also cover opinions on vaccination in general.

In this context, to enhance our understanding of hepatitis B vaccine opinions in France, this study explored the mechanisms by which HL influences the general public's opinion on hepatitis B vaccination. We used a structural equation model [32] to investigate the direct and indirect effects of HL on these opinions. A model with 5 hypotheses was analyzed as follows: (1) a higher HL is associated with a more favorable opinion of hepatitis B vaccination (direct effect represented by the coefficient “A”); (2) a higher HL contributes positively to trust

in the health care system and this trust is associated with a more favorable opinion of hepatitis B vaccination (indirect effect via “D” and “C”); (3) a higher HL has a positive influence on opinions about vaccination in general, which in turn are associated with a more favorable opinion of hepatitis B vaccination (indirect effect via “E” and “B”); (4) together, trust in the health care system and positive opinions of vaccination in general are mediators in the relationship between HL and opinions on hepatitis B vaccination (indirect effect via “D, F, and B”); and (5) the expected effect of HL on opinions of hepatitis B vaccination, in hypotheses 1 to 4, might vary according to gender, age, and financial deprivation.

Methods

Recruitment Procedure and Study Sample

For the present analysis, we used data from SLAVACO-Wave 3 (Suivi Longitudinal des Attitudes à l'Égard d'un Vaccin Contre la COVID-19), which was conducted between December 2 and 17, 2021. The SLAVACO project was a multiwave longitudinal survey conducted across metropolitan France. Its primary objective was to study the evolution of public attitudes toward different aspects of COVID-19 vaccination and attitudes toward vaccines more generally. Data were collected by the French Provence-Alpes-Côte d'Azur Regional Health Observatory using online self-administered questionnaires, lasting approximately 15 minutes, sent to 25,800 French adults selected by random sampling in an online panel of over 750,000 French households (Bilendi panel). The quota sampling method was then used to obtain a final sample of 2022 respondents corresponding to the adult French population in terms of gender (male and female), age (18-24, 25-34, 35-49, 50-64, and 75+ years), type of employment (farmers, craftsmen, executives, intermediate professions, employees, workers, retirees, and other inactives), and population density (<2000, 2000-20,000, 20,000-100,000, and >100,000 inhabitants) in respondents' region of residence (Alsace, Aquitaine, Auvergne, Burgundy, Brittany, Center, Île-de-France, Languedoc, Nord-Pas-de-Calais, Normandy, Pays de la Loire, and Provence-Alpes-Côte d'Azur) [33]. Final adjustments were applied by weighting the data with the raking ratio and the macro Calmar program of Statistical Analysis System. The latter was designed using census data from the French INSEE (National Institute for Statistics and Economic Studies) [34].

Data Collected

After the participants' consent was obtained, we assessed their opinions about vaccination in general using a question taken from the national Health Barometer survey; this survey has been conducted regularly in France over the past 2 decades [35]. The question was as follows: “Are you strongly, moderately, not really or not at all in favour of vaccination in general?” with the following 5 answer options: “yes, strongly,” “yes, moderately,” “I don't have an opinion,” “no, not really,” and “no, not at all.” Opinions specifically on hepatitis B vaccination were also assessed in SLAVACO using a similar question as follows: “Are you strongly, moderately, not really or not at all in favour of hepatitis B vaccination?” with the same 5-option

response scale. Respondents who did not answer both of these 2 questions were excluded from the present analysis.

SLAVACO also assessed HL using the European Health Literacy Survey 2019-2021 Questionnaire, HLS₁₉-Q12 (12-item general health literacy questionnaire used in Health Literacy Survey 2019-2021). This questionnaire has been translated, applied, and validated in 17 countries [36,37], including France. Based on Sorensen's matrix, the HLS₁₉-Q12 comprises 12 items that measure HL in 4 cognitive dimensions (accessing, understanding, evaluating, and applying health information) and in 3 health contexts (health care, disease prevention, and health promotion) [22]. The answers to each question are selected on a 4-point scale from 0 (very difficult) to 3 (very easy). After summing the scores for all 12 items, we standardized the total score, ranging from 0 to 100, where a higher score reflected a higher level of HL. Internal consistency was excellent with a Cronbach α coefficient of 0.91.

To measure trust in the health care system, we used the methodology used in the 2021 Political Confidence Barometer, the main French longitudinal study on public trust in politics [38]. We measured 2 dimensions: trust in government health agencies and trust in medical doctors. A 5-point scale ranging from 0 (no trust at all) to 4 (complete trust) was used for each measure.

Our analysis also included self-reported socioeconomic variables. Specifically, gender was reported using 3 categories (man, woman, and other), and age was categorized into the following groups: 18-24, 25-34, 35-49, 50-64, 65-74, and 75+ years, in line with the INSEE's age categories [39]. Educational attainment was measured using 6 categories: no educational qualification, lower secondary school certificate, upper secondary school certificate, bachelor's degree, master's degree, and doctorate, while employment status was recorded as currently employed, not employed, or retired. Financial deprivation was determined using the question “How easy or difficult is it for you to pay all your bills at the end of the month?” Respondents who answered “difficult” or “very difficult” were classified as having financial difficulties. Finally, the presence of one or more chronic diseases was assessed using a “yes” or “no” question.

Statistical Analyses

Continuous variables were reported in terms of the mean and SD, while categorical variables were reported in terms of frequency and percentages. We performed descriptive analyses to explore covariables associated with opinions on hepatitis B vaccination. To do this, we treated these opinions and opinions on vaccination in general as binary variables: a favorable opinion was defined as an answer of “yes, strongly” or “yes, moderately.” An unfavorable opinion was defined as responding “I don't have an opinion,” “no, not really,” or “no, not at all.” For the bivariate and mediation analyses, a 0 to 4 scale was used (“no, not at all”=0; “no, not really”=1; “I don't have an opinion”=2; “yes, moderately”=3; and “yes, strongly”=4).

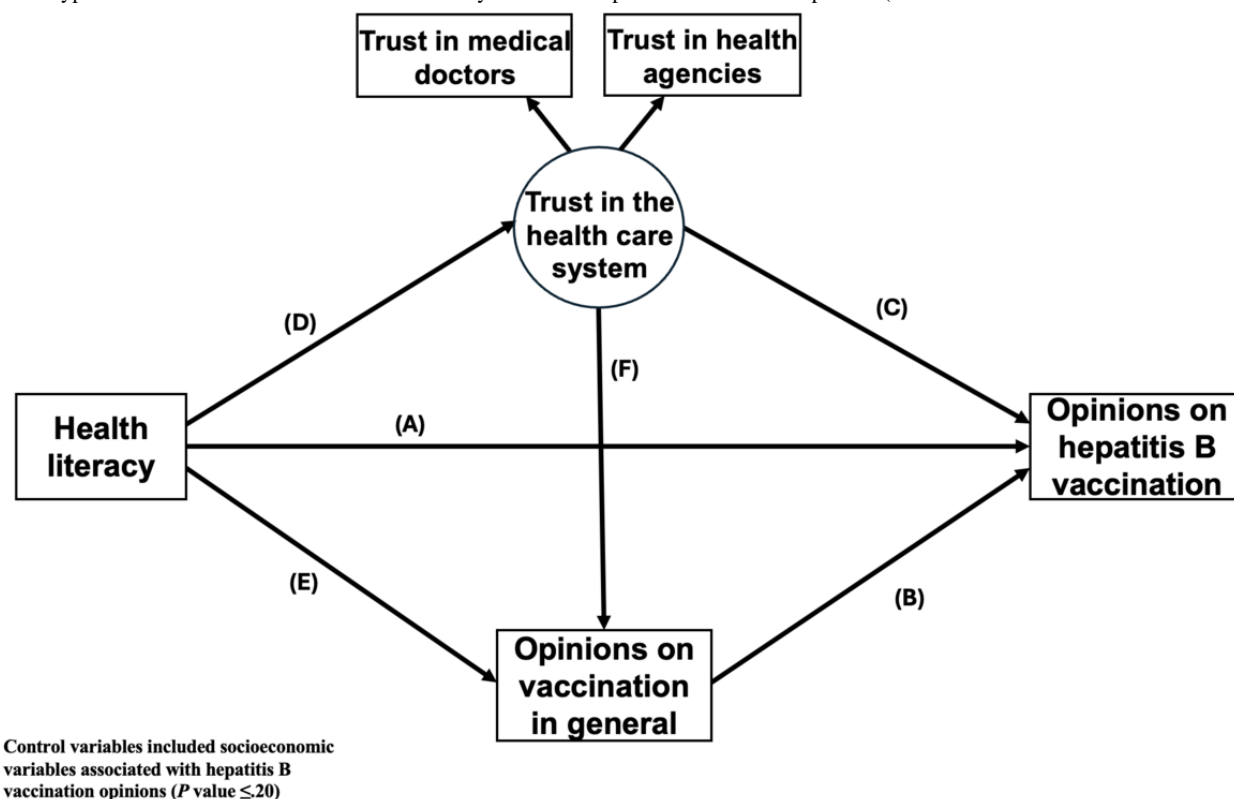
We conducted a Pearson correlation analysis to investigate the bivariate association between the 5 variables of interest (ie, opinions on vaccination in general, opinions on hepatitis B

vaccination, HL level, trust in government health agencies, and trust in medical doctors).

We performed a mediation analysis to explore whether favorable opinions toward vaccination in general and trust in the health care system mediated the association between HL and favorable opinions toward hepatitis B vaccination (Figure 1). Trust in the health care system was modelled using a latent variable based on 2 observed indicators: trust in government health agencies and trust in medical doctors. Possible mediation was then examined after stratification by gender (man vs woman), age

(<50 years vs ≥50 years), and financial deprivation (yes vs no). The control variables included socioeconomic variables associated with hepatitis B vaccination opinions (P value ≤.20). The 95% CI for the direct, indirect, and total effects of the mediation models were estimated using 5000 bootstrap samples. The effects of HL were estimated per 10-point increase in the HL score. We used a series of indicators to assess the goodness-of-fit of the model: Tucker-Lewis Index (considered excellent above 0.95); comparative fit index (considered excellent above 0.95); and root-mean-square error of approximation (RMSEA, considered excellent if below 0.05).

Figure 1. Hypothesized mediation model for health literacy's effect on hepatitis B vaccination opinions (A-F are the coefficients from the Introduction).



All analyses were performed on the weighted database. Analyses were carried out with statistical R software (version 4.4.1; R Foundation), and the significance level was set to 5% for all 2-sided tests.

Ethical Considerations

This study was approved in France by the Ethics Evaluation Committee of the National Institute of Health and Medical Research (IRB00003888) on February 9, 2021 (21-770). After receiving information about SLAVACO-Wave 3, informed consent was obtained from all the participants before they started the survey. In accordance with standards practice for web-based surveys, we did not have access to any data that could identify respondents. Participants received no compensation.

Results

Sample Characteristics

Among the 2022 individuals who participated in SLAVACO-Wave 3, we excluded 90 (4.4%) because of missing answers to the questions on opinions on hepatitis B vaccination and/or vaccination in general. Of the 1932 adults comprising this study's sample, 52.6% ($n=1016$) were women and 34.1% ($n=658$) were retirees (Table 1). Most of the participants ($n=1184$, 61.4%) had at least an upper secondary school certificate, and most ($n=1210$, 62.6%) did not report financial difficulties. Half of the participants ($n=952$, 49.3%) reported one or more chronic diseases. A quarter ($n=495$, 25.6%) expressed an unfavorable opinion about hepatitis B vaccination, and a fifth ($n=375$, 19.4%) towards vaccination in general. Among those hesitant toward hepatitis B vaccination, 58.6% (290/495) were nevertheless favorable to vaccination in general, while 18.6% (290/1557) of those favorable to vaccination in general expressed hesitancy toward hepatitis B vaccination.

Table 1. Description of this study's sample and factors associated with opinions on hepatitis B vaccination in France (N=1932).

Variables	Overall (N=1932)	Opinions on hepatitis B vaccination		P value
		Favorable (n=1437, 74.4%)	Unfavorable (n=495, 25.6%)	
Age group (years), n (%)				.14
18-24	201 (10.4)	157 (78.4)	43 (21.6)	
25-34	282 (14.6)	216 (76.5)	66 (23.5)	
35-49	460 (23.8)	345 (75)	115 (25)	
50-64	466 (24.1)	324 (69.5)	142 (30.5)	
65-74	279 (14.4)	211 (75.8)	68 (24.2)	
75+	244 (12.6)	183 (75.1)	61 (24.9)	
Gender, n (%)				<.001
Man	916 (47.4)	739 (80.7)	177 (19.3)	
Woman	1016 (52.6)	698 (68.7)	318 (31.3)	
Employment status, n (%)				.30
Currently employed	802 (41.5)	611 (76.1)	191 (23.9)	
Unemployed	472 (24.4)	339 (71.9)	133 (28.1)	
Retired	658 (34.1)	487 (74)	171 (26)	
Educational attainment, n (%)				.01
No diploma	121 (6.3)	88 (72.7)	33 (27.3)	
Lower secondary school certificate	626 (32.4)	452 (72.3)	174 (27.7)	
Upper secondary school certificate	405 (21)	283 (69.8)	123 (30.2)	
Bachelor's degree	347 (18)	266 (76.6)	81 (23.4)	
Master's degree	208 (10.8)	171 (82)	37 (18)	
Doctorate	224 (11.6)	177 (78.8)	48 (21.2)	
Financial deprivation, n (%)				<.001
Yes	722 (37.4)	503 (69.7)	219 (30.3)	
No	1210 (62.6)	934 (77.2)	276 (22.8)	
Chronic diseases, n (%)				.02
Yes	952 (49.3)	730 (76.7)	202 (23.3)	
No	980 (50.7)	707 (72.1)	274 (27.9)	
Health literacy score (continuous), mean (SD)	61.1 (17.0)	62.6 (16.9)	57.0 (16.8)	<.001
Opinion on vaccination in general, n (%)				<.001
Favorable	1557 (80.6)	1267 (81.4)	290 (18.6)	
Unfavorable	375 (19.4)	170 (45.3)	205 (54.7)	
"Do you trust government health agencies?" n (%)				<.001
Not at all (0)	358 (18.5)	197 (54.9)	161 (45.1)	
Not really (1)	571 (29.5)	414 (72.5)	157 (27.5)	
No opinion (2)	80 (4.1)	46 (57.9)	33 (42.1)	
Moderately (3)	805 (41.7)	678 (84.2)	127 (15.8)	
Completely (4)	118 (6.1)	102 (86.3)	16 (13.7)	
"Do you trust medical doctors?" n (%)				<.001
Not at all (0)	50 (2.6)	30 (60.6)	20 (39.4)	
Not really (1)	148 (7.6)	90 (60.6)	58 (39.4)	
No opinion (2)	40 (2.1)	22 (55.4)	18 (44.6)	

Variables	Overall (N=1932)	Opinions on hepatitis B vaccination		P value
		Favorable (n=1437, 74.4%)	Unfavorable (n=495, 25.6%)	
Moderately (3)	1232 (63.8)	901 (73.1)	331 (26.9)	
Completely (4)	462 (23.9)	393 (85.2)	69 (14.8)	

Approximately half the sample (n=923, 47.8%) reported trusting government health agencies, while 87.7% (n=1694) reported trusting medical doctors. The mean HL score in the sample was 61.1 (SD 17.0). Individuals with a favorable opinion of hepatitis B vaccination had a higher HL score than those with an unfavorable opinion (62.6 vs 57.0, $P<.001$).

Correlation Analyses

The correlation matrix for all variables in the mediation model is reported in Table 2. A favorable opinion on hepatitis B vaccination was associated with a higher HL level ($r=0.18$, $P<.001$), a favorable opinion on vaccination in general ($r=0.44$,

$P<.001$), a higher level of trust in government health agencies ($r=0.27$, $P<.001$), and a higher level of trust in medical doctors ($r=0.22$, $P<.001$). A higher HL level was positively and significantly correlated with a positive opinion on vaccination in general ($r=0.20$, $P<.001$), with a higher level of trust in government health agencies ($r=0.27$, $P<.001$), and with a higher level of trust in medical doctors ($r=0.27$, $P<.001$). A favorable opinion on vaccination in general was positively associated with a higher level of trust in government health agencies ($r=0.27$, $P<.001$), and with a higher level of trust in medical doctors ($r=0.27$, $P<.001$).

Table 2. Correlation matrix of mediation model variables.

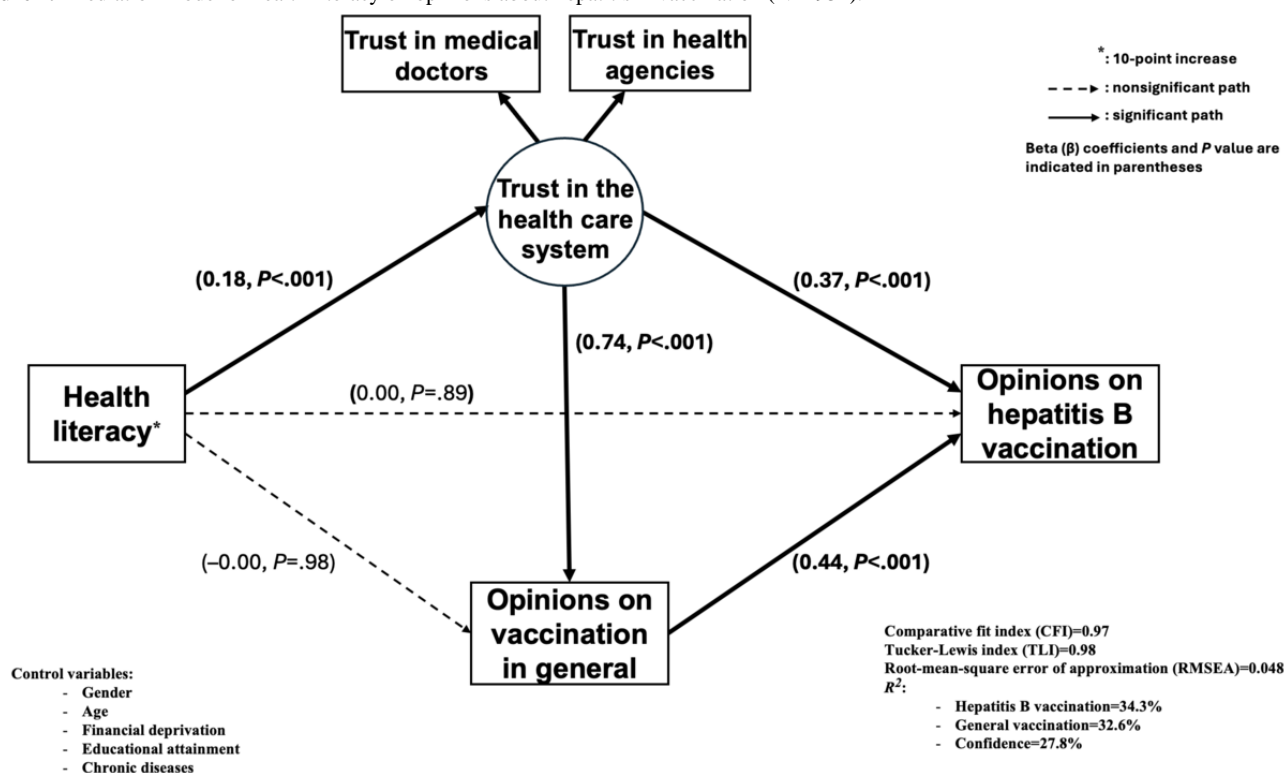
Variables	Health literacy (A)	Opinion on hepatitis B vaccination (B)	Opinion on vaccination in general (C)	Trust in government health agencies (D)	Trust in medical doctors (E)
Health literacy (A)					
<i>r</i>	1	0.18	0.20	0.27	0.27
<i>P</i> value	— ^a	<.001	<.001	<.001	<.001
Opinion on hepatitis B vaccination (B)					
<i>r</i>	0.18	1	0.44	0.27	0.22
<i>P</i> value	<.001	—	<.001	<.001	<.001
Opinion on vaccination in general (C)					
<i>r</i>	0.20	0.44	1	0.27	0.27
<i>P</i> value	<.001	<.001	—	<.001	<.001
Trust in government health agencies (D)					
<i>r</i>	0.27	0.27	0.27	1	0.34
<i>P</i> value	<.001	<.001	<.001	—	<.001
Trust in medical doctors (E)					
<i>r</i>	0.27	0.22	0.27	0.34	1
<i>P</i> value	<.001	<.001	<.001	<.001	—

^aNot available.

Mediation Analyses

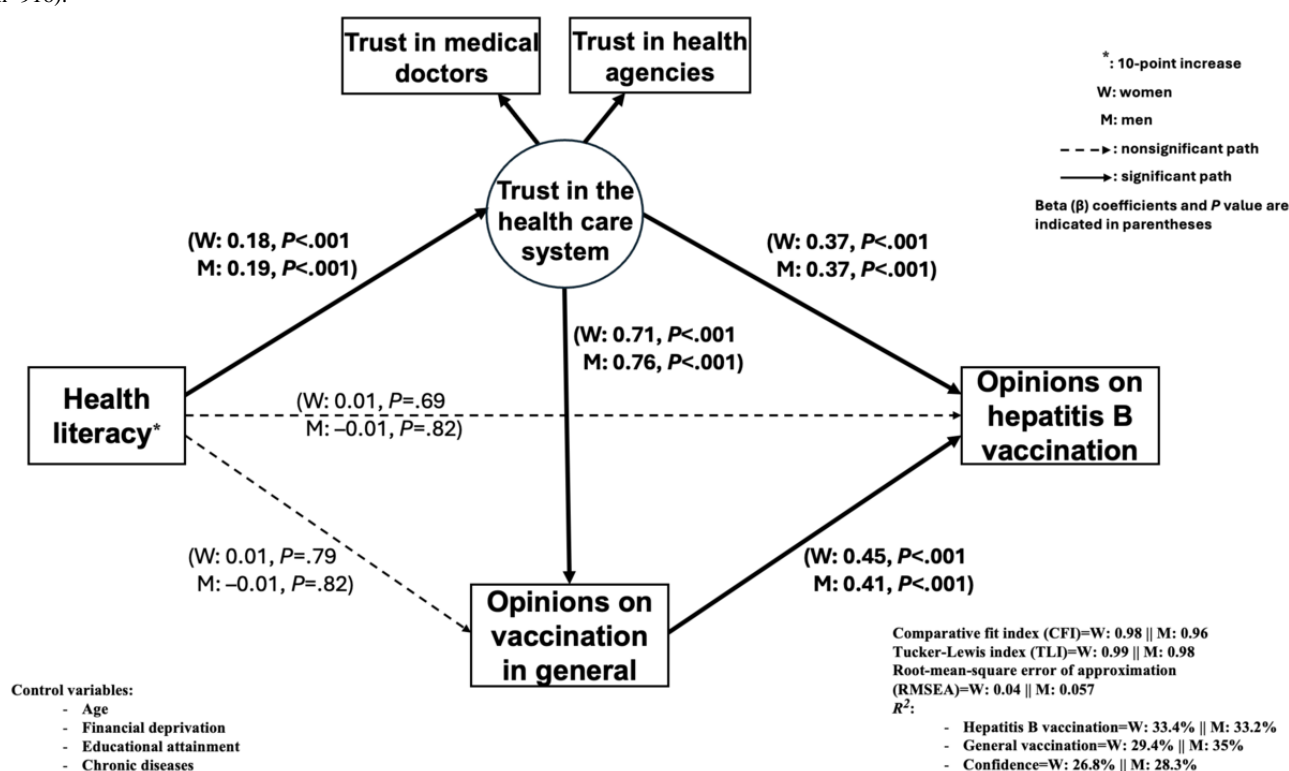
The mediation model for all participants, with 2 mediators and a direct path, is presented in Figure 2. A significant and positive relationship was observed between trust in the health care system and a favorable hepatitis B vaccination opinion ($\beta=0.37$; $P<.001$). There was also a significant positive relationship between a favorable opinion on vaccination in general and a favorable opinion on hepatitis B vaccination ($\beta=0.44$; $P<.001$). A higher level of trust in the health care system had a significant

and strong positive association with a favorable opinion on vaccination in general ($\beta=0.74$; $P<.001$). A higher HL level was positively and significantly associated with a higher level of trust in the health care system ($\beta=0.18$; $P<.001$), but not associated with a favorable opinion on vaccination in general and with a favorable opinion on hepatitis B vaccination ($\beta=0.00$; $P=.89$ and $\beta=-0.00$; $P=.98$, respectively). All estimations were adjusted for educational attainment and the presence of chronic diseases.

Figure 2. Mediation model of health literacy on opinions about hepatitis B vaccination (N=1932).

After stratifying by gender (Figure 3), we found that a higher level of trust in the health care system was positively associated with a favorable opinion on hepatitis B vaccination in women and men ($\beta = 0.37$; $P < .001$ for both). A higher level of trust in the health care system was also significantly associated with a favorable opinion about vaccination in general for both genders

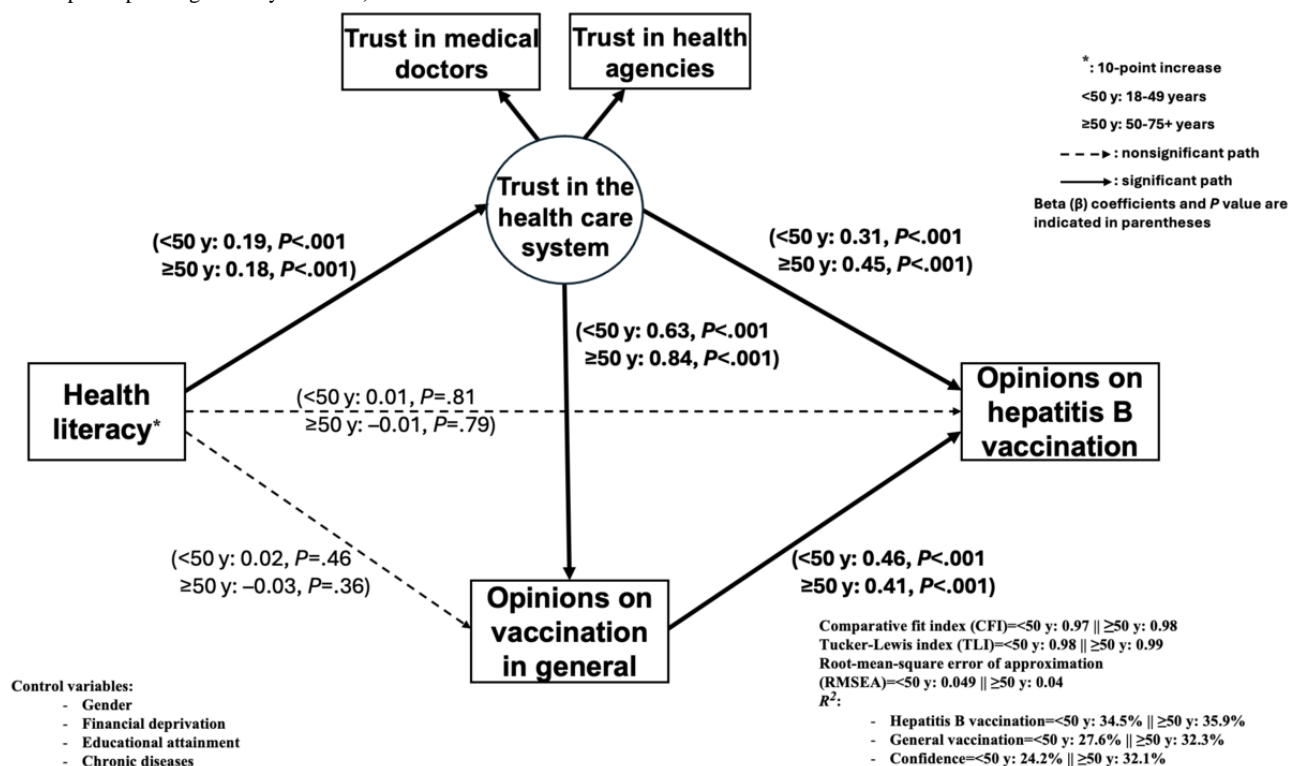
(women: $\beta = 0.71$; $P < .001$ and men: $\beta = 0.76$; $P < .001$). A higher HL level was positively associated with a higher level of trust in the health care system for both genders (women: $\beta = 0.18$; $P < .001$ and men: $\beta = 0.19$; $P < .001$) but had no direct effect on a favorable opinion about vaccination in general or about hepatitis B vaccination.

Figure 3. Mediation model of health literacy on opinions about hepatitis B vaccination according to gender (number of women=1016; number of men=916).

In terms of age (Figure 4), similar associations were observed in the <50 years and ≥50 years age groups. A higher level of trust was positively associated with a favorable opinion on hepatitis B vaccination, with a stronger association observed in adults ≥50 years ($\beta=0.45$; $P<.001$) than in younger adults ($\beta=0.31$; $P<.001$). The association between trust in the health care system and a favorable opinion on vaccination in general

was strong for both age groups (<50 years: $\beta=0.63$; ≥ 50 years: $\beta=0.84$; $P<.001$). A higher HL level had a positive influence on trust in the health care system in both age groups (<50 years: $\beta=0.19$; ≥ 50 years: $\beta=0.18$; $P<.001$) but had no significant direct effect on a favorable opinion about vaccination (general or hepatitis B).

Figure 4. Mediation model of health literacy on opinions about hepatitis B vaccination according to age (number of participants aged <50 years=943; number of participants aged ≥50 years=989).



Lastly, after stratifying by financial deprivation (Figure 5), the association between trust in the health care system and a favorable hepatitis B vaccination opinion was stronger among individuals who did not have financial deprivation ($\beta=0.41$; $P<.001$) than among those who did ($\beta=0.29$; $P=.006$). In contrast, the association between trust in the health care system and a favorable opinion on vaccination in general was more

pronounced among individuals who had financial difficulties ($\beta=0.82$; $P<.001$) than among those who did not ($\beta=0.69$; $P<.001$). A higher HL level remained positively associated with trust in the health care system in both subgroups (no financial deprivation: $\beta=0.19$; financial deprivation: $\beta=0.16$; $P<.001$), although there was no direct effect on favorable vaccination opinions (in general or hepatitis B).

Figure 5. Mediation model of health literacy on opinions about hepatitis B vaccination according to financial deprivation (number of participants with no financial deprivation=1210; number of participants with financial deprivation=722).

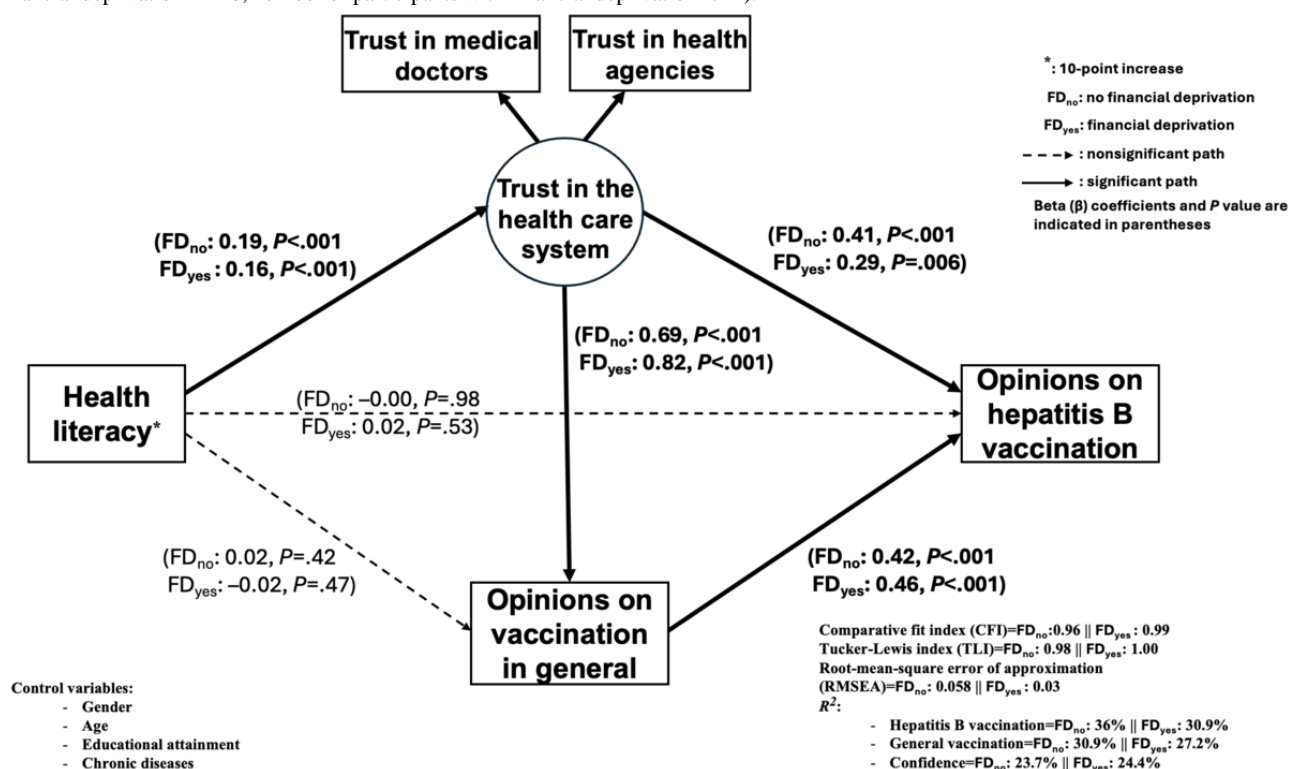


Table 3 shows that the effect of HL on hepatitis B vaccination opinions among all participants was fully mediated by trust in the health care system, after adjusting for educational attainment and the presence of chronic diseases. When trust was the only mediator, the indirect effect of HL was estimated at 0.068 (95% CI 0.042-0.093), accounting for 52.4% (0.068/0.1297) of the total effect. When trust and opinion on vaccination in general were combined as parallel mediators, the indirect effect attributable to HL was 0.059 (95% CI 0.048-0.07), representing 45.5% (0.059/0.1297) of the total effect. Mediation analyses

stratified by gender, age, and financial deprivation status also confirmed the complete mediation of the relationship between HL and hepatitis B vaccination opinion through trust in the health care system, even after adjustment for different sets of control variables depending on the stratum (gender, age, educational attainment, financial deprivation, and chronic diseases). The total effect of HL on hepatitis B vaccination opinion was more pronounced among women and those without financial deprivation.

Table 3. Direct, indirect, and total effects for the mediation model of health literacy on opinions about hepatitis B vaccination (nonstratified model and models stratified by gender, age, and financial deprivation).

Model pathways	Estimated effects	95% CIs	P value
Direct effect (H1; health literacy^a>hepatitis B vaccination)			
All participants ^b (N=1932)	0.003	−0.035 to 0.04	.89
Women ^c (n=1016)	0.01	−0.04 to 0.06	.69
Men ^c (n=916)	−0.006	−0.062 to 0.05	.82
18-49 years ^d (n=943)	0.005	−0.036 to 0.046	.81
50-75+ years ^d (n=989)	−0.006	−0.051 to 0.039	.79
No financial deprivation ^e (n=1210)	−0.001	−0.05 to 0.048	.98
Financial deprivation ^e (n=722)	0.015	−0.033 to 0.063	.53
Indirect effects (H2; health literacy^a>vaccination in general>hepatitis B vaccination)			
All participants ^b (N=1932)	−0	−0.017 to 0.017	.98
Women ^c (n=1016)	0.003	−0.020 to 0.027	.79
Men ^c (n=916)	−0.003	−0.028 to 0.022	.81
18-49 years ^d (n=943)	0.009	−0.015 to 0.032	.47
50-75+ years ^d (n=989)	−0.01	−0.032 to 0.011	.34
No financial deprivation ^e (n=1210)	0.009	−0.013 to 0.031	.43
Financial deprivation ^e (n=722)	−0.01	−0.035 to 0.016	.46
Indirect effects (H3; health literacy^a> trust>hepatitis B vaccination)			
All participants ^b (N=1932)	0.068	0.042 to 0.093	<.001
Women ^c (n=1016)	0.066	0.033 to 0.100	<.001
Men ^c (n=916)	0.071	0.033 to 0.11	<.001
18-49 years ^d (n=943)	0.059	0.031 to 0.087	<.001
50-75+ years ^d (n=989)	0.084	0.042 to 0.126	<.001
No financial deprivation ^e (n=1210)	0.079	0.046 to 0.112	<.001
Financial deprivation ^e (n=722)	0.048	0.012 to 0.083	.008
Indirect effects (H4; health literacy^a>trust>vaccination in general>hepatitis B vaccination)			
All participants ^b (N=1932)	0.059	0.048 to 0.070	<.001
Women ^c (n=1016)	0.058	0.044 to 0.073	<.001
Men ^c (n=916)	0.06	0.044 to 0.077	<.001
18-49 years ^d (n=943)	0.056	0.041 to 0.07	<.001
50-75+ years ^d (n=989)	0.063	0.046 to 0.08	<.001
No financial deprivation ^e (n=1210)	0.056	0.043 to 0.069	<.001
Financial deprivation ^e (n=722)	0.062	0.044 to 0.083	<.001
Total effect			
All participants ^b (N=1932)	0.129	0.101 to 0.157	<.001
Women ^c (n=1016)	0.138	0.101 to 0.177	<.001

Model pathways	Estimated effects	95% CIs	P value
Men ^c (n=916)	0.123	0.08 to 0.165	<.001
18-49 years ^d (n=943)	0.128	0.087 to 0.169	<.001
50-75+ years ^d (n=989)	0.13	0.092 to 0.168	<.001
No financial deprivation ^e (n=1210)	0.143	0.106 to 0.181	<.001
Financial deprivation ^e (n=722)	0.115	0.073 to 0.158	<.001

^a10-point increase.

^bEstimated effects are controlled for gender, age, educational attainment, financial deprivation, and chronic diseases.

^cEstimated effects are controlled for age, educational attainment, financial deprivation, and chronic diseases.

^dEstimated effects are controlled for gender, educational attainment, financial deprivation, and chronic diseases.

^eEstimated effects are controlled for gender, age, educational attainment, and chronic diseases.

For the control variables ([Multimedia Appendix 1](#)), the presence of chronic diseases was significantly associated with a higher level of trust in the health care system ($\beta=0.11$; $P=.004$), particularly among women ($\beta=0.15$; $P=.004$) and individuals without financial deprivation ($\beta=0.14$; $P=.006$). About educational attainment, having only a lower or upper secondary school certificate was negatively associated with the level of trust in the health care system among women (lower secondary school certificate $\beta=-0.29$; $P=.004$; upper secondary school certificate $\beta=-0.23$; $P=.03$) and among financially deprived individuals ($\beta=-0.27$; $P=.01$ and $\beta=-0.26$; $P=.03$, respectively).

All models showed an excellent goodness-of-fit (Tucker-Lewis Index >0.95 , comparative fit index >0.95 , and RMSEA <0.05), except for the men stratum (RMSEA=0.057) and for individuals without financial deprivation (RMSEA=0.058).

Discussion

Principal Findings

France has one of the highest rates of vaccine hesitancy in the world. According to an international study conducted in 2015, a total of 41% of French people considered that vaccines might be dangerous, which was the highest rate among the 67 countries studied [40]. The significant proportion of individuals expressing an unfavorable opinion on hepatitis B vaccination (495/1932, 25.6%) in our present study highlights the persisting skepticism concerning vaccines in the French population. Our findings highlight that this skepticism was more pronounced than for vaccination in general. The moderate correlation between opinions on vaccination in general and those on hepatitis B vaccination ($r=0.44$) indicates that these 2 dimensions only partially overlap; this justifies the detailed focus on this specific vaccine.

The particularly high level of skepticism toward hepatitis B vaccination, which we identified, could be the result of a historical context marked by health controversies, particularly in the 1990s, when cases of central nervous system demyelination after hepatitis B vaccination raised fears in the general public of a potential link [41]. Although subsequent investigations did not establish a causal link [24,42] and even though French authorities officially declared that there was no risk of developing a demyelinating disease from hepatitis B

vaccination [43], the impact of these events on the general perception of hepatitis B vaccination persists today.

Our study results showed that women, people with a lower level of educational attainment, and individuals with no chronic disease were all significantly more likely to have an unfavorable opinion about hepatitis B vaccination. This greater vaccine hesitancy in women might reflect their greater engagement with health information than men. This engagement may, in turn, leave them more exposed to negative discourses, especially if they echo personal or shared experiences linked to past health controversies [44]. Although men in our study were more likely to have a favorable opinion of hepatitis B vaccination, some studies have suggested that women are more invested in health care and child-rearing than men, and so are more likely to get this vaccine [45,46].

The significant association that we found between the presence of chronic diseases and a higher level of trust in the health care system might partly explain the more favorable opinions toward hepatitis B vaccination, which we observed among people with chronic diseases. In addition to a lack of trust in the health care system, the greater reluctance to hepatitis B vaccination we observed in individuals with no chronic disease could be explained by greater complacency, identified as one of the key determinants of vaccine hesitancy. Complacency occurs when the perception of risk from vaccine-preventable diseases is low and when vaccination is not perceived as necessary [47]. Without a perceived risk to their health and without regular contact with health care services, these individuals might develop a less favorable opinion about vaccination.

The association we observed between intermediate educational attainment (ie, having only a lower or upper secondary school certificate) and less trust in the health care system among women and people in financial difficulty suggests that this level of education may sometimes be associated with a more skeptical attitude toward medical recommendations. This association is also reflected in the relatively high proportion of individuals in our study who expressed an unfavorable opinion about hepatitis B vaccination within these 2 subgroups. About the influence of educational attainment on vaccination opinions, findings in the literature are mixed; some studies emphasize its central role in shaping provaccination opinions [40,48], while others show that individuals with higher educational attainment might also

be more likely to adopt skeptical attitudes [49]. These contrasting views highlight the need to develop other, more actionable and multidimensional measures, such as HL.

In our study, a favorable hepatitis B vaccination opinion was significantly positively associated with a higher HL level before mediation was taken into account. In the mediation model, this association was fully mediated by trust in the health care system, even after stratifying by gender, age group, and financial difficulties. There was no significant direct relationship between HL and opinions on vaccination (ie, general or hepatitis B) when trust was considered in all strata. Although no study to date has directly investigated the mediating role of trust in the health care system on the relationship between HL and hepatitis B vaccination opinion, many studies have highlighted the positive influence of HL and trust in the health care system on hepatitis B prevention behaviors. For example, a group study of sociocultural barriers to hepatitis B prevention among Korean Americans suggested that there were specific HL barriers that governed individuals' behavior in terms of hepatitis B prevention and care access [50]. Similarly, in a study in the Democratic Republic of Congo [51], trust in the health care staff increased the public's acceptance and the effectiveness of community initiatives to prevent mother-to-child transmission of the disease, especially initiatives focusing on adherence to vaccination and antiviral uptake. HL could become an essential tool to overcome the challenge of improving trust in the health care system to reduce vaccine hesitancy [52]. By strengthening individuals' ability to understand how the health care system functions, to evaluate the reliability of health information, and to communicate effectively with professionals in order to both avoid negative interactions and engage proactively in their own care [53], HL could contribute to creating sustainable trust in the health care system.

Our key finding—the absence of a direct relationship between HL and a favorable opinion on hepatitis B vaccination—might be specific to this vaccination. This is because, in order to have a favorable opinion, a degree of trust in the expected long-term benefits (which are not visible) is needed, especially given the controversy surrounding this vaccine in France. This finding may also reflect the specific nature of vaccination as a public health issue; vaccination is particularly exposed to conflicting information at the heart of political and social debate, and is increasingly shaped by dynamics of trust or the lack thereof, which in turn are often associated with collective reasoning. Accordingly, the absence of a direct relationship between HL and opinions on vaccination in general, which we observed in the mediation model, might indicate the limitations of using an approach based solely on increasing general HL to combat vaccine hesitancy. This is a very important point, because over the last decade, the vaccine debate has become a way for the French public to express social tensions and political mistrust [54]. As our results suggest, interventions to improve the level of HL, such as cross-cutting strategies, might contribute to strengthening trust in the health care system.

Limitations

This study has limitations. First, its cross-sectional design prevented us from establishing causal relationships between the variables analyzed. Second, the quota sampling method we used does not guarantee the geographical and socioeconomic representativeness of the whole population of French adults. Our findings must therefore be interpreted with caution. Third, the SLAVACO survey was conducted during the COVID-19 pandemic, when vaccination was the subject of intense media attention, frequently affected by misinformation and disinformation. This may have strongly influenced participants' opinions on vaccination and amplified the mediating effect of trust in the health care system, which we observed. Lastly, following the framework by Parker [55], HL is influenced by both internal (cognitive, educational, and socioeconomic) and external (social, health care, and macroeconomic) factors. Our study did not systematically assess these determinants, highlighting the need for tools that capture the full spectrum of HL in future research.

Conclusions

Enhancing the level of HL may lead to greater trust in government health agencies and medical doctors, which are 2 essential dimensions for positively influencing hepatitis B vaccination opinions. To achieve the WHO's goal of hepatitis elimination by 2030, future public health strategies in France should take HL and these 2 dimensions into account to effectively reduce the country's currently high rate of hepatitis B vaccine hesitancy. From a public health perspective, these findings suggest that strategies should not only focus on providing clear information about vaccines and ensuring access, but also on actively strengthening trust in health care institutions and professionals. National communication campaigns aimed at correcting misconceptions about hepatitis B vaccination could be complemented by targeted interventions for groups most likely to hold negative opinions, such as women, individuals with intermediate education levels, those without chronic diseases, and higher-income populations. In parallel, incorporating HL modules into school curricula and community programs could provide a sustainable means of fostering trust and supporting informed decision-making.

For future research, it will be important to develop and apply vaccine-specific HL tools, to longitudinally assess the causal relationships between HL and the key determinants of vaccine hesitancy (7C-model), and to compare these dynamics across different vaccines. A broader assessment of trust encompassing all 6 components of the health care system—governance, financing, service delivery, human resources, health products and interventions, and health information—as defined by the WHO [56], would also provide a more comprehensive understanding. Conducting a similar survey in the post-COVID-19 context could also reveal different trends, reflecting the evolving public perceptions of vaccines and health authorities.

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Data Availability

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request. Information and agreement to use HLS₁₉-Q12 (12-item general health literacy scale) can be found on the M-POHL (Action Network on Measuring Population and Organizational Health Literacy) web page.

Authors' Contributions

BC, JM, and SB conceptualized this study. BC formally analyzed the data. BC wrote the original draft in preparation. BC, JM, and JKW wrote, reviewed, and edited this paper. All authors have read and agreed to the published version of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Table showing estimates of control variables for different mediation models.

[DOCX File, 59 KB - [publichealth_v12i1e82496_app1.docx](#)]

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Abbreviations

- HBV:** hepatitis B virus
HL: health literacy

HLS19-Q12: 12-item general health literacy questionnaire used in Health Literacy Survey 2019-2021

INSEE: National Institute for Statistics and Economic Studies

RMSEA: root-mean-square error of approximation

SLAVACO: Suivi Longitudinal des Attitudes à l'Égard d'un Vaccin Contre la COVID-19

WHO: World Health Organization

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A Critical Health Literacy Podcast to Counter Health Misinformation at Scale: Randomized Controlled Trial

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Abstract

Background: Widespread misinformation and low critical health literacy pose major barriers to public health worldwide. Rapid, scalable, and evidence-informed digital interventions are urgently needed to strengthen the public's ability to make informed health decisions.

Objective: Informed by critical health literacy frameworks, we developed and tested a brief, story-based critical thinking podcast, *Parents Making Informed Health Choices*, that was designed to improve critical health literacy and decision-making among US parents.

Methods: We conducted a 2-phase study. First, 5 parents participated in the user testing of the prototype podcast and provided qualitative feedback to refine content and delivery. The final podcast delivered 9 evidence-based practice principles through relatable scenarios about mental and physical health. In the second phase, we conducted a 2-arm randomized controlled trial (N=250) with a national online sample of US parents. Participants were randomly assigned to listen to either the critical thinking podcast (n=128, 51.2%) or a control podcast (n=122, 48.8%). There were no significant preintervention group differences except for age, which was controlled for in all analyses. Primary outcomes included critical thinking about health claims, intended health behaviors, attitudes toward evidence-based mental health practices, and treatment preferences.

Results: On average, parents were aged 35 (SD 7.8) years; 49% (121/247) were female, 75% (185/248) were White; and 60.0% (148/248) had a bachelor's degree or higher. Parents who listened to the critical thinking podcast demonstrated significantly improved critical thinking about health information compared to the control group (B=2.56; $P<.001$; $\Delta R^2=0.06$). They also reported stronger critical thinking-aligned intended behaviors (B=0.252; $P=.001$; $\Delta R^2=0.015$), and more evidence-informed treatment preferences (B=4.89; $P=.038$; $\Delta R^2=0.02$). The effect sizes were small to moderate across outcomes.

Conclusions: Findings suggest that a brief, story-based digital podcast can meaningfully improve critical thinking about health information, intended behaviors, and evidence-based practice attitudes. Podcasts represent a promising, low-cost, and scalable strategy for promoting critical health literacy and countering health misinformation in the general public.

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KEYWORDS

critical health literacy; evidence-based practice; EBP; health misinformation; digital health intervention; public health education; randomized controlled trial; RCT; parents

Introduction

Background

Health misinformation is now widely recognized as a public health threat [1]. During the COVID-19 pandemic and beyond, inaccurate health claims about vaccines and treatments have spread rapidly across digital platforms, undermining public trust and distorting health-related decision-making. Parents, in particular, face a deluge of conflicting health messages as they seek information about their children's physical and mental

health needs. However, few public health interventions directly aim to strengthen parents' ability to critically assess health claims and make evidence-informed choices. Furthermore, scalable, low-intensity interventions that leverage popular media formats, such as podcasts, represent an underexplored avenue for enhancing critical health literacy at the population level. Accordingly, we developed and tested the effectiveness of a brief, story-based podcast intervention aimed at improving critical health literacy among US parents.

Many individuals lack the critical thinking skills necessary to make empowered and well-informed health choices [2,3]. Low

critical thinking about health can lead to believing and acting on unreliable health information that is easily accessible by word of mouth, through mass media, and the internet [4-6]. Basing mental and physical health treatment decisions on unreliable information may lead to pursuing ineffective or potentially harmful services [7], delaying access to effective services (evidence-based practices [EBPs]), increasing risks, and wasting resources.

Unfortunately, few studies have focused on addressing the health-related critical thinking needs of the public, especially in the United States. Grounded in the Informed Health Choices Key Concepts framework, critical thinking about health extends beyond functional health literacy (ie, basic knowledge of health conditions and services) and involves applying EBP principles to access, understand, and evaluate sources of health information [8-10]. Studies across the world, even among high-income and highly educated populations, have found that the public engages in low levels of critical thinking about health [2,11-13].

Effective decision-making behavior in health care is complex, comprising not only critical thinking skills but also related attitudes and beliefs, among other characteristics and factors. Existing research has found that US adults and adolescents value scientific evidence when making health decisions; however, they have a limited understanding of what it means for practices to be evidence-based [14-16]. Additionally, US adults report that there are situations in which they would trust their doctor's opinion over scientific research [17]. Issues of public trust in medicine and medical research are particularly prominent in relation to vaccines [18]. Indeed, despite their demonstrated efficacy, safety, and benefits, antivaccination or vaccine hesitancy attitudes persist and have resulted in adverse public health consequences (eg, increase in outbreaks of diseases that were under control or eradicated, such as measles) [18,19]. As such, examining critical thinking about health alongside attitudinal factors such as vaccine hesitancy is an important next step toward deepening our understanding of public health literacy and health decision-making.

Considering the potential impact of increasing the public's ability to engage in critical thinking about health, it is crucial to develop and test brief, targeted, and scalable critical thinking interventions. This is especially important for parents, since they are responsible for health care decisions for both themselves and their children. Information and communication technologies play a crucial role in promoting critical health literacy by expanding access to information, fostering interactive learning environments, and enabling individuals to engage more actively with health content. Podcasts, in particular, offer a promising delivery method for addressing these challenges. They are widely accessible, cost-effective, and increasingly used for health communication and education [20-22]. As defined by the World Health Organization, digital health interventions are discrete uses of digital technologies, such as podcasts, to achieve health objectives [23]. Prior research and communication theory suggest that storytelling and narrative formats can improve engagement and promote behavior change, especially when combined with principles of EBP and tailored to target audiences [24]. However, few studies have tested the use of podcasts as

a critical thinking intervention for health, and even fewer have done so using rigorous randomized designs.

Only one prior study has evaluated the effectiveness of such an intervention and focused on parents in Uganda [25]. Semakula et al [25] developed a 10-episode critical thinking podcast based on the needs of the Ugandan families. Via a randomized controlled trial (RCT) of 675 participants, the educational podcast was found to significantly improve parents' critical thinking compared to those who only listened to a public service announcement. Moreover, improvements in critical thinking were observed across varying levels of educational attainment, including those who had only completed elementary education. Unfortunately, this intervention has yet to be adapted for and tested in the United States, and it solely focused on physical health issues, without any mental health examples.

While educating the public is essential across all areas of health care, it is especially urgent in the context of mental health, where treatment decisions are often complex and nuanced. Public discourse in this area is frequently shaped by unscientific or pseudoscientific claims, which can contribute to misinformation and reduce public trust in evidence-based care. This environment poses a significant barrier to individuals' ability to make informed decisions and access appropriate mental health services [26-30]. Despite this, no existing critical health literacy intervention has specifically addressed decision-making in mental health care.

This Study

The ability to critically think about health claims and treatment effectiveness enables the public to make well-informed health care decisions. By evaluating the effectiveness of treatments, the public can avoid potentially harmful or ineffective care and be empowered to take an active role in their health management. Thus, the primary aim of this study was to develop and test whether a brief critical thinking podcast increased critical thinking about health and related intended behaviors in comparison to an active control. The current intervention was adapted from the previously validated podcast used in Uganda [25] with cultural and contextual tailoring for a US-based audience. Additionally, because the original Ugandan podcast focused solely on physical health conditions, the current podcast expands its scope to include decision-making scenarios related to mental health. Given that this was the first evaluation of a critical health literacy podcast in the United States, the study also served as a proof-of-concept assessment to determine whether the approach would translate effectively in a different cultural and health communication context. A secondary aim was to examine the effects of the podcast on EBP attitudes, vaccine safety concerns, and mental health treatment preferences. We hypothesized that the critical thinking podcast would have a positive effect on all measured outcomes.

Methods

Design and Procedures

The study was conducted in the United States and included both community-based and online components. It consisted of two

phases: (1) podcast development and user testing, and (2) podcast evaluation through an online RCT.

Podcast development included reviewing the scripts and storyboards of the Ugandan podcast by Semakula et al [25], and determining the needed adaptations (eg, changing examples about malaria). Communication theory on learning through entertainment informed the podcast design to ensure that messaging was not merely didactic, and there was a sense of relatability in the storylines and characters [24]. The first author and undergraduate research assistants scanned US mass media websites, such as Health News Review, for examples of mental health care claims relevant to US parents. For example, one of the episodes covers a claim regarding vaccines causing autism. Once the podcast script was finalized, it was produced by the Orange Umbrella, a production company housed within the university's School of Communication.

We then conducted user testing where 5 parents from South Florida listened to the podcast prototype and provided feedback. A sample size of 5 is common in usability research where small samples are sufficient to identify most usability issues. For user testing, we recruited parents through the local chapter of the National Alliance on Mental Illness, advertisements in public community spaces, and Facebook posts. Eligible participants were aged at least 18 years, had at least 1 child aged less than 18 years, and were fluent in English. Participants were compensated with a US \$15.00 gift card for their time and feedback. User-testing sessions lasted approximately 60 to 90 minutes, including 32 minutes of estimated individual podcast listening, a 20 to 30-minute semistructured interview, and a 5-minute online satisfaction survey. Their feedback was then reviewed and applied, and the podcast was finalized for testing through an online RCT. The podcast is available in SoundCloud [31].

A total of 250 parents participated in the RCT in May 2019 through Amazon Mechanical Turk (MTurk) [32,33]. A priori power analysis indicated that this sample size would provide adequate power to detect a large effect. As previously demonstrated by Jensen-Doss et al [33], MTurk is an appropriate space for recruiting parents online, especially for mental health care-related studies such as this one where capturing the

perspectives of potential treatment seekers may be pertinent. The study was advertised to MTurk workers in the United States who had an MTurk approval rating of 98% or higher and were not participating in any other related study [3]. In the RCT, participants first provided consent and completed a baseline questionnaire of demographic and other characteristics. As in the original trial of the *Informed Health Choices* podcast by Semakula et al [25], outcome measures were completed after random assignment and after listening to the podcasts. Exposing participants to questionnaires prior to listening to the podcasts would have affected podcast listening, and it was expected that randomization would ensure that participants were equivalent at baseline (see the Randomization Success section). Following completion of baseline measures, participants were randomly assigned on a 1:1 ratio to either the critical thinking podcast or a control podcast. Participants in both conditions could not move on from the podcast listening page until 32 minutes (length of podcasts) had lapsed and they also could not fast forward. We also built in several "listening fidelity" checks (described in the Measures section). After they listened to the entire podcast, participants completed postintervention measures. Participants received a payment of US \$7.25, in line with minimum wage at the time of the study. This study followed the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Checklist 1).

Podcast Intervention and Control Condition

The *Parents Making Informed Health Choices* podcast [31] consisted of nine 2 to 4-minute episodes, including an introduction episode and a conclusion episode. The entire podcast was 32 minutes long. The 7 main episodes covered 9 different EBP principles using medical and mental health conditions (eg, depression). Following the storylines developed for the Uganda *Informed Health Choices* podcast, the US podcast included 2 main characters who engaged in back-and-forth conversations while explaining and applying EBP principles to different medical and mental health conditions. Table 1 lists the EBP principles covered and provides examples of health care claims. The control podcast (a 33-minute-long mindfulness meditation) served as an inert condition that was similar in length to the critical thinking podcast, but included no content related to critical thinking.

Table . Evidence-based practice (EBP) principles [10] addressed in the *Parents Making Informed Health Choices* podcast. Examples are compared to those in the original *Informed Health Choices* podcast used in Uganda [25].

EBP principle	US claim examples	Uganda claim examples
Treatments should be compared.	Elderberry is an effective treatment for child flu.	Quail eggs make you very strong.
Treatments should be compared fairly.	Cognitive-mental therapy for youth anxiety and depression works.	Group support is helpful for someone who is depressed.
Findings from small studies can be misleading.	We can know that vaccines cause autism based on information from one small study.	Washing hands with soap does not stop children from getting diarrhea.
Association is not the same as causation ^a .	Contraceptive pills cause women to gain weight ^a .	A lot of women gain weight when they take contraceptive pills.
Expert opinion is not always right ^a .	Contraceptive pills cause women to gain weight ^a .	Eating some hot pepper will heal ulcers.
Anecdotes are unreliable evidence.	Butter can heal burns.	Putting cooking oil on a burn will heal it.
Treatments might be harmful ^a .	An herbal treatment for ADHD ^b with no side effects exists ^a .	Quinine can cure malaria. It can also give you nausea and make you vomit.
Treatments have benefits and harms. ^a	Herbal treatment for ADHD with no side effects exists ^a .	Herbal medicines exist for malaria treatment that cure malaria and do not have any bad effects.
Common practice does not mean it is beneficial or safe.	Physical discipline is the best strategy for managing child behavior problems.	An herbal treatment called kyogero stops babies from getting infections.

^aCovered within the same episode of the *Parents Making Informed Health Choices Podcast*.

^bADHD: attention-deficit hyperactivity disorder.

Measures

Demographics and Other Characteristics

Participants' age, gender, ethnicity, educational attainment, employment status, podcast listening habits or consumption (listening time in min), and other characteristics data (eg, treatment-seeking history) were collected.

Critical Thinking About Health

We assessed critical thinking about health using 18 items from the Claim Evaluation Tools, which consists of over 100 multiple choice questions that can be used with people aged 10 years and older [34,35]. We selected 18 questions that tapped into 9 different key concepts based on their cultural relevance to the United States and how well they performed in a validation study [34]. We also included 3 new questions that were worded exactly like Claim Evaluation Tools' questions but replaced physical health conditions with mental health conditions. The overall critical thinking score was the number of correct responses out of 21 items. The internal consistency of the final 21-item critical thinking measure was good ($\alpha=.86$).

Intended Behavior

Intended behavior related to critical thinking was assessed through 3 items created and used by Semakula et al [25]. The questions asked about the likelihood that someone will (1) find out what a treatment claim is based on, (2) find out if a claim is based on a research study comparing the treatment to no treatment (a fair comparison), and (3) saying "yes" if asked to participate in a research study comparing 2 treatments for an illness they have. Response options were on a 4-point Likert scale from very unlikely to very likely, and also included an "I don't know" option.

Attitudes Toward EBPs in Mental Health

The Consumer Attitudes Towards Evidence Based Services Scale (CAEBS) [36] consists of 29 items that load onto 4 factors: (1) beliefs regarding therapists' practices, (2) attitudes about mental health policy, (3) negative personal-level attitudes toward EBPs, and (4) negative societal-level attitudes towards EBPs. Items are rated on a 5-point scale from "strongly disagree" to "strongly agree." Internal consistencies in this sample were as follows: factor 1, $\alpha=.77$; factor 2, $\alpha=.59$; factor 3, $\alpha=.88$; and factor 4, $\alpha=.73$. To increase reliability, we removed item 13 from the factor 2 scale (new $\alpha=.73$), and item 24 from the factor 4 scale (new $\alpha=.80$).

Attitudes Regarding Empiricism in Mental Health Treatment

We used 5 items created by Kirk et al [37] that assessed attitudes regarding empiricism in mental health treatment on a 5-point Likert scale, with higher scores indicating more agreement. The internal consistency of this 5-item scale in this sample was adequate ($\alpha=.77$).

Treatment Preferences

We assessed treatment preferences using a measure developed by Kirk et al [37] that asked participants to rate how important various mental treatment components were to them by allocating 99 points across the following: (1) treatment being evidence-based, (2) therapeutic alliance, (3) therapist experience, (4) empathic qualities of the therapist, and (5) client speaking for the majority of sessions [37]. Participants were instructed that more points signify higher preference for that treatment component.

Vaccine Safety Concerns

Following prior studies [38,39], we examined vaccine safety concerns through three items: (1) “vaccines are unsafe,” (2) “vaccines have long-term negative side effects,” and (3) “If I had another infant today, I do not want him/her to get all the recommended vaccinations.” Participants rated these on a 5-point scale with higher scores indicating more negative vaccine attitudes. The internal consistency of this scale in this sample was $\alpha=.93$.

Podcast Listening Fidelity

We assessed participant attention to the podcast through 7 questions about podcast content details that anyone who listened to the entire podcast should be able to answer, with specific questions for each study condition. Questions 1 to 6 were true or false, and question 7 required an open-ended response to a question about content at the end of the podcast. Responses to question 7 were assigned 0 to 2 points by the principal investigator; thus, participants could earn up to 8 points total.

Podcast Satisfaction

Participants in both conditions also rated their satisfaction with the podcast through 5 items that asked about overall satisfaction, likelihood of recommending to others, and relevance.

Ethical Considerations

All procedures were approved by the University of Miami Institutional Review Board (20180596). The submitted protocol document was the one submitted to the institutional review board and received approval. There were no deviations from the protocol. Participants provided informed consent electronically prior to participating in the study. Data were collected anonymously through secure online surveys (Qualtrics) and analyzed in deidentified form. All data were stored on

password-protected, encrypted servers to ensure participant privacy and confidentiality. The 5 user-testing participants were compensated with a US \$15.00 gift card for their time and feedback. RCT participants received a payment of US \$7.25, in line with minimum wage.

Analytic Plan

Analyses were run using SPSS (version 28; IBM Corp). Descriptive statistics examined participant demographics, podcast satisfaction, and measures of data quality. We used multiple measures of data quality, including length of study participation (anticipating it would take at least 60 minutes), attention check questions, and 2 questions measuring consistency in the report of demographic information (age and youngest child age) strategically placed at the beginning and at the end of the study. Analyses checking randomization success examined differences in demographic variables between the 2 study conditions. We tested hypotheses about podcast effects using multiple linear regression for continuous variables and binomial logistic regression for categorical variables. The Cohen d values of 0.20, 0.50, and 0.80 indicated small, medium, and large effects, respectively; and R^2 values of 0.01, 0.09, and 0.25 indicated small, medium, and large effects, respectively [40].

Results

Participants

Five parents participated in the user-testing phase of the study, and 250 parents participated in the online RCT. On average, parents in the RCT were aged 35 (SD 7.8) years with 49% (121/248) being female, 75% (185/248) being White, and 60.0% (148/248) having a bachelor's degree or higher. Table 2 provides additional sample characteristics.

Table . Demographic characteristics of US parents who participated in the study's user-testing and randomized controlled trial phases (N=250). Values in italics in the same row differed significantly ($P<.05$).

Characteristic	User-testing (n=5)	Online RCT ^a (N=250)	Critical thinking podcast (n=128)	Control podcast (n=122)
Age (y), mean (SD; range)	36.40 (6.31; 30 - 43)	34.98 (7.8; 20 - 77)	<i>33.81 (7.5; 20-59)</i>	<i>36.20 (8.0; 23 - 77)</i>
Sex (female) ^c , n (%)	5 (100)	121 (49.0)	59 (48.8)	62 (51.2)
Race or ethnicity ^{bc} , n (%)				
African American	0 (0)	41 (16.5)	19 (14.8)	22 (18.3)
American Indian or Alaska Native	0 (0)	2 (0.8)	1 (0.8)	1 (0.8)
Asian	1 (20)	13 (5.2)	4 (3.1)	9 (7.5)
Hispanic	2 (40)	35 (14.1)	14 (10.9)	21 (17.5)
White	3 (60)	185 (74.6)	101 (78.9)	84 (70)
Highest level of education achieved ^c , n (%)				
Some high school, no diploma	0 (0)	1 (0.4)	1 (0.8)	0 (0)
High school	0 (0)	29 (11.7)	14 (10.9)	15 (12.5)
Some college, no degree	0 (0)	44 (17.7)	22 (17.2)	22 (18.3)
Associate's or technical degree	0 (0)	26 (10.5)	12 (9.4)	14 (11.7)
Bachelor's degree	2 (40)	123 (49.6)	69 (56.1)	54 (43.9)
Master's degree	2 (40)	23 (9.32)	10 (7.8)	13 (10.8)
Doctoral or other graduate degree	0 (0)	2 (0.8)	1 (0.8)	1 (0.8)
Employment status ^c , n (%)				
Currently working	5 (100)	213 (85.9)	115 (89.8)	98 (81.7)
Unemployed	0 (0)	9 (3.6)	3 (2.4)	6 (5)
Retired	0 (0)	2 (0.8)	1 (0.8)	1 (0.8)
Homemaker	0 (0)	22 (8.9)	8 (6.3)	14 (11.7)
Student or other	0 (0)	2 (0.8)	1 (0.8)	1 (0.8)
Annual household income ^c (US \$), n (%)				
Less than 19,999	^d	20 (8.0)	11 (8.6)	9 (7.5)
20,000 to 39,999	—	56 (22.4)	34 (26.6)	22 (18.3)
40,000 to 59,999	—	64 (25.6)	33 (25.8)	31 (25.9)
60,000 to 79,999	—	55 (22)	21 (16.4)	34 (28.4)
80,000 to 99,999	—	24 (9.6)	12 (9.4)	12 (10)
More than 100,000	—	29 (11.6)	17 (13.3)	12 (10)
Insured ^c , n (%)	—	220 (88)	114 (89.1)	106 (86.9)
Children (n), mean (SD; range)	2.20 (0.84; 1 - 3)	1.73 (0.94; 1 - 6)	1.69 (0.96; 1 - 6)	1.77 (0.91; 1 - 6)
Mental health history and service use ^c , n (%)				
Mental health diagnosis	—	109 (43.6)	52 (40.6)	57 (47.5)
Ever received psychotherapy for a psychological problem	—	114 (45.6)	54 (42.2)	60 (50.0)

Characteristic	User-testing (n=5)	Online RCT ^a (N=250)	Critical thinking podcast (n=128)	Control podcast (n=122)
Ever taken medication for a psychological problem	—	91 (36.4)	42 (32.8)	49 (40.8)
Podcast listening habits ^c (min), n (%)				
<30	—	71 (28.4)	33 (25.8)	38 (31.4)
30 - 60	—	84 (33.6)	43 (33.6)	41 (33.9)
61 - 90	—	42 (16.8)	26 (20.3)	16 (13.2)
>90	—	52 (20.8)	26 (20.3)	26 (21.5)

^aRCT: randomized controlled trial.

^bThese percentages do not sum to 100 due to overlap across categories.

^cData missing (n=1-3).

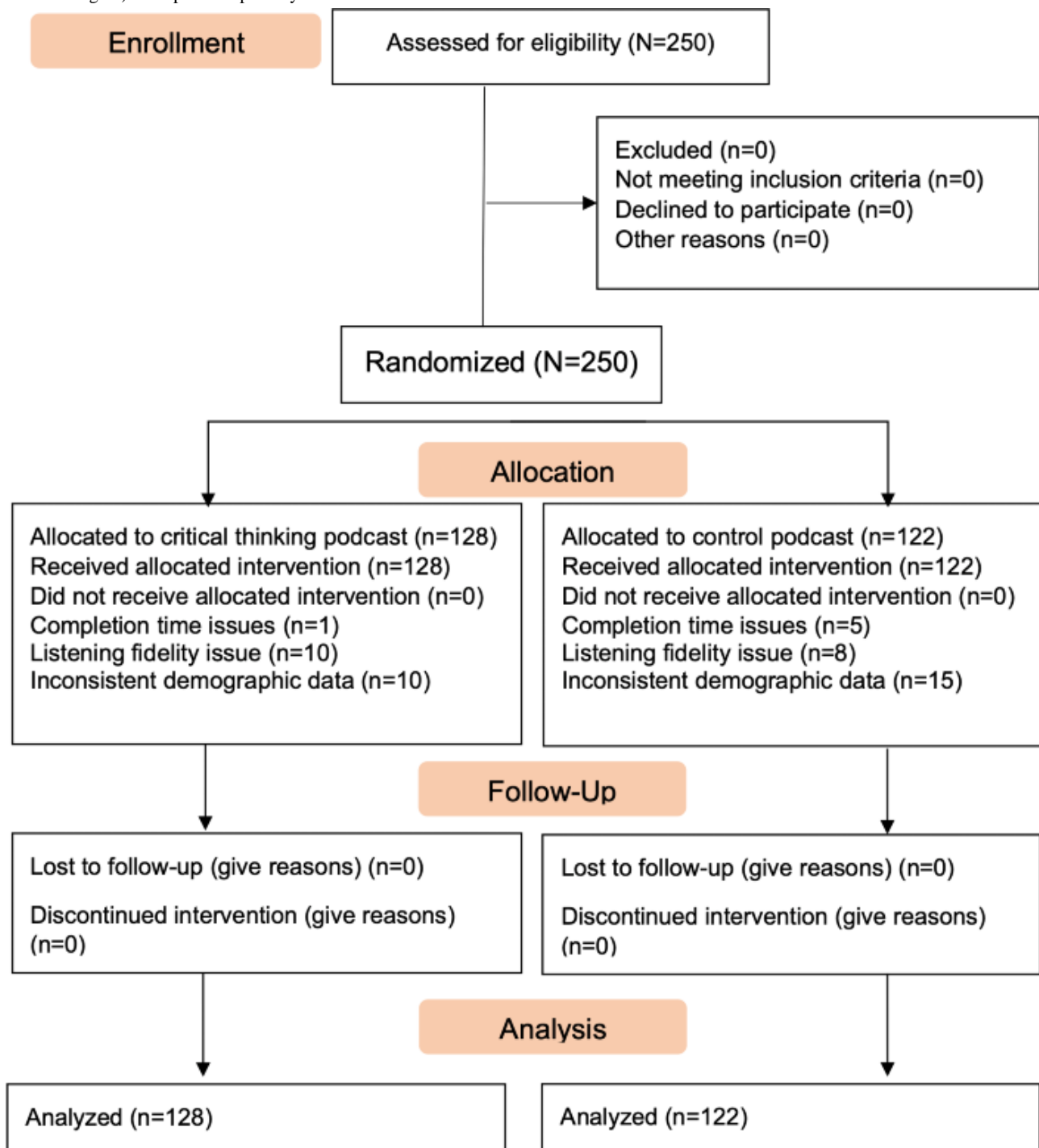
^dNot applicable.

Analysis of Data Quality

Out of 250 participants, 6 (2.4%) completed the study under 42 minutes (70% of the projected completion time); 18 (7.2%) failed attention check questions or obtained a score of 4 or lower on the listening fidelity measure; and 25 (10%) provided inconsistent demographic data. Consistent with an intent-to-treat approach, all randomized participants who completed study

procedures were included in the primary study analyses (Figure 1). For completeness, we report exploratory post hoc analyses excluding the 49 participants with data quality issues at the end of this section. Parents in the critical thinking podcast condition obtained an average score of 6.73 (SD 1.68; range 1 - 8) on the listening fidelity test and parents in the control condition earned an average score of 6.76 (SD 0.84; range 1 - 8).

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of participant flow through the *Parents Making Informed Health Choices Podcast* randomized controlled trial. This figure depicts participant flow for main study analyses where all randomized participants were retained in accordance with an intent-to-treat approach; exploratory post hoc analyses excluding 49 participants with data quality issues (indicated in the allocation section of the figure) are reported separately.



Randomization Success

There were no significant differences between the critical thinking podcast condition and control condition at preintervention based on gender ($\chi^2_1=0.679$; $P=.41$), education level ($\chi^2_1=0.88$; $P=.35$) annual household income ($t_{248}=0.720$; $P=.47$), podcast listening habits ($t_{248}=-0.744$; $P=.46$), and

podcast listening fidelity scores ($t_{248}=0.155$; $P=.88$). However, the control group was significantly older, by 2 years ($t_{248}=2.43$; $P=.02$); therefore, we controlled for age in all analyses. Given some variability and to reduce the possibility that significant relationships were due to third variables, we also included education and listening fidelity as control variables in outcome analyses. Table 3 includes descriptive statistics for study measures, including means and SDs for this sample.

Table . Descriptive data for study variables by condition and overall sample (N=250). Values in italics in the same row differed significantly at $P<.05$ based on regression analyses controlling for age, education, and listening fidelity.

Variable	Overall (N=250)	Critical thinking podcast (n=128)	Control podcast (n=122)
Critical thinking—continuous, mean (SD; range)	14.36 (5.41; 2 - 21)	<i>15.48 (5.19; 2-21)</i>	<i>13.19 (5.42; 2 - 21)</i>
Critical thinking—dichotomous, n (%)			
High score (1=18 or more correct out of 21)	99 (39.6)	<i>67 (52.3)</i>	<i>32 (26.2)</i>
Low score (0=17 or less correct out of 21)	151 (60.4)	<i>61 (47.7)</i>	<i>90 (73.8)</i>
Intended behavior (1-4), mean (SD; range)			
Find out what a claim was based on	3.53 (0.71; 1 - 4)	3.54 (0.73; 1 - 4)	3.52 (0.70; 1 - 4)
Find out if a claim was based on a fair comparison study	3.61 (0.63; 1 - 4)	<i>3.72 (0.55; 1-4)</i>	<i>3.49 (0.69; 1 - 4)</i>
How likely are you to participate in a fair comparison study	3.08 (0.87; 1 - 4)	3.13 (0.85; 1 - 4)	3.03 (0.88; 1 - 4)
EBP ^a attitudes (1-5), mean (SD; range)			
Beliefs regarding therapists' practices	24.74 (3.54; 10 - 30)	24.85 (3.57; 13 - 30)	24.61 (3.51; 10 - 30)
Attitudes about mental health policy	13.40 (3.34; 5 - 20)	13.65 (3.19; 6 - 20)	13.14 (3.48; 5 - 20)
Negative personal-level attitudes towards EBPs	23.97 (7.82; 9 - 45)	<i>23.01 (7.43; 9-41)</i>	<i>24.98 (8.11; 9 - 45)</i>
Negative societal-level attitudes toward EBPs	14.48 (3.47; 5 - 20)	14.36 (3.51; 5 - 20)	14.60 (3.44; 4 - 20)
Empiricism attitudes (1-5)	4.08 (0.63; 2.2 - 5)	4.15 (0.60; 2.4 - 5)	4.01 (0.66; 2.2 - 5)
Vaccine safety concerns (1-5)	6.1 (3.58; 3 - 15)	6.03 (3.57; 3 - 15)	6.12 (3.60; 3 - 15)
Treatment preferences, mean (SD; range)			
Therapeutic alliance	24.66 (16.14; 0 - 99)	23.57 (16.51; 0 - 99)	25.80 (15.73; 0 - 99)
Scientific studies show therapy is highly effective	28.20 (18.82; 0 - 99)	<i>30.02 (20.55; 0-99)</i>	<i>26.29 (16.70; 0 - 89)</i>
Therapist experience	16.33 (10.63; 0 - 49)	16.02 (11.04; 0 - 49)	16.66 (10.21; 0 - 48)
Empathic therapist	18.39 (12.74; 0 - 71)	17.77 (12.53; 0 - 70)	19.05 (12.97; 0 - 71)
Client speaking majority of session	11.42 (10.04; 0 - 52)	11.63 (10.90; 0 - 52)	11.20 (9.09; 0 - 42)
Podcast satisfaction, mean (SD; range)			
Overall satisfaction (1-5)	4.18 (0.89; 1 - 5)	4.16 (0.93; 1 - 5)	4.20 (0.85; 1 - 5)
Continue listening (1-5)	3.61 (1.16; 1 - 5)	3.56 (1.19; 1 - 5)	3.65 (1.14; 1 - 5)
Recommend to others (0 - 10)	6.71 (2.89; 0 - 10)	6.76 (2.79; 0 - 10)	6.66 (3.01; 0 - 10)
Relevance to mental health questions (1-4)	2.97 (0.94; 1 - 4)	3.05 (0.95; 1 - 4)	2.88 (0.92; 1 - 4)
Relevance to physical health questions (1-4)	2.80 (1.03; 1 - 4)	3.14 (0.89; 1 - 4)	2.43 (1.04; 1 - 4)

^aEBP: evidence-based practice.

Effects on Critical Thinking

As hypothesized, parents who listened to the critical thinking podcast performed significantly better on the critical thinking

measure than those who listened to the control podcast ($B=2.56$; $P<.001$), with a small-medium effect size ($\Delta R^2=0.06$). Table 4 presents all results from linear regression analyses.

Table . Results from linear regression analyses examining critical thinking podcast effect on critical thinking, intended behavior, attitudes, treatment preferences, and overall podcast satisfaction (control variables: age, education, and listening fidelity).

Dependent variable	Critical thinking		
	B	SE	β
Critical thinking	2.56	0.515	.237 ^a
Intended behavior			
Find out what a claim was based on	0.042	0.092	.029
Find out if a claim was based on a fair comparison study	0.252	0.078	.201 ^b
How likely are you to participate in a fair comparison study	0.109	0.116	.063
EBP ^c attitudes			
Beliefs Regarding Therapists' Practice	0.073	0.093	.050
Attitudes About Mental Health Policy	0.495	0.416	.074
Negative Personal-Level Attitudes towards EBPs	-1.96	0.893	-.127 ^d
Negative Societal-Level Attitudes towards EBPs	-0.160	0.446	-.023
Attitudes regarding empiricism	0.156	0.080	.124
Vaccine safety concerns	-0.185	0.400	-.026
Treatment preferences			
Therapeutic alliance	-1.82	2.08	-.056
Scientific studies show therapy is highly effective	4.89	2.34	.131 ^d
Therapist experience	-1.50	1.33	-.071
Empathic therapist	-1.59	1.64	-.063
Client speaking majority of session	0.024	1.26	.001
Overall podcast satisfaction	-0.050	0.113	-.028

^a $P<.001$.

^b $P<.01$.

^cEBP: evidence-based practice.

^d $P<.05$.

Effects on Intended Behavior

Compared to control parents, parents in the critical thinking podcast condition reported a significantly higher likelihood of “finding out if a claim was based on a fair comparison study” in the future ($B=0.252$; $P<.001$; $\Delta R^2=.04$). There were no significant differences between the conditions regarding the likelihood of engaging in the other 2 intended behaviors assessed: “finding out what a claim was based on,” and “participating in fair comparison study.”

Effects on Attitudes

Between-group differences in EBP attitudes were examined across the 4 attitudes factors of the CAEBS. Parents in the critical thinking condition had lower scores on the negative personal-level attitudes towards EBPs scale ($B=-1.96$; $P<.05$; $\Delta R^2=0.015$). There were no significant differences between podcast groups in the 3 other CAEBS EBP attitudes scales, attitudes regarding empiricism in mental health, or vaccine safety concerns.

Effects on Treatment Preferences

Parents who listened to the critical thinking podcast expressed a significantly higher preference for “receiving effective therapies backed by scientific studies” compared to the control group ($B=4.89$; $P<.05$; $\Delta R^2=0.02$). All other mental health treatment preferences did not vary significantly based on condition.

Post Hoc Analyses Without Intent to Treat Sample

We also ran analyses excluding the 49 participants who failed data-quality checks. When we excluded these individuals in the comparison analysis of parents’ critical thinking postintervention, we found that the magnitude of the intervention effect on critical thinking increased from 0.06 to 0.11 ($B=0.525$; $P<.001$). In regard to other outcomes, when we removed the intent to treat sample, we found that parents who listened to the critical thinking podcast reported significantly more positive attitudes regarding empiricism in mental health treatment ($B=0.210$; $P<.05$; $\Delta R^2=0.03$), and no longer found a significant difference between podcast groups in the negative personal-level attitudes towards EBPs scale.

Discussion

Principal Findings

To address the public health misinformation crisis at scale, we developed and tested the efficacy of a story-based, educational podcast—the *Parents Making Informed Health Choices Podcast*—a brief, scalable, low-intensity intervention designed to increase critical thinking about health among US parents. Through an online RCT, we found that listening to the podcast improved parent critical thinking and had an effect on intended behaviors, attitudes, and treatment preferences. To our knowledge, this is the first online RCT of a mass media, brief critical thinking intervention for a US audience.

A previous study’s findings of low levels of critical thinking among US parents and young adult college students demonstrated a need for a scalable critical thinking intervention for the US public [3]. The impacts on critical thinking demonstrated in this study add to the growing body of empirical evidence demonstrating the efficacy of critical thinking learning resources designed for the lay public [41–43]. The critical thinking effects observed in this US sample are similar to those observed in the original Ugandan podcast, where they also found a significant difference in postintervention critical thinking performance favoring parents in the critical thinking condition [25].

Out of the 3 intended behaviors assessed, parents who listened to the critical thinking podcast were more likely to report intending to find out if a treatment claim is based on a fair comparison study with control parents, but contrary to the hypotheses, these 2 other intended behaviors were not significantly different between the 2 study conditions. A possible explanation for this may be that the podcast directly and repeatedly mentions “fair comparisons,” whereas the other intended behaviors are less frequently mentioned. These findings also differ from the Ugandan podcast RCT, where they did not

find any significant behavioral intention differences between study conditions.

In terms of attitudinal measures related to critical thinking about health, parents who listened to the critical thinking podcast had less negative personal-level attitudes toward EBPs (as measured by 1 of the 4 factors of CAEBS) [36], and reported a higher preference for receiving effective therapies backed by scientific studies. Contrary to expectations, conditions did not differ on any other EBP attitudes or vaccine safety concerns. Notably, this study was conducted prior to the COVID-19 pandemic; as such, public attitudes regarding vaccines may have changed.

Of the 4 CAEBS factors regarding consumer EBP attitudes (beliefs regarding therapists’ practices, attitudes about mental health policy, negative personal-level attitudes toward EBPs, and negative societal-level attitudes towards EBPs), the personal-level attitudes toward EBP factor is most in line with the content of the critical thinking podcast, with items such as “I don’t feel comfortable making treatment decisions.” Nevertheless, the null findings regarding 3 out of the 4 CAEBS scales were surprising given the general similarity between the concepts covered in the critical thinking podcast and the factors assessed by the CAEBS [36]. Upon closer scrutiny of the CAEBS’ scales and items, possible explanations become apparent. First, while the *Parents Making Informed Health Choices Podcast* centers on EBP principles and making them accessible to the lay public, it rarely mentions “evidence-based” terms because the focus is on teaching a skill rather than *telling* the audience they should seek out EBPs. On the other hand, the CAEBS frequently and explicitly mentions the term “evidence-based” and defines it in the instructions. Perhaps this suggests that evidence-based health care proponents and researchers have some middle ground to reach in regards to balancing efforts to teach *science and health literacy-based skills* (ie, critical thinking about health) and increasing consumer knowledge of *health care terms*. It would be interesting for future studies to examine whether explicitly and repeatedly mentioning EBPs in the podcast has a different effect on EBP attitudes as measured by the CAEBS. Another potential explanation for the null findings is that CAEBS items have a strong emphasis on society and policy themes, whereas the critical thinking podcast solely focused on individual actions around EBP principles.

It should be noted that the *Parents Making Informed Health Choices Podcast* achieved these effects through an online, one-time, brief, audio intervention whereas the original Ugandan podcast RCT used a lengthier podcast listening procedure. Thus, our choosing to prioritize ecological validity based on how the public interacts with health information on the internet did not diminish the intervention’s effects. Notably, parents in this study were tested on their critical thinking abilities and other factors a few minutes after listening to the podcasts. As such, a follow-up study is necessary to examine long-term effects.

Future studies should also determine who is most likely to benefit from these critical thinking interventions. For example, including a sample with a broader range of levels of educational attainment could help determine if education is a moderator. Another important future direction for critical thinking research

is how to incorporate pragmatic tips on how parents can carry out critical thinking in conversations with health care providers, especially in situations where the evidence base may not be strong, but where a treatment is still recommended either because it is the only option or for other valid reasons. There are EBP principles that address these realities (eg, EBP principle “how certain is the evidence?”) [44], and future intervention or podcast development should focus on creating additional short episodes that capture these EBP principles in decision-making (eg,[45].

Furthermore, critical thinking interventions could complement a shared-decision making framework [46,47] in that critical thinking interventions encourage patient activation. Thus, future studies might consider combining or embedding critical thinking interventions within shared decision-making frameworks. Indeed, although this is not directly communicated in the *Parents Making Informed Health Choices Podcast*, characters in the stories often do model appropriate interactions with health care providers; however, the storylines do not conclude in a shared decision about health care services.

Limitations

As with any investigation, this study has several limitations that suggest additional directions for future research. First, although online-convenience samples of parents generally provide reliable data [33] and this study sample was relatively diverse, especially in regard to socioeconomic status, they may not always be representative of all US parents, especially of parents in low-resource, community settings. Thus, future studies should focus on testing the efficacy of the podcast with more representative samples of parents from community settings that could greatly benefit from interventions such as this one. Along those lines, the *Parents Making Informed Health Choices Podcast* is currently only available to English-speaking parents,

creating a disparity for parents who speak other languages, especially predominantly Spanish-speaking parents, who make up the fastest growing linguistic population in the United States. Future efforts should focus on translating these materials and testing their efficacy in other languages, especially Spanish. Some of this work is already starting with children in Spain [48]. Second, we have found evidence of only the very short-term efficacy of the *Parents Making Informed Health Choices Podcast*. Therefore, an important future direction is to conduct a long-term follow-up assessment of critical thinking with parents who participated in this online RCT, especially given that a 1-year follow-up study on the effects of the Ugandan critical thinking podcast found a decline in critical thinking abilities [49]. Finally, all outcome variables were about parent attitudes and preferences regarding mental health services for themselves, but we did not specifically ask about their attitudes and preferences in regards to mental health services for their children, which may be an important addition to future studies.

Conclusions

This pilot trial provided empirical evidence regarding the efficacy of a brief, story-based critical health literacy podcast for US parents—a population frequently targeted by health misinformation. We found that listening to a brief podcast significantly improved parents’ critical thinking about health, as well as increased self-reported intended behavior, positive attitudes toward EBPs, and preference for EBPs. By delivering accessible, engaging content in a familiar digital format, podcasts may represent a scalable public health strategy to promote evidence-based decision-making and strengthen critical health literacy. Future research should examine long-term effects, implementation in diverse communities, and potential integration into broader digital health and health education ecosystems.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Checklist 1

CONSORT checklist.

[PDF File, 137 KB - [publichealth_v12i1e78003_app1.pdf](#)]

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Abbreviations

CAEBS: Consumer Attitudes Towards Evidence Based Services Scale

CONSORT: Consolidated Standards of Reporting Trials

EBP: evidence-based practice

MTurk: Mechanical Turk

RCT: randomized controlled trial

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Original Paper

A Social Media Campaign to Promote COVID-19 Vaccination: Cost-Effectiveness Analysis

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Abstract

Background: Vaccine hesitancy has increased in recent decades internationally, which sets up a critical barrier to the rapid deployment of novel vaccines against infection with SARS-CoV-2.

Objective: This study used a quasi-experimental design to evaluate the cost-effectiveness of a social media intervention to reduce COVID-19 vaccine hesitancy implemented in Nigeria in 2022.

Methods: The intervention targeted health care providers and adults from the general population who were users of a specific social media platform. We used published estimates from a quasi-experimental evaluation of the campaign's effectiveness compared to the status quo across 6 intervention states and 31 comparison states over a 10-month period. We estimated the cost-effectiveness of the campaign in terms of cost (2022 US dollars) per person vaccinated using a decision tree analysis and probabilistic sensitivity analysis.

Results: On the basis of the quasi-experimental trial, the campaign led to a crude 6.4–percentage point increase (219/692, 31.6% vs 117/463, 25.3%; $P=.045$) in vaccination rates and an adjusted 7.8–percentage point increase (95% CI 1.68–14.2; $P=.02$) controlling for age group, gender, educational level, religion, and occupation among the 20% (1933/9607) of the overall sample who were unvaccinated and in the persuadable middle. Scaled to the overall population, the campaign led to a 1.57–percentage point (95% CI 0.337–2.87; $P=.02$) increase in the proportion of those vaccinated against COVID-19 among those reached by the social media campaign. The social media campaign resulted in 58.3 million impressions and 1.87 million people reached for a total societal cost of US \$1.15 million, or US \$0.61 per person reached. This resulted in an incremental cost-effectiveness ratio of US \$54.70 (95% uncertainty interval US \$20.90–\$163) per person vaccinated.

Conclusions: A social media–based campaign to address COVID-19 vaccine hesitancy in 6 states in Nigeria resulted in an increase in vaccination rates. The cost-effectiveness of the campaign compared to no campaign is comparable to that of other campaigns promoting COVID-19 vaccine uptake. The cost per person vaccinated due to the social media campaign was 1% to 8% of the estimated cost per life year saved by vaccination against COVID-19 in low- and middle-income countries. Investing in social media campaigns would likely be a cost-effective approach to increase vaccine uptake and save lives.

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KEYWORDS

COVID-19; vaccination; social media; cost-effectiveness; health promotion

Introduction

The COVID-19 pandemic led to the death of 15 to 20 million people worldwide up to 2021 [1,2]. In response to this threat, governments and private companies demonstrated high capacity for innovation; the rapid development and testing of multiple effective vaccines stands out as a critical success [3]. The pandemic also highlighted ongoing systemic failures in global and national public health systems, including limited capacity for surveillance, communication, and distribution of preventive materials and services [4]. These failures exacerbated existing health inequities within and between countries.

The potential impact of the successful development, manufacture, and distribution of effective vaccines was not fully realized due to the public health system's inability to communicate the safety and benefit of the new vaccines in the context of widespread mis- and disinformation about the pandemic and the public health response. Building on well-established antivaccine movements, COVID-19 vaccine hesitancy emerged as a major barrier to the control of the pandemic [5]. By November 2023, a total of 80% of people living in high-income countries had received at least one dose of a COVID-19 vaccine compared to 33% of people living in low-income countries [6]. In the years before the COVID-19 pandemic, researchers were evaluating the potential use of social media communication campaigns to address vaccine misinformation and increase vaccine uptake. Previous vaccine promotion campaigns addressing vaccine hesitancy have mostly targeted a narrow set of vaccines (eg, influenza and human papillomavirus in high-income countries and diphtheria, tetanus, pertussis, and polio in middle- and low-income countries) [7]. Reviews of health promotion campaigns covering communicable and noncommunicable diseases on social media have found limited or mixed evidence of reported or observed behavior changes (ie, high engagement) and more reports of interaction with posts or changes in knowledge and attitudes (ie, low to medium engagement) [8,9].

With this promising but mixed and limited research base, and accompanied by calls for development of theoretically based and practice-based social marketing strategies [10], funders and public health organizations rapidly implemented social media campaigns to promote COVID-19 vaccine uptake. Initial evaluations of efforts to promote COVID-19 vaccination or other disease control behaviors through social media campaigns have been positive but with low to moderate effects, leading the public health community to consider whether and how to invest in a sustainable public health social media communication infrastructure [11-14]. Social media campaigns have the potential to reach targeted audiences with tailored messages in ways that may improve both impact and efficiency compared to mass media campaigns [15].

We evaluated the cost-effectiveness of a targeted social media campaign to promote vaccination against COVID-19 among health care providers and other adults in their social environment

in Nigeria in 2022. By May 2022, after recording 250,000 COVID-19 cases, Nigeria had received enough COVID-19 vaccines to cover 25% of the population and had administered the first dose to 13% and the second dose to 8% of the population [16]. High levels of vaccine acceptance (76%) in late 2020 were being reported to be much lower as more data were published in 2021 (40%-60%) [16,17]. The World Bank, which classifies Nigeria as a lower-middle-income country, reported that 38% of the Nigerian population accessed the internet in 2022 [18]. A rapid rise in the use of social media in Nigeria and its complex role in the response to COVID-19 had been reported by the time the social media campaign in this paper had been implemented [19].

In this analysis, we aimed to evaluate the cost of implementing a social influencer-based social media campaign and estimate the value of the campaign in terms of cost per person vaccinated, which can be compared to other campaigns targeting vaccine uptake.

Methods

Overview

The prospective economic analysis plan was included in the overall analysis plan submitted to the funder and has not been published elsewhere. This project followed the guidelines of the Second Panel on Cost-Effectiveness in Health and Medicine and the reporting guidelines from the Consolidated Health Economic Evaluation Reporting Standards checklist [20,21]. The data used in the model synthesis were collected from 2021 to 2022. The analysis was completed in 2023.

Intervention Description

This cost-effectiveness analysis is based on the implementation and quasi-experimental evaluation of a 10-month social media campaign promoting vaccination against COVID-19 in Nigeria among health care workers and those in their social networks in 2022 [22]. The campaign was designed and implemented by a team of designers and local organizations and delivered through Facebook and Instagram. The campaign included provaccination social norms and vaccine hesitancy reduction messages delivered by social influencers (eg, local celebrities, health care providers, and religious and business leaders). The campaign theory of change was based on the theory of diffusion of innovations; social norms theory; and the motivation, opportunity, and ability framework [23-25].

Study Population and Setting

The intervention was implemented in 6 states in Nigeria (Anambra, Bauchi, Lagos, Niger, Rivers, and Sokoto), with participants in the control condition recruited from the Federal Capital Territory and all other states. Participants were eligible if they were aged ≥ 18 years, had a Facebook account registered in Nigeria and received recruitment advertising in their live feed promoting a study on COVID-19 vaccination, had not been previously vaccinated against COVID-19, and were defined as members of the "persuadable middle" [22]. Those who

responded “Definitely” or “Definitely not” to the question “Would you take a COVID-19 vaccine that is approved for use in Nigeria if offered to you?” were excluded based on not being in the persuadable middle. While people in low- and middle-income countries (LMICs) generally have higher vaccine acceptance than those in high-income countries, Nigeria faced vaccine availability and other challenges that may have impacted vaccine hesitancy differently than in higher-income settings, including perceptions that safety and efficacy had not been adequately evaluated in that setting [26-28].

Cost Evaluation

We used the standard microcosting approach, for which we evaluated all component costs of the intervention instead of using a global project budget. Microcosting includes 3 main steps: identification, measurement, and valuation. To identify the resources used, we prospectively developed a detailed description of the intervention activities and identified necessary resources for each activity. Resources were measured and valued using actual reported expenditures from implementing partners and reported or estimated opportunity costs for the nonbudgeted time from implementing partners, influencer organizations, and participants. Direct costs were all reported in US dollars by the implementing partners and were adjusted for inflation to 2022 US dollars. Opportunity costs accrued in Nigeria were estimated in 2022 Nigerian naira. Nigerian currency was converted to purchasing power parities, with total costs reported in 2022 purchasing power parities, which is equivalent to 2022 US dollars. Costs were converted in 2023. As we did not assess health or economic benefits of vaccination, we did not include opportunity costs of individuals or direct health care sector costs for receipt of the vaccine.

Intervention Reach

The intervention included 245 distinct advertising campaigns implemented on the Facebook social media platform, which means that the campaigns may have included distinct creative content or audience-targeting and promotion methods and their unique individual reach could not be combined with that of other campaigns. For each of these campaigns, the platform reported the total number of unique individuals receiving campaign messages (reach), the total impressions (ie, the number of times the campaign message was displayed on the target audience member's screen), and a range of engagement metrics for each of these campaigns. Because we did not have access to the total number of unique individuals reached across all campaigns, we estimated reach based on the largest reported reach across all campaigns. Due to a lack of data on the degree of overlap within a targeted campaign, we based our reach estimate on a conservative assumption that there was complete audience overlap across campaigns.

Cost-Effectiveness Analysis

We used a societal and payer perspective, which captured both the budgetary costs of implementing a similar campaign in the future and the opportunity costs of implementing partners and individuals engaging with campaign messages. The comparator was the status quo (ie, the current state of affairs in the absence of this intervention), which was chosen based on the intervention

design and effect estimate. The time horizon for this study was 1 year to capture planning and implementation; we did not have the capacity to model longer-term health and cost effects following a change in vaccination rates. We did not discount costs or benefits over the 1-year time horizon.

Outcome Measurement

The primary outcome for this study was vaccination against COVID-19. The incremental effect of exposure to the advertising campaign was estimated from a survey of 10,965 participants who were users of the Facebook social media platform. Of the initial 10,965 participants screened for eligibility, 6198 (56.5%) were excluded as already vaccinated, 1476 (13.5%) were excluded for not being in the persuadable middle, 675 (6.2%) were excluded for missing baseline data, 648 (5.9%) were excluded for not meeting the age criteria, and 35 (0.3%) were excluded for having a duplicate ID. The remaining 17.6% (1933/10,965) of the participants were enrolled in the study. Surveys were fielded to the same cohort, with baseline data collection taking place during the period from December 1 to 31, 2021; first follow-up data collection taking place during the period from March 1, 2022, to April 30, 2022; and second follow-up data collection taking place during the period from October 1 to 4, 2022. Of the 1933 participants enrolled in the study, 1155 (59.8%) completed the first follow-up, and 462 (23.9%) completed the second follow-up. Exposure was based on state of residence, with the intervention implemented in 6 states (Anambra, Bauchi, Lagos, Niger, Rivers, and Sokoto) and control participants recruited from all other states in Nigeria.

Participants were recruited through a social media-based research platform called Virtual Lab. Recruitment was stratified by whether participants were health care providers, with the goal of recruiting 50% of the sample from the health care provider community. COVID-19 vaccination uptake was measured through a single question: “Have you received a COVID-19 vaccine?” Participants could respond as follows: “Yes, a single-dose vaccine”; “Yes, the first dose of a two-dose regimen”; “Yes, both doses of a two-dose regimen”; and “No.” Due to changes in the types of vaccines available, as well as recommendations for boosters, we collapsed the outcome into a binary “vaccinated or not vaccinated” outcome.

The effect of the intervention was estimated using a linear regression model predicting vaccination status at the midpoint and final survey. The primary independent variable in each model was exposure to the intervention. Adjusted models included the following control variables: age group, gender, educational level, religion, and occupation. We used clustered SEs to account for nesting within state of residence. Additional details on the evaluation of the intervention on vaccine uptake are reported elsewhere [22].

For the purposes of this cost-effectiveness analysis, we estimated the reach of the campaign in the intervention states based on the impressions reported by the Facebook social media platform. Impressions are defined as an individual user's exposure to specific content on the platform that may or may not result in active engagement, such as liking, commenting, or following the account that disseminated or originated the content [29].

Impressions have been shown to account for most of the information exposure on social media, have low correlation with active engagement or “expression,” and be independently correlated with user-reported influence of a given information source [29].

Uncertainty Analyses

We conducted a probabilistic sensitivity analysis by sampling from the distributions of all parameters with measured

uncertainty (Table 1). We included the following scenario analysis: instead of using the effect estimate from the first follow-up from the original outcome study [22], we used the effect estimate from the second follow-up period from the same study. We did not evaluate the heterogeneity of the intervention effect or distributional effects of the intervention. Decision tree models and the probabilistic sensitivity analysis were conducted using TreeAge Pro (R2.0; TreeAge Software, LLC).

Table 1. Summary of inputs for the cost-effectiveness analysis of the COVID-19 vaccine promotion social media campaign in Nigeria in 2022.

Variable	Source	Point estimate (95% uncertainty interval)	Distribution (parameters)
Target population already vaccinated at the start of the campaign (%)	Quasi-experimental trial data [22]	64.5 (63.5 to 65.5)	Binomial ($p^a=0.645$, $n^a=9607$)
Persuadable middle population among those unvaccinated (%)	Quasi-experimental trial data [22]	56.7 (55.1 to 58.3)	Binomial ($p=0.567$, $n=3409$)
Percentage point increase in vaccination status due to treatment among the persuadable middle	Quasi-experimental trial data [22]	7.8 (1.68 to 14.2)	Normal (mean 0.078, SD 0.032)
Campaign reach	Meta advertiser platform	1,870,000	— ^b
Average engagement time per media impression (s)	Publisher analysis [30]	1.7	—
Total campaign impressions	Meta advertiser platform	58,300,000	—
Total cost (US \$)	Campaign microcosting	1,150,000	—
Cost per person reached (US \$)	Calculation	0.613	—
Sensitivity and scenario analyses			
Scenario 1: percentage point increase in vaccination status due to treatment among the persuadable middle using the second follow-up	Quasi-experimental trial data [22]	11.0 (−0.00337 to 0.225)	Normal (mean 0.110, SD 0.058)

^aParameters of each named distribution, where p denotes the probability and n denotes the number of trials.

^bNot applicable.

Ethical Considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This evaluation was approved by the George Washington University Institutional Review Board (NCR213708), as well as by the National Health Research Ethics Committee in Nigeria (NHREC/01/01/2007-04/10/2021). No identifiable data were used in this study. All participants provided informed consent to participate in the study following the institutional review board–approved protocol. Participants were compensated with 400 naira (approximately US \$1) for completion of the 40-item survey implemented through the Facebook Messenger chat function.

Results

The intervention generated 58,255,000 total impressions across 245 distinct advertising campaigns, which, on the Meta platform

(the company that owns Facebook), included one or more sets of individual advertisements. Distinct campaigns were run to allow the intervention to best measure and optimize performance against advertising objectives. The mean reach (unique individuals generating one or more impressions) per campaign was 100,000 (SD 176,000; range 1000–1,873,000). On the basis of an assumption that there was complete overlap across distinct advertising campaigns, the intervention reached 1,873,000 unique individuals.

We summarize intervention costs by activity category in Table 2. Due to the use of marketing labor in the United States and the United Kingdom as well as dollar-denominated contracts with partners in Nigeria, the payer costs accounted for 93% of the total societal costs even though the paid hours to implement the project constituted 14% of the total person-time included in the societal perspective.

Table 2. Cost of the COVID-19 vaccine promotion social media campaign by activity in Nigeria in 2022.^a

	Payer perspective (US \$)	Societal perspective (US \$)
Government liaison	73,400	73,400
Monitoring and evaluation	98,300	98,300
Campaign development	360,000	360,000
Advertising expenditure	102,000	102,000
Advertising campaign implementation	134,000	134,000
Stakeholder management	293,000	293,000
Participant engagement with advertising	— ^b	77,700
Influencer campaign implementation	—	7520
Total	1,060,000	1,150,000

^aCosts may not add up due to rounding.

^bThere are no participant opportunity costs included in the payer perspective.

Across both the control and intervention samples (excluding those who were ineligible based on age, duplicate ID, and missing baseline data), 64.5% (6198/9607) of the participants were already vaccinated at baseline. The vaccination rate among this sample of Facebook users was substantially higher than the 13% single-dose uptake reported at a similar point in the rollout (eg, May 2022) [16]. Of the 3409 participants screened in the study who were not vaccinated and were otherwise eligible, 1933 (56.7%) were considered to be in the persuadable middle and were enrolled in the study. In a previous study, we estimated that the intervention led to a 7.8–percentage point increase (95% CI 1.68–14.2) in vaccine uptake controlling for demographic variables among those in the persuadable middle.

In the primary analysis, we estimated that the incremental cost of the intervention per person reached was US \$0.63 and the incremental percentage point increase in vaccination prevalence

was 0.0157 (95% uncertainty interval [UI] 0.00337–0.0287). This resulted in an incremental cost-effectiveness ratio of US \$54.70 (95% UI US \$20.90–\$163), which means that it cost US \$54.70 more than the status quo (ie, the current state of affairs without the intervention) for every additional vaccination.

In scenario analysis 1, we used the effect estimate from the second follow-up of the same study as the primary analysis. In this scenario, the larger percentage point increase in vaccinations per person (0.0221 vs 0.0157) than in the no-intervention condition reduced the incremental cost-effectiveness ratio almost by half (US \$29.60, 95% UI negative to US \$180; Table 3). The UI includes 0 due to the smaller sample at the second follow-up and resulting marginally significant coefficient reported in the evaluation study. We found that using this estimate resulted in 3% of all model iterations having a negative effect.

Table 3. Cost-effectiveness results of the COVID-19 vaccine promotion social media campaign in Nigeria in 2022.

	Mean (95% uncertainty interval)
Incremental cost per person reached (US \$)	0.613 (0.613 to 0.613)
Incremental increase in COVID-19 vaccinations per person exposed to the campaign	0.0157 (0.00337 to 0.0287)
Incremental cost-effectiveness ratio (US \$ per vaccination)	54.70 (20.90 to 163)
Scenario 1: incremental COVID-19 vaccination per person	0.0221 (–0.000649 to 0.0452) ^a
Scenario 1: incremental cost-effectiveness ratio (US \$ per vaccination)	29.60 (negative to 180) ^b

^aFor scenario 1, we used an alternative estimate of the effectiveness of the intervention from the second follow-up period of the same intervention used for the primary analysis.

^bA total of 3% of the model iterations were negative.

Discussion

Principal Findings

In this cost-effectiveness analysis of a social media campaign promoting vaccination against COVID-19 among health care workers and adults in their social environment in Nigeria in 2022, we found that the intervention increased vaccination rates among the target audience at a cost in line with similar efforts in the field.

Incremental cost-effectiveness estimates of media campaigns promoting vaccine uptake vary substantially. On the basis of an analysis of attitude changes as a result of social media campaigns run by 174 public health organizations during the COVID-19 pandemic and another study linking attitudes to vaccination outcomes, Athey et al [31] estimated that the campaigns cost US \$5.68 per person vaccinated. The study by Athey et al [31] only incorporated the cost of advertising, which accounted for only 12% of the total costs of running and participating in the campaign in our study. This suggests that

our estimate of US \$54.70 is likely consistent with that of the analysis by Athey et al [31] (which estimated that it would cost US \$48 per person vaccinated assuming a similar cost structure) and highlights the importance of incorporating as many relevant costs as feasible when presenting the cost-effectiveness of social media campaigns.

Because there is no willingness-to-pay threshold for the cost of an incremental person vaccinated, it may be useful to integrate the findings of this study with those of others that have measured the cost per year of life saved (YLS) or cost per disability-adjusted or quality-adjusted life year. A study estimating health benefits and donor costs of increase in COVID-19 vaccination rates in 91 LMICs found that spending on vaccination would cost between US \$670 per YLS and US \$7820 per YLS depending on the level of vaccination achieved [32]. The authors noted that the cost per YLS for COVID-19 vaccination was similar to the cost for antiretroviral therapy for HIV under the President's Emergency Plan for AIDS Relief, which they estimated at US \$4310 per YLS using the total budget and life years saved from the President's Emergency Plan for AIDS Relief 2004 to 2013 [31]. The cost per person vaccinated in this study (US \$54.70) was between 1% and 8% of the estimated cost per YLS by vaccination against COVID-19 in the 91 LMICs in the aforementioned study [32]. To further contextualize the value of the social media campaign evaluated in this study, vaccination against COVID-19 in LMICs was estimated to prevent 20.39 deaths per 10,000 people vaccinated; each death from COVID-19 was separately estimated to lead to 16 years of life lost [33,34]. This means that, for each person vaccinated, there was an average of 0.0326 ($20.39 \times 16/10,000$) years of life lost prevented. On the basis of the estimates of the variable cost of vaccination delivery after rollout of a national campaign (US \$10 for the vaccine and US \$2.46 for delivery) and the cost of promotion obtained from this study (US \$54.70), the marginal cost for each vaccination delivered would be US \$67.16, leading to an estimate of US \$2060 per year of life lost averted. The value of rapidly disseminating science-based vaccine promotion in terms of within-country health benefits likely underestimates the benefits of responding to shared global vulnerabilities with shared investments in mutually beneficial solutions such as vaccination. Baker et al [35] highlight this need for rapid collaboration as they paint an alarming picture of our new era of globally shared infectious disease risk caused by the confluence of climate change, urbanization, migration, travel, and intensifying trade of plants and animals.

Much of the work to prepare and launch this specific campaign to increase COVID-19 vaccine uptake could support other public health communications campaigns in Nigeria and potentially other countries. Moving the intervention to scale, such as all 37 states instead of the 6 in the intervention arm of this study, would spread fixed costs across a much larger population and reduce the cost per person vaccinated substantially. Goulbourne and Yanovitzky [36] argue that the COVID-19 pandemic clarified the role of health communication infrastructure as a social determinant of health and that public health organizations will need to invest in hyperlocal health communication capacity across populations to address health inequities. They suggest that training and providing ongoing technical support to trusted

intermediaries is one approach to providing hyperlocal health communication at scale. The intervention evaluated in this study did implement the COVID-19 vaccine promotion social media campaign through 12 local health organizations and 10 other local influencers. The involvement of local influencers to shape and deliver health messages was considered an essential component of the campaign. This approach could limit the degree to which the intervention could be scaled at a lower marginal cost.

A primary limitation of this cost-effectiveness analysis is that we were not able to obtain a specific estimate of the total unique individuals reached by the intervention on the Meta platform. To be conservative, we estimated a total intervention reach of 1.87 million unique users based on the reach of the largest single campaign and not the 24.5 million reached if we summed the reported reach estimates for all campaigns. Our estimated US \$0.61 per person reached by the campaign would instead be US \$0.05, shifting the cost per vaccination from US \$54.70 to US \$2.98. This order of magnitude difference in the cost-effectiveness of the intervention emphasizes the importance of understanding how social media reach metrics are reported and how studies estimating the same cost-effectiveness outcomes (eg, cost per person vaccinated against COVID-19) are using these metrics. The lack of comparability across studies may be further compounded when studies only use active engagement or expression as a measure of campaign reach [29].

The extent of competing social media and other communication campaigns promoting vaccination against COVID-19, as well as the high levels of mis- and disinformation about the pandemic and the vaccines on the same social media platforms, created another limitation. The incremental effect of the intervention campaigns on the message environment was lower than it would have been in a nonpandemic context. We were not able to assess any competing or synergistic effects of the campaign due to variation in individual or community media environments, nor were we able to evaluate how the campaign interacted with other public health campaigns on the same platform or across channels. Extrapolation of findings from this study period to future pandemics may be limited by the rapidly changing nature of the social media landscape, including as it relates to platform responsibility to address public health misinformation. The recent divergence in the degree of regulatory control over content moderation between the European Union's Digital Services Act requirement that platforms address the systemic risks posed by misinformation and American jurisprudence's strengthening of free speech protections of content moderation means that mostly American corporations will potentially pursue jurisdictionally fragmented approaches to misinformation during the next pandemic [37].

We used a self-reported measure of vaccination, which could potentially overestimate the effect of the intervention. Stephenson et al [38] reported that, among a sample of approximately 2000 patients with both self-reported and recorded COVID-19 vaccination status in a hospital setting, the self-reported and recorded vaccination status matched for 95% of the participants. While we used existing studies on the cost-effectiveness of vaccination in similar settings [32], we did not directly estimate how the campaign affected health

outcomes, which may vary based on, among other factors, the vaccination level in the community, underlying demography and health status of the population, type of vaccine used, and health care system cost and effectiveness. Incorporating these factors within evaluation of new health communication and other strategies is likely infeasible for most interventions but could be accomplished by partnering with modeling groups that do address these factors or through sustained support of modeling consortia that could share modeling capacity more rapidly during future pandemics [39].

Conclusions

We found that a local influencer-based social media campaign implemented in 6 states in Nigeria during the COVID-19

pandemic increased COVID-19 vaccination rates among those exposed to the campaign. The campaign demonstrated comparable cost-effectiveness to that of other COVID-19 vaccination campaigns when accounting for differences in cost data included across studies. When combined with existing estimates of the effect of vaccination against COVID-19 on mortality and years of life lost per death due to COVID-19, this intervention achieved a lower cost per year of life lost averted (US \$2060) than debated but recognized thresholds of 3 times the national gross domestic product per year of life lost averted [40]. Boosting the reach of vaccination efforts through influencer-based social media campaigns such as the one implemented in this study is likely to be a cost-effective approach to save lives.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: MWL, JBB, and WDE

Data curation: MWL

Formal analysis: MWL

Funding acquisition: WDE

Investigation: MWL, JBB, KN, DD, NR, S Akaba, S Agha, and WDE

Methodology: MWL, JBB, and WDE

Project administration: S Akaba

Supervision: WDE

Writing—original draft: MWL

Writing—review and editing: MWL, JBB, KN, DD, NR, S Akaba, S Agha, and WDE

Conflicts of Interest

NR has ownership interests in Virtual Lab, LLC, a company that uses open-source software described in this paper (Virtual Lab) to provide paid services. S Agha, the project officer, who was an employee of the funder at the time this project was initiated, participated in discussions about the study design and data collection. At the time of this manuscript preparation, S Agha was no longer with the funder. S Agha did participate in the development of the manuscript as noted in the Authors' Contributions section.

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Abbreviations

LMIC: low- or middle-income country

UI: uncertainty interval

YLS: year of life saved

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Clinical Epidemiology of Cancer in People Living With HIV in Germany: Retrospective, Observational, Multicenter Federated Claims Data Analysis

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Abstract

Background: People living with HIV are at increased risk for developing cancer, a leading cause of death in this population. The management of cancer in people living with HIV is particularly challenging, necessitating specialized, interdisciplinary care. However, insights into cancer care provision for people living with HIV in Germany remain scarce.

Objective: This study analyzed inpatient cancer care for people living with HIV, comparing treatment patterns and complications with those of an HIV-negative control group. Using claims data from 3 German university hospitals related to admissions between 2005 and 2022, we aimed to identify care disparities and provide evidence to support improved cancer management.

Methods: A customized federated approach was used to analyze inpatient claims data of patients across the 3 data-holding institutions. The data included demographics, diagnoses, procedures, and treatment codes as well as discharge information. Using nearest-neighbor matching, we analyzed demographic features, cancer diagnoses, anticancer therapies, and outcomes in people living with HIV and cancer and for a control group of HIV-negative patients with cancer.

Results: Among 162,380 patients, 907 (0.6%) were people living with HIV and cancer. The count of cancer diagnoses declined over time, particularly for AIDS-defining cancers (total cancer diagnoses: $P=.001$; AIDS-defining cancers: $P=.002$), with a shift toward older age at diagnosis. Compared with matched controls, people living with HIV and cancer had longer hospital stays, experienced more postchemotherapy complications (cancer with HIV: 64/907, 15.6%; cancer without HIV: 20/907, 5.5%; $P<.001$), and showed higher rates of metastasis after initial diagnosis (cancer with HIV: 128/267, 47.9%; cancer without HIV: 97/287, 33.8%; $P<.001$). People living with HIV and cancer also showed increased in-hospital mortality, although mortality declined

over time ($P=.02$). Our data suggested differences in documented therapy modalities between the compared groups, with people living with HIV and cancer receiving more chemo- and immunotherapy and less surgery.

Conclusions: Using federated analysis techniques, we were able to show that cancer diagnoses and mortality among people living with HIV in Germany have decreased over time; however, disparities in treatment and outcomes persisted as compared with HIV-negative patients with cancer. Our findings underscore the need for tailored, multidisciplinary care strategies to improve cancer management for this population.

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KEYWORDS

secondary data analysis; federated analysis; real-world data; HIV; cancer; malignancy; people living with HIV and cancer; inpatient care; claims data; Section 21 German Hospital Fees Act

Introduction

Despite advances in treatment and prevention, HIV remains a major global health threat, with 39.9 million cases recorded worldwide in 2023 [1]. In Germany, HIV incidence has stabilized, and treated individuals no longer exhibit increased mortality, which is seen as a contributing factor to a rise in HIV prevalence [2]. The decline in AIDS-related deaths is largely attributed to effective antiretroviral therapy (ART) [3-6]. However, people living with HIV still face a significantly higher cancer risk, particularly for infection-related cancers. These occur approximately 30 times more frequently in female people living with HIV and up to 100 times more frequently in male people living with HIV as compared with the general population [7-10].

HIV-associated cancers in people living with HIV can be categorized as AIDS-defining (AD) and non-AIDS-defining (NAD), with AD cancers including Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer [11]. NAD cancers are further divided into virus-associated (virus-NAD) and non-virus-associated NAD types. Virus-NAD cancers linked to coinfections include lung, anal, vulvar, penile, oral, and pharyngeal cancers; Hodgkin lymphoma; and hepatocellular carcinoma [8,9,12,13].

Since the introduction of ART, the incidence of AD cancers has decreased, whereas the incidence of virus-NAD and non-virus-associated NAD cancers has increased [7,14,15]. Due to increased life expectancy, both virus-associated and non-virus-associated NAD cancers have become leading causes of death among people living with HIV, surpassing deaths directly attributable to HIV infection [5,16,17]. Although combination ART has improved survival and enables full-dose chemotherapy [18], managing cancer in people living with HIV remains complex. Immunosuppression, drug interactions with ART, and increased treatment toxicity pose significant challenges, requiring a multidisciplinary care approach involving oncology, hematology, infectious diseases, pharmacy, and supportive care specialists [19]. Given these complexities, people living with HIV and cancer may need to travel longer distances to access appropriate, specialized care.

While cancer epidemiology in people living with HIV is well-documented [7-10,12-15,19], evidence on cancer care in people living with HIV—particularly regarding treatment and outcomes—remains limited. Existing data, primarily from US

registries, suggest that people living with HIV may receive cancer treatment less frequently than HIV-negative patients [20,21].

Using claims data from 3 German university hospitals, we analyzed inpatient cancer care for people living with HIV in Germany and compared it to that of an HIV-negative control group.

Methods

Study Data

This multicenter retrospective study used claims data collected under Section 21 of the German Hospital Fees Act (German: Krankenhausentgeltgesetz, KHEntgG). This law requires hospitals to report individual patient billing records to the federal institute for the hospital payment system (Institut für das Entgeltsystem im Krankenhaus). The data were sourced from data integration centers [22,23] of university hospitals in 3 large German cities (Frankfurt, Freiburg, and Munich).

The raw data included patient demographics and basic diagnostic- and treatment-related information (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10]*), as well as operation and procedure codes (Operationen- und Prozedurenschlüssel [OPS]; for more details, refer to Table S1 in [Multimedia Appendix 1](#)).

Cohort Selection

Inclusion criteria required patients to be aged 18 years or older at the time of inpatient admission. The observation period was defined from January 1, 2005, to December 31, 2022. For inclusion, each patient also required at least 1 documented *ICD-10* code indicating either a cancer diagnosis or an HIV infection (Table S2 in [Multimedia Appendix 1](#)).

Federated Data Analysis Approach

To analyze sensitive patient data distributed across multiple university hospitals, we used a federated approach; this means individual patient data were not transferred to a central computer to conduct pooled analysis. Instead, analysis scripts were sent to and executed locally at each participating hospital. Only aggregated or anonymized data were subsequently transferred to be jointly analyzed.

Data Preprocessing and Patient Matching

A harmonized input data model (Table S3 in [Multimedia Appendix 1](#)) was developed to enable consistent and standardized analysis across study sites. Uniform value formats and restrictions were defined to ensure that only valid and consistent cases and data entries were included. A case was defined as a single hospitalization for a given patient. Using pseudonymized patient identifiers, individual hospital stays were linked to the same patient, allowing for multiple documented cases per patient during the observation period. Special focus was placed on plausibility checks to correctly classify main cancer and HIV diagnoses as well as therapeutic interventions (Tables S2, S4, and S5 in [Multimedia Appendix 1](#)). The data preprocessing resulted in a ready-for-analysis data model customized for the purpose of our study (Table S6 in [Multimedia Appendix 1](#)).

Included patients were categorized into 1 of 3 groups: cancer with HIV (cancer+/HIV+), cancer without HIV (cancer+/HIV–), and HIV without cancer (cancer–/HIV+) (Tables S2 and S5 in [Multimedia Appendix 1](#)). For patients with cancer, the first recorded cancer diagnosis was designated as the primary cancer diagnosis. For each patient group, frequencies of demographic and cancer-related, case-related, and therapy-related variables were summarized annually.

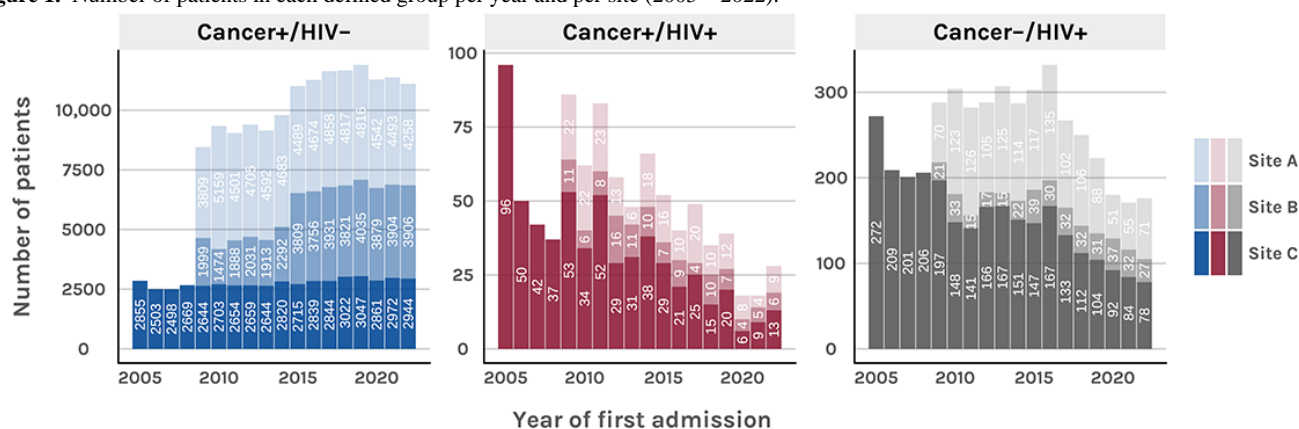
Patients in the cancer+/HIV+ group were matched with patients in the cancer+/HIV– group using 1:1 nearest-neighbor matching

[24], based on age at cancer diagnosis, sex, year of cancer diagnosis, cancer topography group, presence of carcinoma in situ, and comorbidity score at the time of diagnosis (Table S7 in [Multimedia Appendix 1](#)). The comorbidity score was calculated using van Walraven weights for the Elixhauser comorbidity groups [25]. HIV infection and AIDS were assigned to a weight of zero, and cancer diagnoses beyond the primary diagnosis were considered comorbidities. Patient matching was performed to compare therapy-related data, including anticancer therapy frequencies, complications following chemotherapy (eg, transfer to the intensive care unit, dialysis, and mechanical ventilation), and outcomes (derived from the last recorded discharge reason) between the cancer+/HIV+ and cancer+/HIV– groups.

Statistical Analysis

Relative frequencies of individual characteristics were calculated for each group across the entire study period (2005 - 2022). For matched group comparisons, *P* values from the Fisher exact test were calculated. Trend analyses were based on data from 2009 to 2022, the period for which data were available from all 3 sites ([Figure 1](#)). Poisson regression models were used to assess temporal trends in age at cancer diagnosis and cancer-related diagnoses within the cancer+/HIV+ group. When overdispersion was detected, negative binomial regression models were used as an alternative [26].

Figure 1. Number of patients in each defined group per year and per site (2005 - 2022).



For each regression model, the number of patients or diagnoses was used as the dependent variable, with the year of cancer diagnosis as the predictor. In contrast, for therapy-related trends, linear regression models were fitted using proportions as the dependent variable.

To assess travel distances for each patient group, the geographical distance between the centroid of each patient's postal code area at the time of first admission and the hospital location was estimated using the Haversine formula [27], providing an approximation of how far patients in the 3 subgroups traveled to receive care. Additionally, the catchment areas of the individual sites were visualized by mapping the distribution of patients to 3-digit postal code areas for each group ([Figure S1 in Multimedia Appendix 1](#)).

All statistical analyses were conducted using R (version 4.3.2; R Foundation for Statistical Computing) [28]. Nearest-neighbor matching was performed with the MatchIt package [24]. The Fisher exact test as well as linear and Poisson regression models were computed with the stats package [28], while negative binomial regressions were modeled using the MASS package [29]. Travel distances for the patient subgroups were calculated with the geosphere [27] and sf [30] packages.

Ethical Considerations

This retrospective study was conducted after consultation with the responsible ethics committees (research ethics committee, Faculty of Medicine, Goethe University Frankfurt; 274/18; research ethics committee, University of Freiburg; 22-1279-S1-retro). In accordance with national law, no informed consent was obtained since only pseudonymized patient data was used for analysis. Furthermore, the federated data analysis

approach ensured data privacy through aggregation of individual-level data.

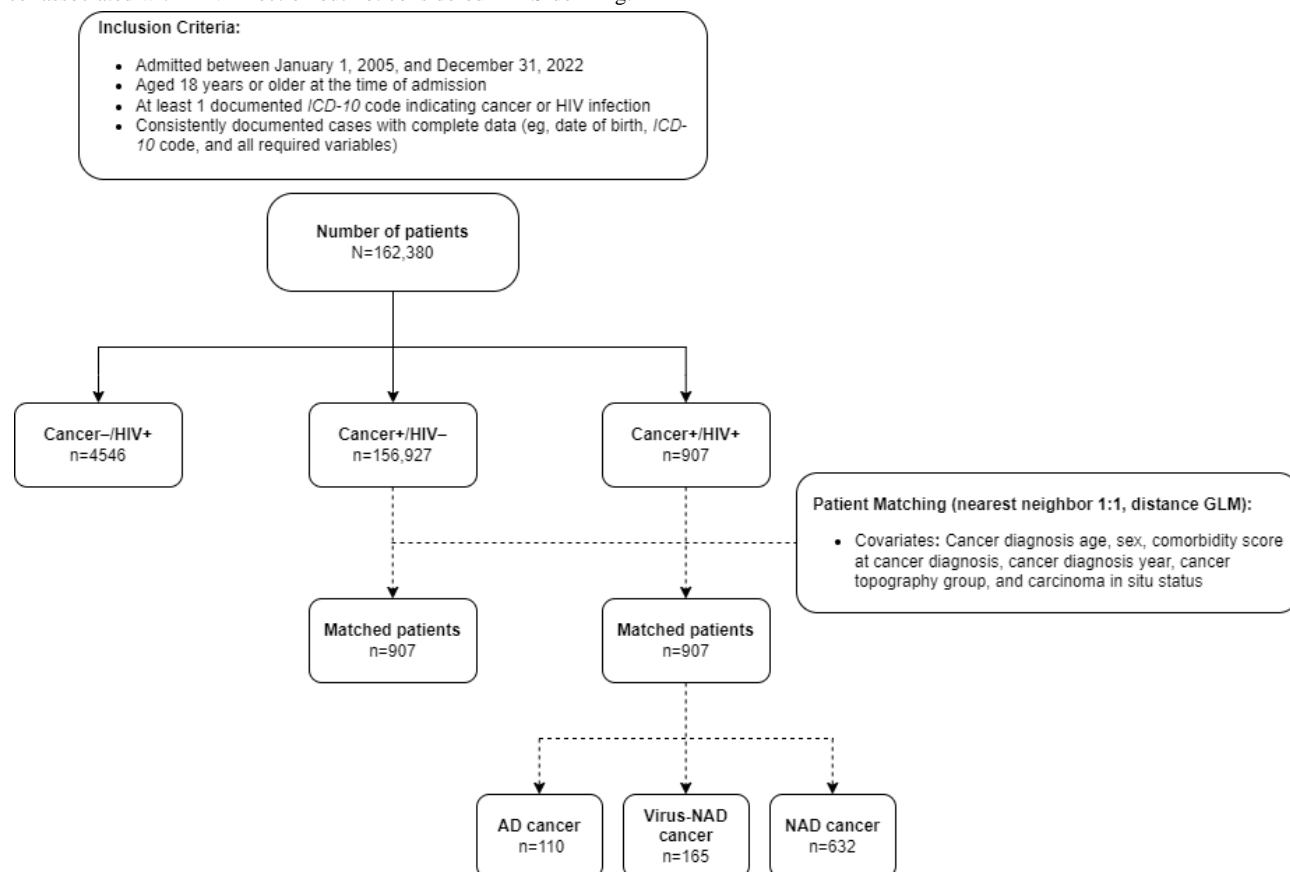
Results

Study Cohort

Between 2005 and 2022, a total of 162,380 eligible inpatients were recorded across all 3 sites and patient groups (Figure 2).

Among these, 907 (0.6%) patients were classified as people living with HIV and cancer (cancer+/HIV+), exhibiting at least 1 *ICD-10* code from both diagnosis groups. A total of 156,927 (96.8%) patients had at least 1 cancer-related *ICD-10* code without an HIV diagnosis (cancer+/HIV–), while 4546 (2.8%) patients were identified as people living with HIV without cancer (cancer–/HIV+). Figure 1 shows the annual distribution of patients in each group by site.

Figure 2. Inclusion, grouping, and matching of patients with the respective number of patients. AD: AIDS-defining; *ICD-10*: *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; GLM: generalized linear model; NAD: non-AIDS-defining; Virus-NAD: cancer associated with HIV infection but not considered AIDS-defining.



Patient demographics and admission-related characteristics for the 3 patient groups are displayed in Table 1. At the time of first admission, people living with HIV and cancer (cancer+/HIV+) were younger than HIV-negative patients with

cancer (cancer+/HIV–), but older than people living with HIV without a cancer diagnosis (cancer–/HIV+). Fewer than one-quarter (214/907, 23.6%) of people living with HIV who have cancer were female.

Table . Demographic and admission-related characteristics of the 3 patient groups (2005-2022).

Characteristics	Cancer+/HIV- (n=156,927), n (%)	Cancer+/HIV+ (n=907), n (%)	Cancer-/HIV+ (n=4546), n (%)
Female patients	72,231 (46.0)	214 (23.6)	1441 (31.7)
Age (years) at first relevant (cancer or HIV associated) admission			
18 - 39	13,373 (8.5)	176 (19.4)	1781 (39.2)
40 - 59	44,984 (28.7)	536 (59.1)	2204 (48.5)
60 - 79	80,335 (51.2)	192 (21.2)	547 (12.0)
>80	18,235 (11.6)	3 (0.3)	14 (0.3)
Admission count per patient			
1	58,444 (37.2)	144 (15.9)	2438 (53.6)
2 - 4	62,840 (40.0)	351 (38.7)	1674 (36.8)
5 - 10	27,877 (17.8)	301 (33.2)	356 (7.8)
More than 10	7766 (4.9)	111 (12.2)	78 (1.7)
Average length of stay per admission (days)			
Up to 7	77,096 (49.1)	307 (33.8)	2204 (48.5)
7 - 14	49,898 (31.8)	298 (32.9)	1191 (26.2)
14 - 30	23,194 (14.8)	233 (25.7)	835 (18.4)
More than 30	6739 (4.3)	69 (7.6)	316 (7.0)

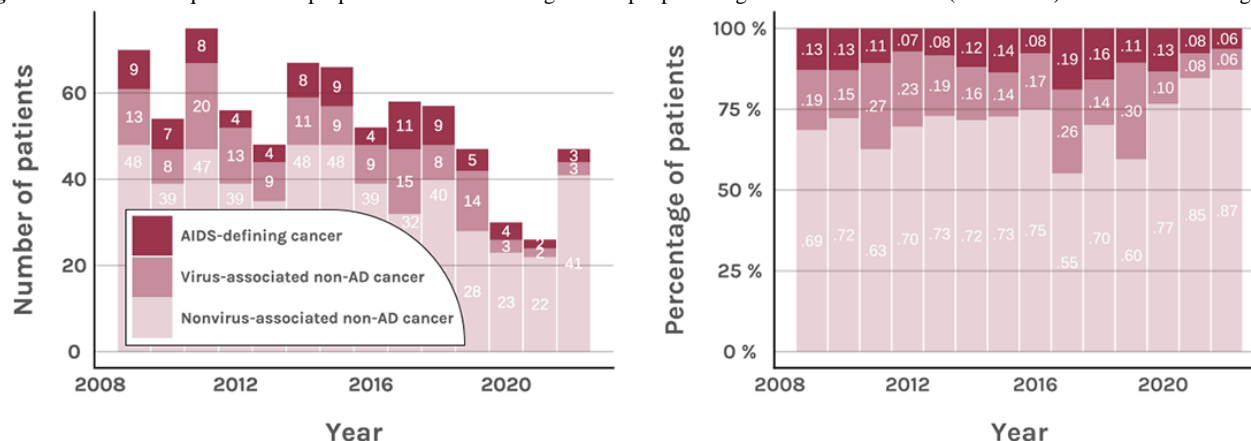
On average, patients in the cancer+/HIV+ group exhibited the highest admission frequencies among the 3 groups: 2 to 4 admissions in 38.7% (351/907), 5 to 10 admissions in 33.2% (301/907), and >10 admissions in 12.2% (111/907) of all observed patient histories.

Cancer Incidence and Cancer Types in People Living With HIV

Among 907 patients with both diagnoses (cancer+/HIV+), the data suggest that 504 (55.6%) patients received HIV and cancer diagnoses simultaneously or within a short time interval. In 332 (36.6%) patients, the HIV diagnosis preceded the cancer diagnosis, whereas in 71 (7.8%) patients, the first recorded

cancer diagnosis was documented before the HIV diagnosis (Table S8 in [Multimedia Appendix 1](#)).

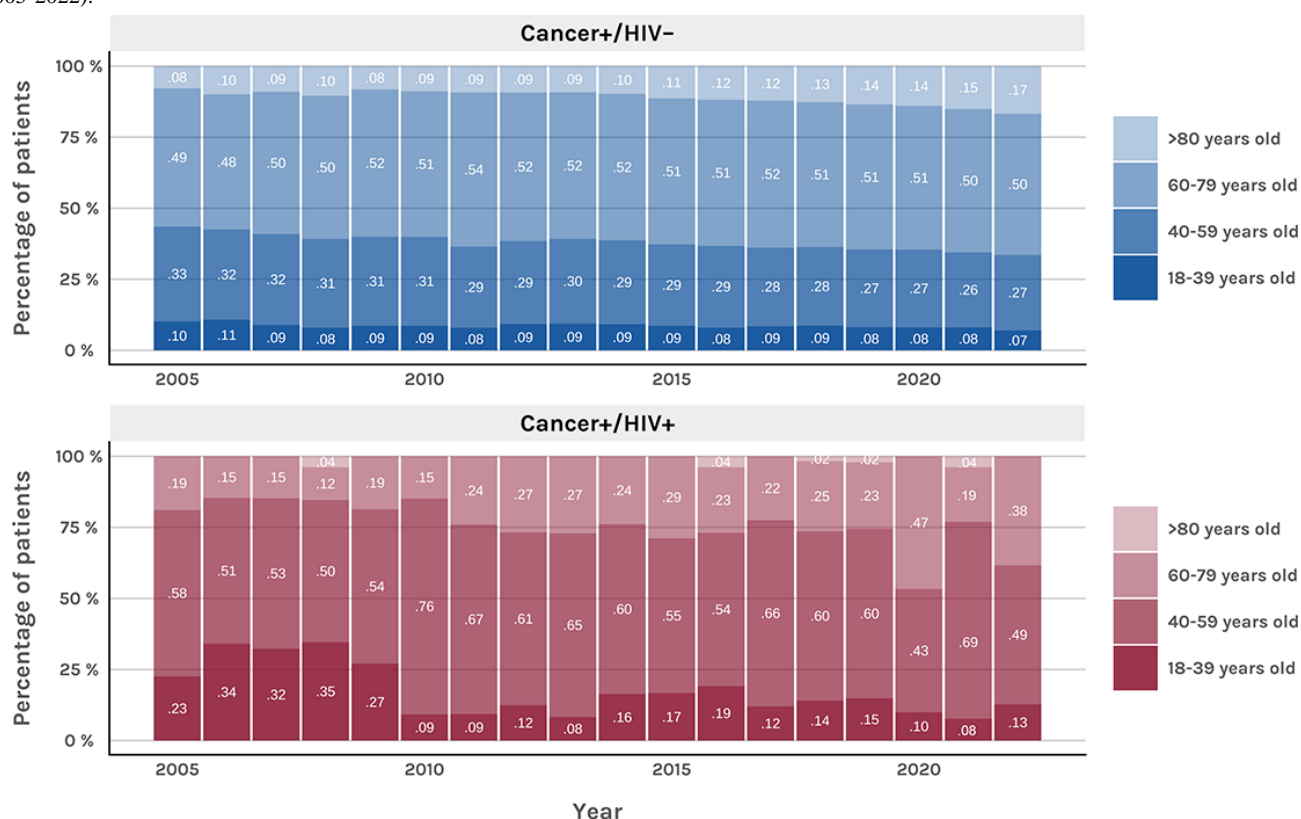
While fluctuating over the observation period, the total number of cancer diagnoses in people living with HIV decreased significantly ($P=.002$). Among the cancer groups (AD, virus-NAD, and non-virus-associated NAD; [Figure 3](#)), the most notable decline was observed in the frequency of virus-associated NAD cancer diagnoses. In total, 110 (12.1%) diagnoses were classified as AD, 165 (18.2%) as virus-associated NAD, and 632 (69.7%) as non-virus-associated NAD. Among specific cancer subtypes, a significant reduction was observed in diagnoses involving lymphoid and hematopoietic tissues ($P=.005$), especially in non-Hodgkin lymphomas ($P=.002$) and nonfollicular lymphomas ($P=.008$).

Figure 3. Absolute frequencies and proportions of cancer categories in people living with HIV and cancer (2009-2022). AD: AIDS defining.

We observed an increase in the age at cancer diagnosis in both people living with HIV and HIV-negative patients with cancer ([Figure 4](#)). Consistent with this finding, regression analysis

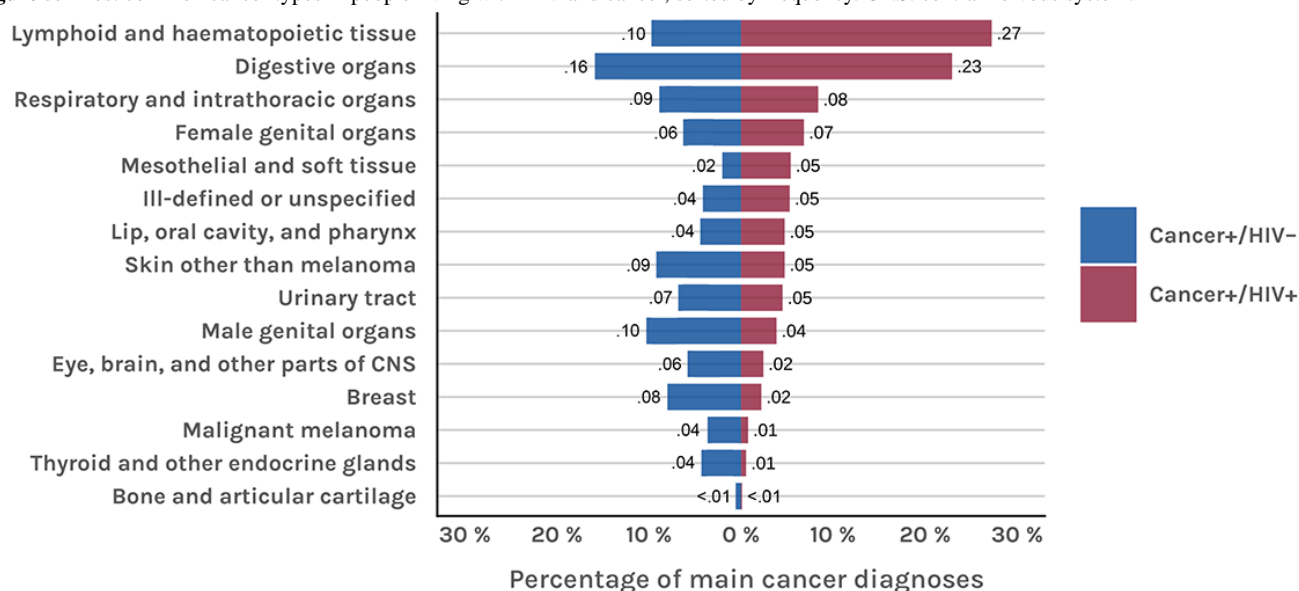
indicated a significant decrease in the proportion of patients younger than 60 years between 2009 and 2022 ($P=.002$).

Figure 4. Proportions of grouped age at cancer diagnosis in people living with HIV and cancer and (unmatched) HIV-negative patients with cancer (2005-2022).



A comparison of cancer topography frequencies between people living with HIV and cancer (cancer+/HIV+) and HIV-negative patients with cancer (cancer+/HIV-) is presented in Figure 5.

Figure 5. Most common cancer types in people living with HIV and cancer, sorted by frequency. CNS: central nervous system.



In the matched comparison between cancer+/HIV+ and cancer+/HIV-, results showed an overall comparable prevalence of metastasis; however, metastasis was present at time of cancer diagnosis more often in the cancer+/HIV- group, whereas patients in the cancer+/HIV+ group seemed to develop metastasis after initial diagnosis more often than their HIV-negative matches (cancer+/HIV+: 128/267, 47.9%; cancer+/HIV-: 97/287, 33.8%; $P < .001$).

Anticancer Treatment of People Living With HIV

People living with HIV and cancer (cancer+/HIV+) received anticancer therapies at rates comparable to those of HIV-negative patients with cancer (cancer+/HIV-) but were more frequently treated with chemotherapy and immunotherapy, whereas patients in the cancer+/HIV- group seemed to have received more stem cell therapy (Table 2). Our results show a significant decrease in the use of chemotherapy in the

cancer+/HIV+ group between 2009 and 2022 ($P=.02$). People living with HIV and cancer presumably showed a higher rate of adverse events following chemotherapy than patients in the control group (cancer+/HIV+: 64/409, 15.6%; cancer+/HIV-: 20/361, 5.5%; $P<.001$). Additionally, the cancer+/HIV+ group

was less frequently discharged home (516/713, 72.4%; $P<.001$) compared with the cancer+/HIV- group (583/714, 81.7%) and showed higher in-hospital mortality (cancer+/HIV+: 135/713, 18.9%; cancer+/HIV-: 90/714, 12.6%; $P=.001$).

Table . Comparison between people living with HIV and cancer and the matched patients with cancer without HIV.

Characteristics	Cancer+/HIV-, n (%)	Cancer+/HIV+, n (%)	<i>P</i> value ^a
Metastasis occurrence (n=907)			
Metastasis documented	287 (31.6)	267 (29.4)	.33
Metastasis at time of cancer diagnosis	190 (66.2)	139 (52.1)	<.001
Metastasis after cancer diagnosis	97 (33.8)	128 (47.9)	<.001
Therapy modalities (n=907)			
Any major therapy documented	631 (69.6)	639 (70.5)	.72
Surgery	285 (31.4)	251 (27.7)	.09
Chemotherapy	361 (39.8)	409 (45.1)	.03
Immunotherapy	90 (9.9)	138 (15.2)	<.001
Radiotherapy	158 (17.4)	169 (18.6)	.54
Stem cell therapy	84 (9.3)	33 (3.6)	<.001
Bone marrow transplant	12 (1.3)	0 (0.0)	.001
Complications after chemotherapy (n=907)			
Chemotherapy documented	361 (39.8)	409 (45.1)	.03
Complication after chemotherapy	20 (5.5)	64 (15.6)	<.001
Average length of stay per admission (days; n=714) ^b			
Up to 7	319 (44.7)	228 (31.9)	<.001
7-14	207 (29.0)	232 (32.5)	.17
14-30	133 (18.6)	198 (27.7)	<.001
More than 30	55 (7.7)	56 (7.8)	>.99
Last documented discharge category ^c			
Home	583 (81.7)	516 (72.4)	<.001
Deceased	90 (12.6)	135 (18.9)	.001
Other hospital	24 (3.4)	28 (3.9)	.58
Rehabilitation or residential care	11 (1.5)	20 (2.8)	.11
Hospice care	6 (0.8)	14 (2.0)	.08

^a*P* values were calculated using the Fisher exact test.

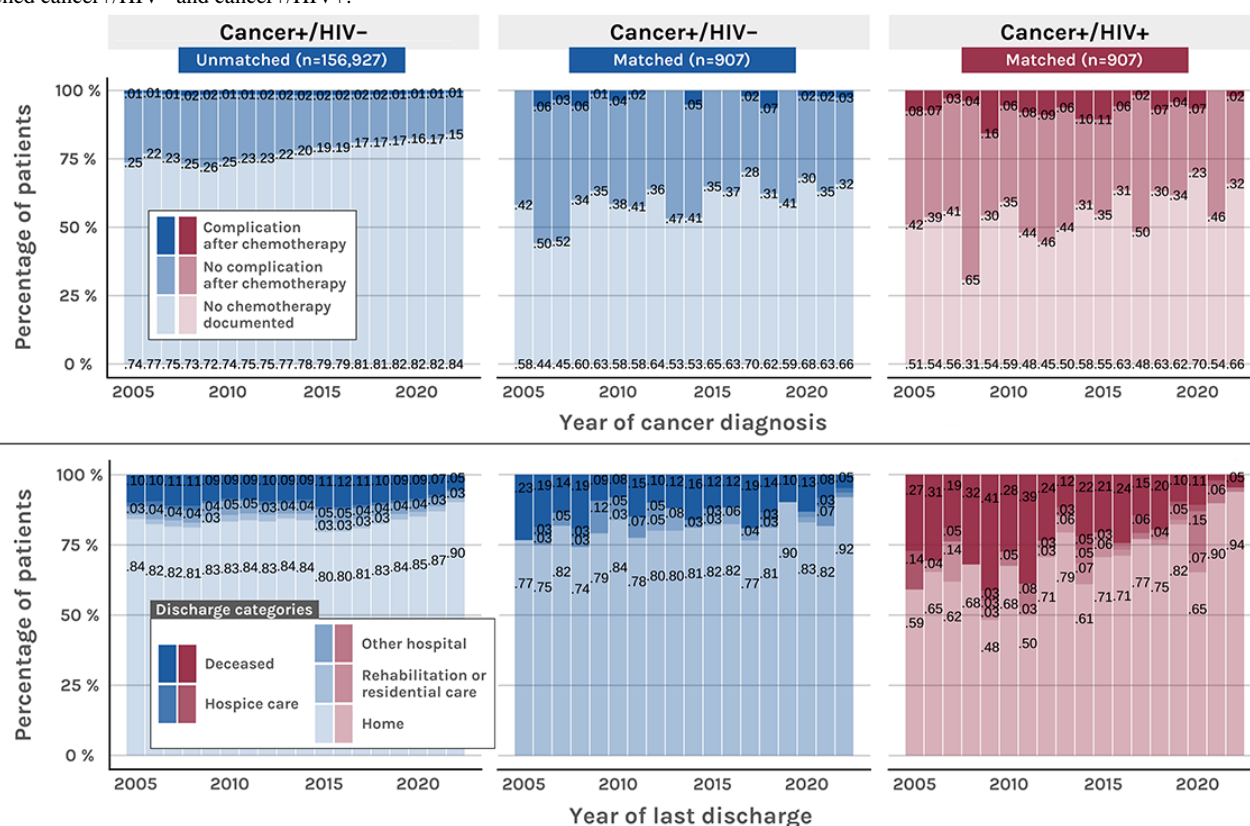
^bData were available from only 2 sites (n=714 for both groups).

^cData were available from only 2 sites (n=714 for cancer+/HIV- and n=713 for cancer+/HIV+).

Figure 6 depicts a comparison of temporal trends in complication rates after chemotherapy and discharge reasons across the total

observed HIV-negative cancer population and the matched cancer groups.

Figure 6. Comparison of complication rates after chemotherapy and last documented discharge categories between unmatched cancer+/HIV– and matched cancer+/HIV– and cancer+/HIV+.



For more detailed results, refer to Tables S7, S8, and S9 in [Multimedia Appendix 1](#). A visual abstract of the study is presented in [Multimedia Appendix 2](#).

Discussion

Principal Findings

In this study, we examined epidemiological as well as treatment- and outcome-related characteristics of inpatients affected by HIV and cancer in 3 selected German university hospitals.

The overall number of cancer diagnoses in the cancer+/HIV+ group decreased between 2009 and 2022, primarily driven by a decline in AD cancers. This reduction was largely attributable to fewer cases of non-Hodgkin lymphomas, particularly within the nonfollicular lymphoma subgroup. Previous studies examining earlier observation periods found that following the introduction of ART, diagnoses of AD cancers, which had predominated in the early HIV era, began to decline, whereas NAD cancers became increasingly common over time [14,15].

The most frequently observed topographical categories in our study are consistent with those reported in previous research [8,10]. Lymphoma was the most frequent cancer diagnosis among people living with HIV, followed by cancers of the lung and bronchi, and the anus and anal canal. Previous studies have shown that, among NAD cancers, lung and anal cancers represent the greatest disease burden in high-income countries [31], which is in line with our findings. No increase over time was observed for typical age-related cancers, such as prostate cancer or malignant melanoma of the skin. However, it remains

unclear whether this reflects stable incidence rates or a shift toward outpatient care.

The results showed an increase in the age at cancer diagnosis among people living with HIV, with fewer cases occurring in younger adults (<60 years). This trend could be explained by the decline in AD cancer diagnoses and is consistent with findings from previous studies [32]. Despite age matching, people living with HIV were diagnosed with cancer at younger ages compared with HIV-negative controls. This observation reflects the need for targeted screening strategies and emphasizes the importance of preventive measures for cancers linked to modifiable risk factors, such as smoking in the case of lung cancer [19,31] and human papillomavirus infection in cervical cancer [33].

Despite similar overall cancer treatment rates, people living with HIV received chemotherapy and immunotherapy more frequently but underwent slightly fewer surgical interventions. This disparity may be explained by differences in cancer type, stage at diagnosis, and tumor operability, as well as HIV-related factors such as immunosuppression, elevated postoperative infection risk, and potential interactions between ART and anesthesia [32,34]. Deviating from previous findings [19], cancers in our observed cohort of people living with HIV were more often diagnosed at premetastatic stages, which contradicts the lower prevalence of surgical therapy in this group.

Our findings highlight the need for improved posttreatment care. The longer and more frequent hospitalizations observed among people living with HIV and cancer require further investigation to determine whether they stem from greater

comorbidity burden or distinct clinical challenges associated with HIV infection.

Chemotherapy use during hospitalization declined among people living with HIV, suggesting a shift toward outpatient care [35,36]. To confirm this hypothesis, further analyses of outpatient care data are necessary. The study also showed a decrease in mortality among people living with HIV over time. Together, these trends suggest that cancer care and outcomes for people living with HIV have improved over the past 2 decades; however, additional research focusing on outpatient care is needed.

Contrary to our results, we initially hypothesized that people living with HIV and cancer would need to travel longer distances to access complex, multidisciplinary care. According to a recent study [37], HIV prevalence in Germany tends to be higher in urban compared with rural areas, which may explain shorter travel distances to urban university hospitals for people living with HIV in our study. Further research is needed to examine rural health care settings and to determine whether local care delivers comparable treatment outcomes or if traveling longer distances offers substantial benefits for specific patient groups like people living with HIV and cancer.

Federated Data Analysis

The use of federated data analysis offered significant advantages, including improved data privacy by keeping sensitive patient information at its original site while enabling collaboration across multiple institutions. Nonetheless, challenges such as data heterogeneity, data inconsistencies, and technical limitations required repeated script adjustments for each center. This led to increased time and staffing costs, as well as minor discrepancies between site-specific results. Specialized federated analysis software such as DataSHIELD (DataSHIELD Research Project) [38] could mitigate these drawbacks but was not available in this study. All script modifications were recorded in a GitLab repository to maintain transparency and traceability.

Limitations

A key limitation of this study is that the results cannot be generalized to the overall care of people living with HIV and

cancer in Germany, as the analysis was based on data from 3 university hospitals representing the tertiary care sector. Further studies are needed to include nonuniversity hospitals and the outpatient sector.

Our study used large retrospective claims data, which the hospitals primarily documented for the purpose of billing services. Although data processing involved thorough plausibility checks, the risk that procedures or diagnoses were missing is high; furthermore, relevant information such as cancer staging and systemic therapy substances or dosage information was not part of the available data.

Sample size variations arose due to technical issues, leading to stratified analyses for the periods 2005 to 2008, 2009 to 2014, and 2015 to 2022 (Tables S6 and S7 in [Multimedia Appendix 1](#)). Other limitations include potential misclassification of disease onset and the inability to associate specific therapies with cancer types in patients with multiple diagnoses, both of which may have influenced the findings.

In our study, we chose to categorize malignancies as AD vs NAD. Different categorizations such as hematological vs solid tumors could have led to more nuanced insights. Further research should critically consider such decisions and potentially include multiple categorizations.

Conclusions

Our study offers valuable insights into the inpatient care of people living with HIV and cancer in Germany, revealing shifts in cancer epidemiology and an aging patient population. Although the incidence of AD cancers has declined, people living with HIV continue to experience longer hospital stays and higher rates of posttreatment complications. Reduced mortality and inpatient chemotherapy use suggest that cancer care and outcomes for people living with HIV have improved over the past 2 decades; however, additional research focusing on outpatient care is needed.

The study also highlights the potential of federated data analysis for multicenter research, while emphasizing the need for standardized data collection to overcome technical challenges and data inconsistencies across sites.

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During the preparation of this work, the authors used ChatGPT from OpenAI for proofreading. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Data Availability

The datasets generated or analyzed during this study are not publicly available. We conducted a federated approach to data analysis, which means all individual-level patient data remain with the participating sites and are not publicly available due to health data privacy regulations. The aggregated data returned from site-specific analyses can be considered sufficiently anonymized.

Due to unclear use and access policies at the participating hospitals, these datasets are not made publicly available at this time; however, they can be provided by the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: BR, DM, JJV, MS, SA

Data curation: AH, AL, AP, BR, FPA, JW, MH, SA

Formal analysis: BB, BR, DM, LS, SA

Funding acquisition: JJV

Investigation: BB, BR, DM, LS, SA

Methodology: BB, BR, DM, LS, SA

Project administration: BR, DM, MM, SA

Resources: FA, JJV, JW

Software: BR

Supervision: CS, DM, JJV, JR, JW, MM, US

Visualization: BB, BR, LS, SA

Writing – original draft: BB, BR, DM, IS, LS, SA

Writing – review and editing: AH, AL, AP, BB, BR, CS, DM, FA, FPA, IS, JJV, JR, JW, LS, MH, MM, MS, SA, US

Conflicts of Interest

SA owns stock in HAVN Life Sciences, Heidelberg Pharma AG, and Pfizer. LS has received travel compensation from IQVIA. CS has received honorarium fees from the following pharmaceutical companies for scientific lectures, presentations, manuscript writing, educational events, or participation in scientific advisory boards: Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme (MSD), Shionogi, Thera-Technologies, and ViiV Healthcare. Furthermore, the pharmaceutical companies AbbVie, Gilead Sciences, and Janssen have covered his travel, accommodation, and registration fees for scientific conference participation. DM has received speaker honoraria from the Free University Berlin and travel compensation from IQVIA. JJV has received personal fees from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, German Centre for Infection Research (DZIF), University Hospital Freiburg/Congress and Communication, Academy for Infectious Medicine, University Manchester, German Society for Infectious Diseases (DGI), Ärztekammer Nordrhein, University Hospital Aachen, Back Bay Strategies, German Society for Internal Medicine (DGIM), Shionogi, Molecular Health, Netzwerk Universitätsmedizin, Janssen, NordForsk, Biontech, and APOGEPHA, and has received grants from Merck/MSD, Gilead, Pfizer, Astellas Pharma, Basilea, German Centre for Infection Research (DZIF), German Federal Ministry of Education and Research (BMBF), Deutsches Zentrum für Luft- und Raumfahrt (DLR), University of Bristol, Rigshospitalet Copenhagen, and Network University Medicine. All other authors declare no other conflicts of interest.

Multimedia Appendix 1

Supplementary tables containing structural and semantic metadata as well as detailed study results.

[DOC File, 862 KB - [publichealth_v12i1e81092_app1.doc](#)]

Multimedia Appendix 2

Visual abstract.

[PNG File, 338 KB - [publichealth_v12i1e81092_app2.png](#)]

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Abbreviations

AD: AIDS-defining

ART: antiretroviral therapy

ICD-10: *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*

KHEntgG: German Hospital Fees Act (German: Krankenhausentgeltgesetz)

NAD: non-AIDS-defining

OPS: operation and procedure classification system (German: Operationen- und Prozedurenschlüssel)

virus-NAD: cancer associated with HIV infection but not considered AIDS-defining

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Original Paper

Profiles of Willingness to Use Pre-Exposure Prophylaxis Modalities and an HIV Vaccine Among Sexual and Gender Minority Individuals in Brazil, Mexico, and Peru: Cross-Sectional Online Survey

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Abstract

Background: HIV incidence continues to disproportionately affect sexual and gender minority (SGM) individuals in Latin America. Pre-exposure prophylaxis (PrEP), including long-acting products, urgently need scaling up in the region. Understanding PrEP modality preferences can help design effective implementation.

Objective: This study examined willingness to use different PrEP modalities and an HIV vaccine among SGM individuals aged 18 years or older from Brazil, Mexico, and Peru and factors associated with willingness to use 4 PrEP modalities.

Methods: We conducted a cross-sectional online survey in 2021; participants were recruited via apps (Grindr and Hornet) and social media (Facebook, Instagram, and WhatsApp). We used multivariate Poisson regression with robust variance ($\alpha=.05$) to estimate prevalence ratios, identifying differences in willingness to use daily oral, event-driven oral, monthly oral, and bimonthly injectable PrEP. Models were constructed for each PrEP modality and adjusted for age, country, race, education, income, HIV risk score, HIV testing, and HIV risk perception. Variables were retained in the final adjusted models regardless of statistical significance.

Results: Among 16,951 respondents, 10,385 (61.3%) were Brazilian, 4996 (29.5%) Mexican, and 1570 (9.3%) Peruvian. Median age was 32 (IQR 26-39) years. Among the total respondents, 12,621 (74.4%) were willing to use monthly oral PrEP; 11,153 (65.8%) daily oral PrEP; 10,212 (60.2%) bimonthly injectable PrEP; and 14,044 (82.8%) an HIV vaccine. Only 6442 (38%) were willing to use event-driven oral PrEP. In Brazil, 6082 (66.8%) were willing to use daily oral, 3162 (36.1%) event-driven, 7640 (74.9%) monthly oral, and 6450 (63.3%) injectable PrEP; in Mexico, 3242 (67.8%) daily oral, 1958 (41%) event-driven, 3728 (76.5%) monthly oral, and 2805 (57.5%) injectable PrEP; in Peru, 799 (53.1%) daily oral, 584 (39.9%) event-driven, 830 (62.5%) monthly oral, and 610 (45.9%) injectable PrEP. In multivariable models, willingness to use each of the 4 PrEP modalities was positively associated with high self-perceived HIV risk (adjusted prevalence ratios [aPRs] 1.10-1.25) and higher HIV Incidence

Risk Index scores (aPRs 1.08-1.22). Having lower education was associated with lower willingness for monthly oral and bimonthly injectable PrEP (aPR=0.93, 95% CI 0.89-0.97 and aPR=0.94, 95% CI 0.90-0.99, respectively). Never having been tested for HIV and testing more than 6 months ago were associated with lower willingness for daily oral PrEP (aPR=0.89, 95% CI 0.83-0.95 and aPR=0.95, 95% CI 0.91-0.99, respectively) and bimonthly injectable PrEP (aPR=0.80, 95% CI 0.74-0.86 and aPR=0.90, 95% CI 0.86-0.94, respectively).

Conclusions: Our results suggest a strong preference for long-acting formulations, including monthly oral and bimonthly injectable, among SGM individuals in Latin America. Further research is needed to address gaps in the understanding of prevention modalities. As additional PrEP modalities are included in HIV prevention programs, the development of accessible tools and community-based strategies will be essential to support informed PrEP choices and ensure equitable implementation across the region.

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KEYWORDS

HIV prevention; vaccine; men who have sex with men; transgender women; cabotegravir; lenacapavir

Introduction

In 2024, an estimated 2.5 million people were living with HIV in Latin America [1]. Latin America is one of the few regions where HIV incidence has risen, with a 13% increase from 2010 to 2024 [2]. The incidence of HIV remains disproportionately higher among sexual and gender minority (SGM) individuals, who accounted for 66% of cases in Latin America in 2022. HIV prevalence among gay, bisexual, and other men who have sex with men (MSM) and transgender persons aged 15 to 49 years (2019-2023) was 10% and 9.5%, respectively [3]. Additionally, a study conducted in Brazil and Peru found high annualized HIV incidence among SGM individuals not using pre-exposure prophylaxis (PrEP; 3.9%, 95% CI 2.9-4.9), with higher incidence among participants from Peru, those aged 18 to 30 years, and those reporting lower incomes [4].

Currently, the World Health Organization (WHO) recommends daily or on-demand oral emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg (FTC/TDF), long-acting injectable cabotegravir (CAB-LA), long-acting injectable lenacapavir (LEN), and the dapivirine vaginal ring as effective HIV PrEP modalities [5]. As of July 2024, a total of 152 countries worldwide had adopted WHO recommendations on PrEP into their national guidelines, and 12 countries had adopted policies for CAB-LA [6]. In Latin America, oral PrEP was implemented as part of public policy in most countries, with Brazil initiating the provision of PrEP through the public health system (Sistema Único de Saúde [SUS]) in 2017, Mexico in 2021, and Peru in 2023 [7-9]. In 2024, a total of 286,862 persons were using PrEP in the region, with Brazil accounting for 58% of them [10]. In addition to regional disparities, more is needed to reach those who are at higher vulnerability to HIV. During the ImPrEP study, the largest PrEP implementation study in Latin America, younger participants, those who were Black or of mixed race (*pardo* or *mestizo*), those with lower educational attainment, and transgender women had higher HIV incidence and increased odds of discontinuing PrEP, lower adherence, and reduced persistence [11-13]. Similarly, PrEP uptake and persistence are worse among younger, Indigenous, and Black Brazilians according to Brazilian national data [14]. In response to implementation concerns with existing oral PrEP regimens,

long-acting products need to be offered and accessible to those who need them most.

In 2021, CAB-LA was shown to be a highly effective alternative to daily oral FTC/TDF for HIV prevention among cisgender women, cisgender MSM, and transgender women [15,16]. Recently, subcutaneous LEN, administered twice yearly, was superior to FTC/TDF among cisgender women and SGM individuals in the phase 3 PURPOSE 1 and PURPOSE 2 clinical trials [17,18]. The frequency of administration of CAB-LA and LEN, bimonthly or biannually, respectively, is attractive for people who have difficulty adhering to an oral pill regimen. However, barriers to implementing injectable PrEP must be considered, including cost-effectiveness, staffing and other implementation constraints, acceptability and preferences among potential users, factors influencing timely attendance at injection visits, the prolonged subtherapeutic pharmacokinetic effect, and the feasibility of alternative administration sites [19,20]. While CAB-LA and LEN are not widely available in Latin America, Brazil is conducting the ImPrEP CAB Brasil and the ImPrEP LEN Brasil studies to evaluate the implementation of CAB-LA and LEN for SGM individuals aged 18 to 30 years in the public health system [21-23].

Different PrEP technologies, such as monthly oral, infusion of monoclonal antibodies, topical microbicides, and other long-acting products, are being developed [20,24]. For instance, subdermal implants have several advantages, such as easy removal; biodegradability; minimal health care system interaction; lower daily dosage; and more consistent, predictable drug release [20,25]. Islatravir delivered through a subdermal implant demonstrated promise as a potentially effective and well-tolerated approach for HIV prevention [26].

PrEP urgently needs to be scaled-up among SGM individuals in Latin America, including the provision of long-acting products, such as CAB-LA and LEN [3]. In this sense, understanding the willingness to use PrEP modalities could provide information for future adaptations or implementation of HIV prevention policies. We aimed to describe willingness to use different PrEP modalities and an HIV vaccine among SGM individuals in Brazil, Mexico, and Peru. We also assessed factors associated with willingness to use 4 PrEP modalities

(daily oral, event-driven oral, monthly oral, and bimonthly injectable).

Methods

Study Design

A cross-sectional online survey was conducted between April and August 2021 among individuals who self-identified as SGM individuals and aged 18 years or older from Brazil, Peru, and Mexico. Respondents were recruited using a convenience sampling approach through advertisements on dating apps, such as Grindr (3236/16,943, 19.1%) and Hornet (6400/16,943, 37.8%), and social media platforms, such as Facebook (3374/16,943, 19.9%), Instagram (2994/16,943, 17.7%), and WhatsApp (431/16,943, 2.5%), as well as other online sources (508/16,943, 3%). Each advertisement included a link to the survey website, where participants were provided with detailed information about the study aims, procedures, and confidentiality measures. Those who provided their electronic informed consent were able to access and complete a computer-based questionnaire that included information on sociodemographics, behavior, HIV testing, and prevention. We excluded participants who reported living with HIV.

Anonymity was ensured by not collecting any personally identifiable information. The survey platform prevented multiple submissions from the same device using browser cookies and IP restrictions. Participants were permitted to select only 1 response option per question to ensure data consistency and avoid multiple selections.

Variables

Outcomes

Participants were asked to report their willingness to use each of the PrEP modalities using the following question: "Considering that all PrEP modalities are available, how likely would you be to use them?" with answers recorded using a 4-point Likert scale: very unlikely, unlikely, likely, and very likely. "Very likely" answers were classified as "willing," following the definition from previous studies [27,28]. We evaluated willingness to use the following PrEP modalities: daily oral, event-driven oral, monthly oral, bimonthly injectable in the gluteal muscle, daily topical, event-driven topical, patch, implant, infusion of monoclonal antibodies, and subcutaneous monoclonal antibodies. We also inquired whether participants were willing to use a vaccine to prevent HIV. Only factors associated with 4 PrEP modalities (daily oral, event-driven oral, monthly oral, and bimonthly injectable) were reported, as these were currently available, implemented, or under investigation in Latin America when the survey was launched.

Sociodemographics

For gender identity, participants answered the question "What gender do you currently identify with?" with the following possible options: cisgender man, cisgender woman, transgender woman, transgender man, queer or nonbinary, and other. Age was categorized as 18 to 24, 25 to 30, and more than 30 years. Ethnicity or race was classified as White, mixed race (*pardo* or *mestizo*), and Black, Asian, Indigenous, or other. Level of

education was dichotomized as complete secondary education or less (lower education) and more than secondary education (higher education). Regarding individual monthly income, we considered the minimum wage per country in 2021 (Brazil: US \$213 per month, Mexico: US \$215 per month, and Peru: US \$257 per month) and dichotomized as minimum wage or less (lower income) and more than minimum wage (higher income).

Perceived Risk of HIV Acquisition, HIV Incidence Risk Index, and HIV Testing

The perceived risk for HIV was evaluated using the question "Considering your current sexual practices, in your opinion, what is your risk of acquiring HIV in the next 12 months?" which was recategorized as low (none, low, or moderate) and high (high, or certainty of infection). The HIV Incidence Risk Index (HIRI) was constructed by combining sexual behavior and substance use variables, as described previously [29]. Scores equal to or greater than 10 were considered as "engaging in high HIV sexual exposure." Regarding HIV testing, participants answered the question "When was the last time you took an HIV test?" which was categorized as never, 6 months or less, and more than 6 months.

Ethical Considerations

Ethics approval for the study was obtained from the respective ethical review boards in each country. In Brazil, the study was approved by the Institutional Review Board of Instituto Nacional de Infectologia Evandro Chagas-FIOCRUZ (CAAE 82021918.0.0000.5262); in Mexico, by the Research Ethics Committee of the National Institute of Psychiatry Ramón de la Fuente Muñiz (CEI/C/038/2018); and in Peru, by the Ethical Committee for Research with Human Subjects at Universidad Peruana Cayetano Heredia (101460). All participants signed electronic informed consent form before initiating the study. No personally identifiable information was collected, except IP addresses, which were used exclusively for quality control purposes (duplicate entry prevention) and were not linked to survey responses. Data were stored on secure servers and analyzed in deidentified form. We provided no compensation to participants.

Statistical Analysis

Statistical analyses were conducted using Stata (version 18.0; StataCorp). Frequencies and percentages of sociodemographic and behavior characteristics and HIV testing were compared by country (Brazil, Mexico, and Peru) using the χ^2 test. We also described these variables according to the willingness to use 4 PrEP modalities (daily oral, event-driven oral, monthly oral, and bimonthly injectable) for each country. Descriptive analyses were based on observed data.

Missing data were assessed using Little's MCAR (missing completely at random) test, which indicated that the data were not missing completely at random ($\chi^2_{121}=5239$; $P<.001$). Therefore, missing values in outcome and covariate variables were handled using multiple imputation by chained equations under the assumption of missing at random. Binary variables were imputed using logistic regression models and multinomial variables using multinomial logistic regression models. A total

of 20 imputed datasets were generated, and parameter estimates were combined using the Rubin rules.

We conducted multivariate Poisson regression models with robust variance to estimate adjusted prevalence ratios (aPRs) and 95% CIs for willingness to use each PrEP modality (daily oral, event-driven oral, monthly oral, and bimonthly injectable). Models were adjusted for covariates selected a priori (age, country, race, education, income, HIRI score, HIV testing, and HIV risk perception). Variables were retained in the final adjusted models regardless of statistical significance.

Results

A total of 35,541 individuals accessed the online questionnaire, of whom 7952 (22.4%) were ineligible for the following reasons: 1903 (23.9%) did not provide informed consent, 1523 (19.2%) had participated previously, 686 (8.6%) self-identified as cisgender women, 62 (0.8%) were younger than 18 years, 895 (11.3%) were men who did not self-identify as SGM individuals, and 2883 (36.2%) reported living with HIV (Figure 1). Among 27,589 eligible individuals, 10,638 (38.6%) were excluded for not answering questions about PrEP modalities. Overall, 16,951 (61.4%) respondents were included in this analysis; 10,385 (61.3%) Brazilians, 4996 (29.5%) Mexicans, and 1570 (9.3%) Peruvians. Among these, 16,183 (95.5%) self-identified as cisgender men, 99 (0.6%) as transgender women, 60 (0.4%) as transgender men, 423 (2.5%) as nonbinary or queer persons, and 165 (1%) as other. Median age was 32 (IQR 26-39) years; almost half of the respondents (7483/16,285, 46%) self-declared mixed race, and more than three-quarters (12,627/16,509, 76.5%) received more than 1 minimum wage per month (higher income). In addition, 10,379 (61.2%) respondents were identified as having high HIV sexual exposure according to the HIRI, 1961 (11.6%) had never been tested for HIV, and 6688 (39.6%) had their last HIV test more than 6 months ago.

Study population characteristics were compared by country (Table 1). More Peruvians (164/1570, 10.5%) self-identified as transgender or nonbinary persons compared with Brazilians (224/10,384, 2.2%) and Mexicans (379/4996, 7.6%) and were aged 18 to 24 years (Peru: 716/1570, 45.6%; Mexico: 1057/4996, 21.2%; Brazil: 1304/10,385, 12.6%). Regarding race, most Brazilians (5873/10,385, 56.5%) self-defined as White, while most Mexicans (3249/4330, 75%) and Peruvians (1109/1570, 70.6%) self-identified as mixed race. Most individuals in Brazil and Mexico received more than minimum wage monthly (8179/10,385, 78.8% and 3738/4729, 79%, respectively) compared with Peru (710/1395, 50.9%). In addition, more Peruvians (180/1194, 15.1%) perceived themselves to be at high risk of acquiring HIV compared with Brazilians (964/10,385, 9.3%) and Mexicans (439/4996, 8.8%); conversely, more Brazilians (6676/10,385, 64.3%) had high HIV sexual exposure according to HIRI scale compared with Mexicans (2965/4996, 59.4%) and Peruvians (738/1570, 47%). Additionally, a higher proportion of Peruvians (328/1550, 21.2%) had never been tested for HIV compared with Mexicans (757/4972, 15.2%) and Brazilians (876/10,385, 8.4%).

Regarding PrEP modalities, most of the respondents were willing to use monthly oral PrEP (12,621/16,951, 74.4%), daily

oral PrEP (11,153/16,951, 65.8%), and bimonthly injectable PrEP (10,212/16,951, 60.2%), while only 38% (6442/16,951) were willing to use event-driven PrEP. Other PrEP modalities received lower willingness levels: 25.1% (4109/16,398) for daily topical, 25.6% (4202/16,398) for event-driven topical, 31.7% (5204/16,399) for a patch, 35.9% (5885/16,398) for an implant, 28.4% (4660/16,397) for infusion monoclonal antibodies, and 31.3% (5139/16,398) for subcutaneous monoclonal antibodies. Additionally, 82.8% (13,579/16,398) of participants reported willingness to use an HIV vaccine. Figure 2 shows the percentages of willingness to use these less common PrEP modalities and an HIV vaccine in each country.

We also found country-level differences in the willingness to use at least one of the 4 PrEP modalities evaluated (daily oral, event-driven oral, monthly oral, and bimonthly injectable). Mexicans reported the highest overall willingness (4449/4903, 90.7%), followed by Brazilians (8965/10,034, 89.4%) and Peruvians (1195/1423, 84%). Within each country, there were substantial differences in the willingness to use each of these 4 PrEP modalities. Peruvians were less willing to use daily oral (799/1506, 53.1%), monthly oral (830/1328, 62.5%), and bimonthly injectable (610/1328, 45.9%) compared with Brazilians (daily oral: 6082/9106, 66.8%; monthly oral: 7640/10,197, 74.9%; bimonthly injectable: 6450/10,197, 63.3%) and Mexicans (daily oral: 3242/4784, 67.8%; monthly oral: 3728/4875, 76.5%; bimonthly injectable: 2805/4875, 57.5%). Willingness to use event-driven PrEP was lower for Brazilians (3162/8761, 36.1%).

In all 3 countries, cisgender MSM were more willing to use monthly oral PrEP compared with transgender or nonbinary participants (Table 2). In Brazil (4376/5780, 75.7%) and Mexico (619/788, 78.6%), White individuals were more willing to use monthly oral PrEP, while in Peru (610/951, 64.1%), mixed-race individuals showed higher willingness. In Mexico (469/788, 59.5%) and Peru (80/168, 47.6%), White participants were more willing to use bimonthly injectable PrEP, whereas in Brazil (884/6450, 64.7%), Black, Asian, or Indigenous individuals showed greater willingness. In Brazil and Mexico, daily oral PrEP was more preferred among individuals with lower education (2165/6082, 68.7% and 983/1429, 68.8%, respectively) and lower income (1368/2032, 67.3% and 664/969, 68.5%), while in Peru, it was more preferred among participants with higher education (519/958, 54.2%) and income (378/671, 56.3%). In Brazil and Mexico, participants who had an HIV test within the past 6 months showed greater willingness to use monthly oral PrEP (4148/5462, 75.9% and 1576/2010, 78.4%, respectively), while in Peru, this modality was more preferred by people who had an HIV test more than 6 months ago (313/491, 63.8%).

In the multivariable analysis (Table 3), willingness to use each of the 4 evaluated PrEP modalities was positively associated with high HIV self-perceived risk and higher HIRI scores. Peruvian respondents showed lower willingness to use 3 modalities (daily oral: aPR=0.81, 95% CI 0.75-0.87; monthly oral: aPR=0.84, 95% CI 0.78-0.91; and injectable: aPR=0.76, 95% CI 0.69-0.83). Mexican and Peruvian respondents reported higher willingness to use event-driven oral PrEP (aPR=1.14, 95% CI 1.08-1.22 and aPR=1.11, 95% CI 1.01-1.22,

respectively) compared with Brazilian respondents. Having secondary education or less was associated with lower willingness to use monthly oral and bimonthly injectable PrEP (aPR=0.93, 95% CI 0.89-0.97 and aPR=0.94, 95% CI 0.90-0.99, respectively). Having a minimum wage or less was associated with lower willingness for bimonthly injectable PrEP (aPR=0.95,

95% CI 0.90-1.00). Never having been tested for HIV and testing for more than 6 months ago were associated with lower willingness to use daily oral PrEP (aPR=0.89, 95% CI 0.83-0.95 and aPR=0.95, 95% CI 0.91-0.99, respectively) and bimonthly injectable PrEP (aPR=0.80, 95% CI 0.74-0.86 and aPR=0.90, 95% CI 0.86-0.94, respectively).

Figure 1. Study flowchart. PrEP: pre-exposure prophylaxis.

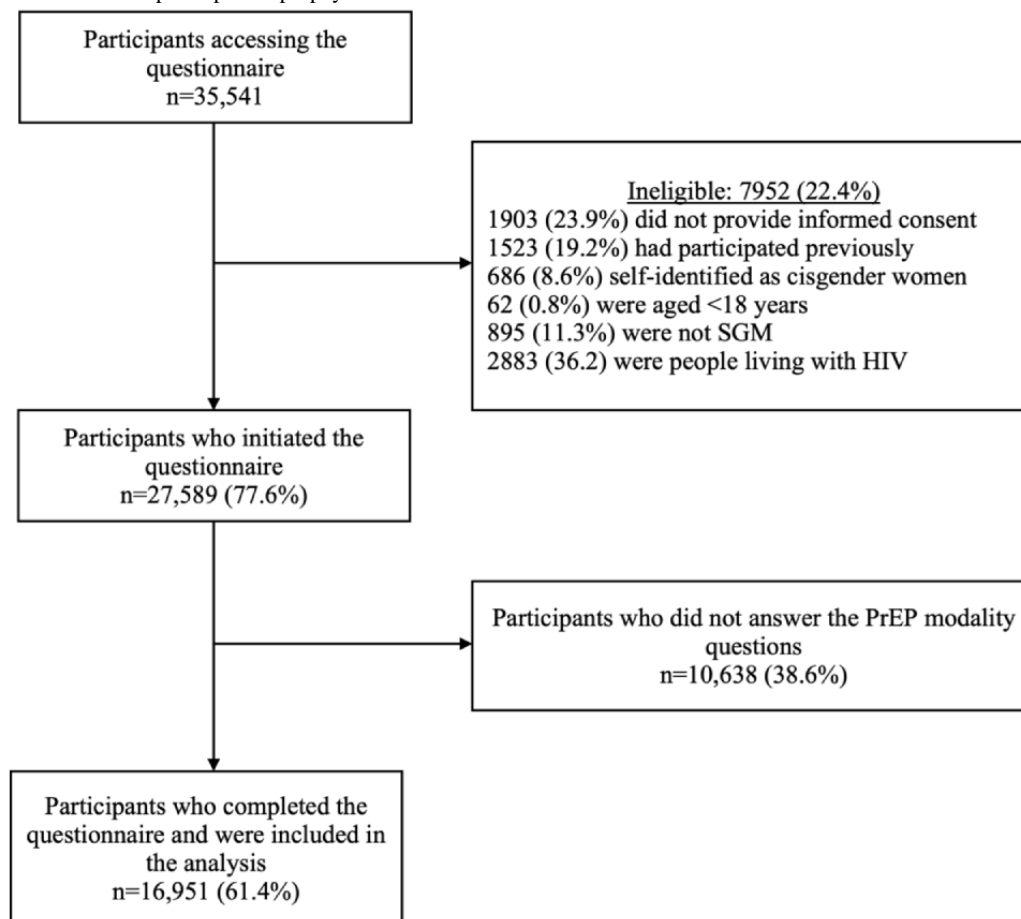


Table 1. Characteristics of an online sample of sexual and gender minority individuals (N=16,951) in Brazil (n=10,385, 61.3%), Mexico (n=4996, 29.5%), and Peru (n=1570, 9.3%) in 2021.

Characteristics	Total (n=16,951), n (%)	Brazil (n=10,385), n (%)	Mexico (n=4996), n (%)	Peru (n=1570), n (%)	P value
Gender identity (n=16,950)					<.001
Cisgender men	16,183 (95.5)	10,160 (97.8)	4617 (92.4)	1406 (89.5)	
Transgender or nonbinary persons	767 (4.5)	224 (2.2)	379 (7.6)	164 (10.5)	
Age (years; n=16,951)					<.001
18-24	3077 (18.1)	1304 (12.6)	1057 (21.2)	716 (45.6)	
25-30	4604 (27.2)	2712 (26.1)	1456 (29.1)	436 (27.8)	
>30	9270 (54.7)	6369 (61.3)	2483 (49.7)	418 (26.6)	
Race (n=16,285)					<.001
White	6879 (42.2)	5873 (56.5)	808 (18.7)	198 (12.6)	
Mixed race (<i>pardo</i> or <i>mestizo</i>)	7483 (46)	3125 (30.1)	3249 (75)	1109 (70.6)	
Black, Asian, or Indigenous	1923 (11.8)	1387 (13.4)	273 (6.3)	263 (16.8)	
Education level (n=16,951)					<.001
Less than or equal to secondary education	5455 (32.2)	3419 (32.9)	1474 (29.5)	562 (35.8)	
More than secondary education	11,496 (67.8)	6966 (67.1)	3522 (70.5)	1008 (64.2)	
Monthly income (n=16,509)					<.001
Less than or equal to 1 minimum wage	3882 (23.5)	2206 (21.2)	991 (21)	685 (49.1)	
More than 1 minimum wage	12,627 (76.5)	8179 (78.8)	3738 (79)	710 (50.9)	
HIV risk perception (n=16,575)					<.001
None, low, or moderate	14,992 (90.5)	9421 (90.7)	4557 (91.2)	1014 (84.9)	
High	1583 (9.5)	964 (9.3)	439 (8.8)	180 (15.1)	
HIRI^a (n=16,951)					<.001
Low risk	6572 (38.8)	3709 (35.7)	2031 (40.6)	832 (53)	
High risk	10,379 (61.2)	6676 (64.3)	2965 (59.4)	738 (47)	
Last HIV test (n=16,907)					<.001
Never	1961 (11.6)	876 (8.4)	757 (15.2)	328 (21.1)	
Less than or equal to 6 months	8258 (48.8)	5543 (53.4)	2055 (41.3)	660 (42.6)	
More than 6 months	6688 (39.6)	3966 (38.2)	2160 (43.4)	562 (36.3)	

^aHIRI: HIV Incidence Risk Index.

Figure 2. Willingness to use pre-exposure prophylaxis (PrEP) modalities and an HIV vaccine among sexual and gender minority individuals in Brazil, Mexico, and Peru.

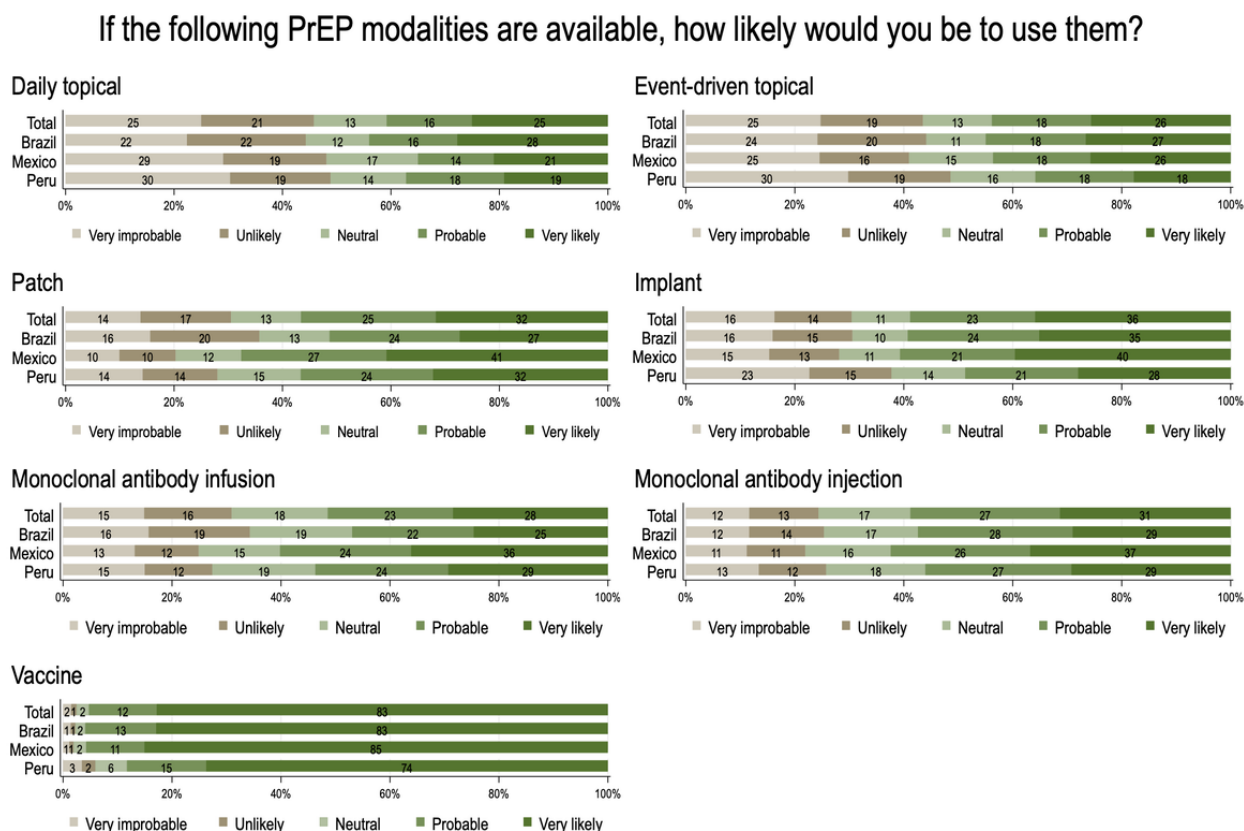


Table 2. Characteristics of sexual and gender minority individuals willing to use each pre-exposure prophylaxis (PrEP) modality by country, 2021 (N=16,951).

Characteristics	Brazil (PrEP modality)				Mexico (PrEP modality)				Peru (PrEP modality)			
	Daily, n (%)	ED ^a , n (%)	Month-ly, n (%)	Inject n, (%)	Daily, n (%)	ED, n (%)	Month-ly, n (%)	Inject, (%)	Daily, n (%)	ED, n (%)	Month-ly, n (%)	Inject, n (%)
Willingness to use												
Yes	6082 (66.8)	3162 (36.1)	7640 (74.9)	6450 (63.3)	3242 (67.8)	1958 (41)	3728 (76.5)	2805 (57.5)	799 (53.1)	584 (39.9)	830 (62.5)	610 (45.9)
Gender identity												
Cisgender men	5953 (66.9)	3088 (36.1)	7477 (75)	6316 (63.3)	2995 (67.8)	1812 (41.1)	3473 (77.2)	2603 (57.8)	723 (53.6)	531 (40.1)	761 (63.3)	557 (46.3)
Transgender or nonbinary	129 (62.6)	74 (37.2)	163 (73.8)	134 (60.6)	247 (66.9)	146 (40)	255 (68)	202 (53.9)	76 (48.1)	53 (37.6)	69 (55.2)	53 (42.4)
Age (years)												
18-24	817 (66.8)	401 (34.1)	947 (74)	763 (59.6)	724 (70.2)	431 (43.3)	783 (76.2)	533 (51.9)	359 (51.4)	270 (40.1)	377 (62.2)	252 (41.6)
25-30	1689 (70.1)	876 (37.8)	2017 (75.9)	1706 (64.2)	1008 (70.9)	599 (42.5)	1098 (77.1)	855 (60)	217 (52.7)	161 (39.7)	240 (63)	194 (50.9)
>30	3576 (65.3)	1885 (35.8)	4676 (74.7)	3981 (63.6)	1510 (64.7)	928 (39.1)	1847 (76.2)	1417 (58.5)	223 (56.5)	153 (39.8)	213 (62.5)	164 (48.1)
Race												
White	3296 (64.6)	1755 (35.6)	4376 (75.7)	3609 (62.4)	510 (67.1)	327 (42.3)	619 (78.6)	469 (59.5)	92 (48.2)	78 (42.4)	98 (58.3)	80 (47.6)
Mixed race (<i>par-do or mestizo</i>)	1915 (69.1)	946 (35.8)	2275 (74.6)	1957 (64.2)	2107 (67.6)	1280 (41.1)	2456 (77.5)	1872 (59.1)	574 (54)	423 (40.4)	610 (64.1)	435 (45.7)
Black, Asian, or Indigenous	871 (70.9)	461 (38.7)	989 (72.4)	884 (64.7)	186 (71.5)	126 (47.6)	193 (71.8)	138 (51.3)	133 (53)	83 (35.6)	122 (58.4)	95 (45.5)
Education level												
Secondary educa-tion or less	2165 (68.7)	1057 (35.3)	2368 (71)	1976 (59.3)	983 (68.8)	587 (42)	1054 (73.2)	784 (54.4)	280 (51.1)	223 (43.1)	286 (59.3)	204 (42.3)
More than sec-ondary education	3917 (65.8)	2105 (36.5)	5272 (76.8)	4474 (65.2)	2259 (67.3)	1371 (40.6)	2674 (77.9)	2021 (58.8)	519 (54.2)	361 (38.2)	544 (64.3)	406 (48)
Monthly income												
Minimum wage or less	1368 (67.3)	708 (36.7)	1543 (71.7)	1256 (58.3)	664 (68.5)	401 (42.6)	721 (74.6)	520 (53.8)	340 (51.1)	255 (39.9)	336 (58.7)	249 (43.5)
More than mini-mum wage	4714 (66.6)	2454 (35.9)	6097 (75.8)	5194 (64.6)	2428 (68.2)	1462 (40.8)	2810 (77)	2153 (59)	378 (56.3)	274 (41.1)	409 (66.8)	312 (51)
HIV risk perception												
None, low, or moderate	5345 (64.9)	2809 (35.4)	6851 (74.1)	5730 (62)	2887 (66)	1734 (39.8)	3364 (75.7)	2501 (56.3)	517 (52.8)	409 (40.3)	633 (62.4)	454 (44.8)
High	737 (84.9)	353 (42.3)	789 (83.2)	720 (76)	355 (87)	224 (53)	364 (84.9)	304 (70.9)	131 (79.4)	90 (50)	125 (69.4)	99 (55)
HIRI^b												
Low risk	1972 (56.8)	1114 (33.7)	2523 (69.7)	1950 (53.9)	1190 (59.8)	746 (38.6)	1423 (72)	1018 (51.5)	367 (45.8)	277 (38.2)	355 (60.2)	249 (42.2)
High risk	4110 (72.9)	2048 (37.5)	5117 (77.8)	4500 (68.4)	2052 (73.4)	1212 (42.6)	2305 (79.5)	1787 (61.7)	432 (61.4)	307 (41.6)	475 (64.4)	361 (48.9)
Last HIV test												
Never	545 (62.7)	280 (34.7)	597 (70.8)	443 (52.6)	470 (62.7)	272 (38.6)	537 (74.1)	350 (48.3)	130 (40.6)	108 (37.5)	143 (58.6)	80 (32.8)

Characteristics	Brazil (PrEP modality)				Mexico (PrEP modality)				Peru (PrEP modality)			
	Daily, n (%)	ED ^a , n (%)	Monthly, n (%)	Inject n, (%)	Daily, n (%)	ED, n (%)	Monthly, n (%)	Inject, n (%)	Daily, n (%)	ED, n (%)	Monthly, n (%)	Inject, n (%)
6 months or less	2983 (69.2)	1544 (37.1)	4148 (75.9)	3684 (67.5)	1363 (73.1)	851 (43)	1576 (78.4)	1299 (64.6)	362 (59.2)	262 (41.7)	371 (63.6)	295 (50.6)
More than 6 months	2554 (65)	1338 (35.2)	2895 (74.4)	2323 (59.7)	1398 (65.1)	830 (40)	1600 (75.5)	1144 (54)	298 (53.8)	207 (38.9)	313 (63.8)	232 (47.3)

^aED: event-driven.

^bHIRI: HIV Incidence Risk Index.

Table 3. Factors associated with willingness to use each pre-exposure prophylaxis modality among sexual and gender minorities in Brazil, Mexico, and Peru in 2021.

Characteristics	Daily oral, aPR ^a (95% CI)	Event-driven, aPR (95% CI)	Monthly oral, aPR (95% CI)	Injectable, aPR (95% CI)
Country				
Brazil	Reference	Reference	Reference	Reference
Mexico	1.02 (0.97-1.06)	<i>1.14 (1.08-1.22)</i> ^b	1.02 (0.98-1.07)	<i>0.93 (0.89-0.98)</i>
Peru	<i>0.81 (0.75-0.87)</i>	<i>1.11 (1.01-1.22)</i>	<i>0.84 (0.78-0.91)</i>	<i>0.76 (0.69-0.83)</i>
Age (years)				
18-24	1.01 (0.96-1.07)	1.02 (0.94-1.10)	1.04 (0.98-1.11)	0.95 (0.89-1.01)
25-30	1.03 (0.99-1.08)	1.04 (0.98-1.11)	1.01 (0.97-1.06)	1.00 (0.95-1.05)
>30	Reference	Reference	Reference	Reference
Race				
White	Reference	Reference	Reference	Reference
Mixed (Black and <i>pardo</i>)	1.04 (0.99-1.09)	0.99 (0.93-1.05)	0.99 (0.95-1.04)	1.02 (0.98-1.07)
Black, Asian, or Indigenous	1.07 (1.00-1.14)	1.05 (0.96-1.14)	0.95 (0.89-1.01)	1.01 (0.95-1.08)
Education level				
Secondary education or less	1.02 (0.98-1.07)	0.98 (0.92-1.04)	<i>0.93 (0.89-0.97)</i>	<i>0.94 (0.90-0.99)</i>
More than secondary education	Reference	Reference	Reference	Reference
Monthly income				
Minimum wage or less	0.98 (0.94-1.03)	1.02 (0.95-1.09)	0.96 (0.92-1.01)	<i>0.95 (0.90-1.00)</i>
More than minimum wage	Reference	Reference	Reference	Reference
HIV risk perception				
None, low, or moderate	Reference	Reference	Reference	Reference
High	<i>1.25 (1.18-1.32)</i>	<i>1.21 (1.12-1.32)</i>	<i>1.10 (1.04-1.17)</i>	<i>1.17 (1.10-1.25)</i>
HIRI^c				
Low risk	Reference	Reference	Reference	Reference
High risk	<i>1.22 (1.17-1.27)</i>	<i>1.08 (1.02-1.14)</i>	<i>1.10 (1.06-1.14)</i>	<i>1.21 (1.16-1.26)</i>
Last HIV test				
Never	<i>0.89 (0.83-0.95)</i>	0.92 (0.85-1.00)	0.97 (0.91-1.03)	<i>0.80 (0.74-0.86)</i>
6 months or less	Reference	Reference	Reference	Reference
More than 6 months	<i>0.95 (0.91-0.99)</i>	0.95 (0.90-1.01)	0.99 (0.96-1.03)	<i>0.90 (0.86-0.94)</i>

^aaPR: adjusted prevalence ratio.

^bItalicization indicates statistical significance ($P < .05$).

^cHIRI: HIV Incidence Risk Index.

Discussion

Principal Findings

In this paper, we provide information about willingness to use PrEP modalities and an HIV vaccine among SGM individuals from 3 countries in Latin America. Overall, participants were more interested in monthly oral PrEP, with daily oral and bimonthly injectable PrEP also being widely accepted and event-driven oral PrEP being the least preferred. Most participants reported willingness to use an HIV vaccine. Participants perceiving themselves at higher HIV risk and engaging in higher HIV sexual exposure were more willing to use all 4 PrEP modalities. Individuals with lower education were less willing to use long-acting PrEP (monthly oral and bimonthly injectable). Participants who had never tested for HIV or had been tested more than 6 months ago were less willing to use daily oral PrEP and bimonthly injectable. Our study provides insight into PrEP preferences among SGM individuals in Latin America and can guide the implementation of new PrEP modalities in prevention programs.

Higher willingness to use monthly oral and bimonthly injectable PrEP indicates a preference for long-acting formulations among SGM individuals in Latin America. In a discrete-choice experiment conducted in Brazil, SGM individuals preferred long-acting PrEP requiring less frequent dosing (monthly, bimonthly, or annually) as long as efficacy and side effects were similar or lower than those of oral PrEP [30]. Additionally, participants did not show a stronger preference for annual dosing compared with monthly or bimonthly dosing [30]. Previous studies identified injectable PrEP as the most preferred modality; however, they did not consider monthly oral PrEP as an option [31–33]. Currently, monthly oral PrEP is not available, although MK-8527, a novel investigational nucleoside reverse transcriptase translocation inhibitor, is under evaluation as an alternative to daily oral PrEP [34]. Two phase 3 clinical trials (EXPrESSIVE 10 and 11) are investigating the efficacy, safety, and tolerability of MK-8527 monthly compared with daily oral PrEP (FTC/TDF) among cisgender women and SGM individuals in several regions, including Latin America [35].

Long-acting injectables have been considered highly acceptable among SGM populations for HIV prevention [36]. This is corroborated by findings from a survey conducted among 3665 Brazilian SGM individuals in 2024 [37]. In the ImPrEP CAB Brasil study, most participants (83%) chose CAB-LA over daily oral PrEP [38]. Long-acting injectables offer potential advantages, such as reducing the frequency of clinic visits and improving adherence compared with daily oral PrEP [39]. Our study also revealed that individuals with lower education were less willing to use long-acting PrEP formulations, similar to findings related to injectable PrEP in Brazil [31]. This suggests that people using PrEP need accessible information to better understand the important features of these modalities.

Daily oral PrEP was also widely accepted; however, Peruvians were less likely to be willing to use this modality compared with Brazilians and Mexicans. This result is consistent with results from the ImPrEP study, which reported lower persistence and adherence to daily oral PrEP among MSM and transgender

women from Peru compared with Brazil [11,12]. Possible contributing factors included low awareness of oral PrEP, HIV-related stigma during sexually transmitted infection clinic visits, and concerns about medication efficacy and side effects [27]. These concerns may be more noticeable with newer PrEP modalities, particularly long-acting formulations, due to the lack of information and perceived loss of autonomy in administration, which may contribute to a preference for the daily oral modality [33,40]. Additionally, familiarity with and routine use of a daily oral pill could also have contributed to this preference [40].

Differences among countries may also reflect structural and contextual barriers. Brazil and Mexico incorporated daily oral PrEP into their public health systems in 2017 and 2021, respectively, and have since implemented large-scale, community-supported programs that promote familiarity with and confidence in PrEP [8,41]. In contrast, the Peruvian Ministry of Health initiated offering oral PrEP to populations at high vulnerability for HIV in 2023 [9]. This delayed implementation, with limited-service availability, may have reduced visibility and accessibility among potential users. Strengthening PrEP implementation in Peru through decentralized service delivery, stigma reduction initiatives, and targeted communication campaigns could help improve uptake and promote more equitable access across the region.

Event-driven oral PrEP was the least acceptable among our participants. This finding aligns with previous studies [31,32], except for a study conducted in the United States, in which MSM reported that most of condomless anal sex events are either infrequent or can be anticipated [42]. In contrast, participants in the ImPrEP study showed low interest in switching from daily oral to event-driven oral PrEP [43]. Reasons included that fewer than 25% reported having sex less than 2 days per week (indicating infrequent sex), most were satisfied with the daily regimen, considered event-driven PrEP a difficult regimen to follow, and had concerns about its efficacy and anxiety about their own HIV risk [43].

Individuals who perceived themselves at high risk for HIV and who were engaging in high HIV sexual exposure were more likely to use any PrEP modality. A high perceived risk of HIV has been identified as a facilitator of PrEP acceptability and willingness to use it [44–46]. For example, in Mexico, transgender women reported a high willingness to use daily oral PrEP (95.5%) if they had high HIV risk perception [47]. Additionally, Torres et al [31] reported that higher HIRI scores increased the willingness of use injectable PrEP, while lower HIRI scores were associated with a preference for event-driven PrEP in Brazil and Mexico. In another Latin American study, Assaf et al [48] found that a higher risk for HIV was associated with PrEP awareness in Brazil but not among MSM in Mexico and Peru. Importantly, a study from Brazil [27] found that PrEP awareness was associated with willingness to use it, indicating the importance of continuous education campaigns about HIV prevention, including current and future PrEP modalities.

PrEP modalities involving topical agents, patches, implants, and monoclonal antibodies received lower willingness to use compared with the oral and injectable modalities. In contrast,

HIV vaccines were widely accepted by participants. Many of these alternative PrEP formulations are still in the clinical research phase [20,49], while no HIV vaccine has been efficacious to date. Limited awareness of the options still under study could have generated distrust. However, previous study from South Africa have reported high acceptability of topical agents among different populations, including SGM individuals [49]. Although there is currently no approved HIV vaccine, the MOSAICO study (HPX3002/HVTN706) enrolled Latin American participants before being discontinued due to lack of efficacy [50]. Nevertheless, previous studies from Brazil found a high willingness to use a hypothetical effective HIV vaccine, even if it was not free of charge [51,52].

We acknowledge that this study has certain limitations. Participants were recruited through dating apps and social media platforms and accessed the online survey using smartphones or other internet-connected devices. This recruitment strategy was appropriate for reaching SGM communities but may have introduced selection bias by excluding individuals with limited digital access, meaning that our sample may not be representative of all SGM individuals in Latin America, Brazil, Mexico, or Peru. Additionally, the cross-sectional design of our study limited our ability to establish causality. Notably, when the data were collected in 2021, only daily oral PrEP was

available in these countries. However, oral PrEP information was more widely disseminated in Brazil, where it had been included in their public health care system since 2017 [41]. Finally, all responses were based on participants' self-reports, and social desirability bias may have occurred; however, online anonymous data collection may have reduced this bias. It is also important to note that "willingness" reflects hypothetical acceptability and may not directly translate into actual intention or behavior, which should be considered when interpreting these findings.

Conclusions

We found that SGM individuals from Latin America were more willing to use long-acting PrEP, including monthly oral and bimonthly injectable PrEP, but daily oral PrEP was also highly accepted. Further research and education are needed to better understand and address the gaps in knowledge about prevention modalities. The availability of additional choices to better address the prevention needs of SGM populations could empower individuals to use these methods. As additional PrEP modalities are included in HIV prevention programs, the development of accessible tools and community-based strategies will be essential to support informed PrEP choices and ensure equitable implementation across the region.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

aPR: adjusted prevalence ratio

CAB-LA: long-acting injectable cabotegravir

FTC/TDF: emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg

HIRI: HIV Incidence Risk Index

LEN: long-acting injectable lenacapavir

MSM: men who have sex with men

PrEP: pre-exposure prophylaxis

SGM: sexual and gender minority

WHO: World Health Organization

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The Gendered Mediation Effects of Social Support on Fertility Intentions Among Childless Adults of Reproductive Age in China: National Cross-Sectional Study

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Abstract

Background: China is currently facing a low fertility rate, making it crucial to explore the influence of psychosocial factors on fertility intentions to address demographic structural challenges. Social support, as a potentially significant influencing factor, is not yet fully understood in terms of its specific pathways and gender differences.

Objective: This study aimed to explore how social support impacts fertility intentions among Chinese adults aged 20 - 49 years, with an emphasis on gender-specific differences and the mediating roles of self-efficacy and conscientiousness.

Methods: Data were obtained from the Psychology and Behavior Investigation of Chinese Residents (PBICR). This study included 2653 childless adults of reproductive age. A decision tree model was used to identify key factors influencing fertility intentions. A mediation analysis was conducted to explore the mediating effects of self-efficacy and conscientiousness while controlling for demographic confounders.

Results: Among all 2653 participants, 71.3% (1892/2653) had fertility intentions. The proportion was significantly higher in men (weighted 79%, 95% CI 76.5%-81.3%) than in women (weighted 64.5%, 95% CI 61.8-67.1; $P<.001$). Participants with fertility intentions had a higher total social support score (mean 61.25, SD 14.02 vs mean 58.23, SD 13.01; $P=.001$). For women, family support significantly influenced fertility intentions, whereas support from friends was more relevant for men. Mediation analysis revealed that for men, self-efficacy significantly mediated the relationship between social support and fertility intention, with an indirect effect of 0.06 (95% CI 0.04-0.09; $P=.001$) and a mediation proportion of 52.54%. For women, conscientiousness played a significant mediating role, with an indirect effect of 0.011 (95% CI 0.002-0.018; $P=.001$) and a mediation proportion of 10.25%.

Conclusions: Enhancing targeted social support can increase fertility intentions, with implications for addressing demographic challenges. Tailored policies should prioritize providing family support and fostering conscientiousness for women, while boosting self-efficacy and friend-based social support for men.

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KEYWORDS

fertility intention; social support; gender differences; self-efficacy; conscientiousness

Introduction

China is currently facing a profound demographic transition brought about by a low birth rate. According to the latest statistical data, the total number of births in China in 2023 was 9.02 million, with the birth rate dropping to 6.39‰ [1]. This trend has made China one of the countries with the lowest fertility rates in the world, with a total fertility rate of only 1.30 in 2020, significantly lower than the level required to maintain population replacement [2]. The low birth rate directly accelerates the process of social aging: the seventh national

census shows that the proportion of people aged 65 years and older has risen from 8.92% in 2010 to 13.52%, with a total of over 190 million people [3]. To address this challenge, China has gradually relaxed birth restrictions since 2015 and implemented policies for 2 and 3 children [4]. However, policy adjustments have not brought about the expected rebound in fertility, and the trend of negative population growth continues [5]. In this context, it is urgent to delve into the influencing factors of reproductive behavior in the Chinese context.

Fertility intention refers to an individual's expectations and attitudes toward having children within a specific period [6]. It includes two aspects: rhythm intention and quantity intention. Rhythm intention involves the timing of childbirth, while quantity intention refers to the number of children expected to be born [7]. The willingness to have children is influenced by various factors, which can be divided into micro- and macrolevels, including personal characteristics, family environment, and social influence [8]. Previous studies have shown that the economic development of a society has a huge impact on fertility intentions and that sociocultural trends also influence people's perceptions of fertility [9]. A study of 6680 students nationwide in China showed that child health services or support were significantly associated with higher fertility intentions [10]. Thus, social support, as an important influencing factor, is gradually receiving attention.

Previous studies have shown that social support is an important factor affecting fertility intentions. It comes from emotional, informational, and instrumental assistance from family, friends, and partners and plays a crucial role in individuals' fertility decisions [11–13]. Specifically, social support can alleviate parenting-related pressures and enhance individuals' confidence in their parenting abilities [14]. Positive family communication and good subjective well-being have also been found to help increase the fertility intention of childless women of childbearing age [15]. However, the role of social support extends beyond its potential direct effect on fertility intentions to its mediating mechanisms. For instance, it may act as a mediator in the relationship between other psychological traits, such as self-efficacy or conscientiousness, and fertility intentions. In addition, due to the different roles and responsibilities assigned to men and women by social expectations and norms, there may be significant gender differences in the impact of social support on fertility intentions [16]. Therefore, the specific psychological pathways through which social support affects fertility intentions, and how these pathways differ between men and women, still need to be clarified through empirical research.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Age 18 years and older.
- Chinese citizenship.
- Permanent residency in China (with an annual absence of ≤ 1 month).
- Voluntary participation with signed informed consent.
- The ability to comprehend questionnaire items and the capacity to complete the survey independently or with noninterferential assistance.

Exclusion criteria:

- Impaired consciousness or psychiatric abnormalities.
- Cognitive impairment.
- Concurrent participation in comparable research.
- Unwillingness to participate.

For this analysis, we applied additional filters to this dataset to define our target subpopulation. We restricted our analysis to

Therefore, this national cross-sectional study is designed to specifically investigate the psychological pathways through which social support influences fertility intentions among childless adults of reproductive age in China, with a central focus on delineating gender-specific mechanisms. It aims to (1) quantify the direct associations between multidimensional social support and fertility intentions, (2) empirically test the mediating roles of key factors within these associations, and (3) explicitly compare the strength and significance of these direct and indirect pathways between man and woman respondents.

Methods

Study Design and Population

Our data were derived from the large-scale cross-sectional Psychology and Behavior Investigation of Chinese Residents (PBICR). The survey used a multistage sampling design to ensure the representativeness and generalizability of the collected data. A total of 23 provinces, 5 autonomous regions, and 4 directly administered municipalities (Beijing, Tianjin, Shanghai, and Chongqing) were directly incorporated into the first stage of sampling in this study. Additionally, 2 to 6 cities in each nonprovincial capital prefecture-level administrative region of each province and autonomous region were randomly selected using a random number table, amounting to a total of 120 cities. In the second stage of sampling, a quota sampling method was used for the residents in each selected community, using quotas based on gender, age, and urban-rural distribution. The gender ratio was stipulated at 1:1, and the age distribution was similar to the age distribution in the Seventh National Population Census of China (2020).

The survey data were acquired through one-on-one interviews, using an electronic questionnaire administered via a networking questionnaire tool. The eligibility criteria for the overarching PBICR survey are shown in [Textbox 1](#). The initial survey involved 11,031 participants.

childless participants of childbearing age, specifically those aged 20 to 49 years. Consequently, the final analytical sample

for this study comprised 2653 participants. Figure 1 shows the complete sample selection process.

Figure 2 shows the comprehensive experimental design framework for analyzing social support and fertility intentions.

Figure 1. Flowchart of participant selection for the analysis of social support and fertility intentions in a national cross-sectional study.

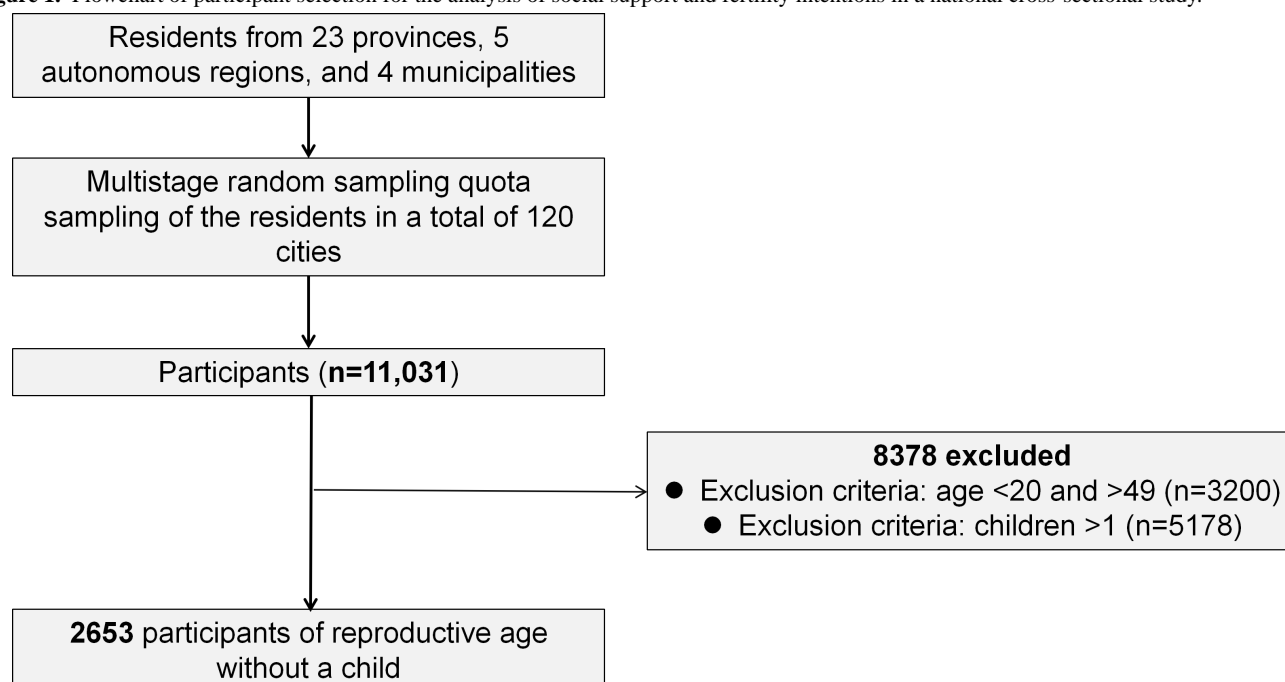
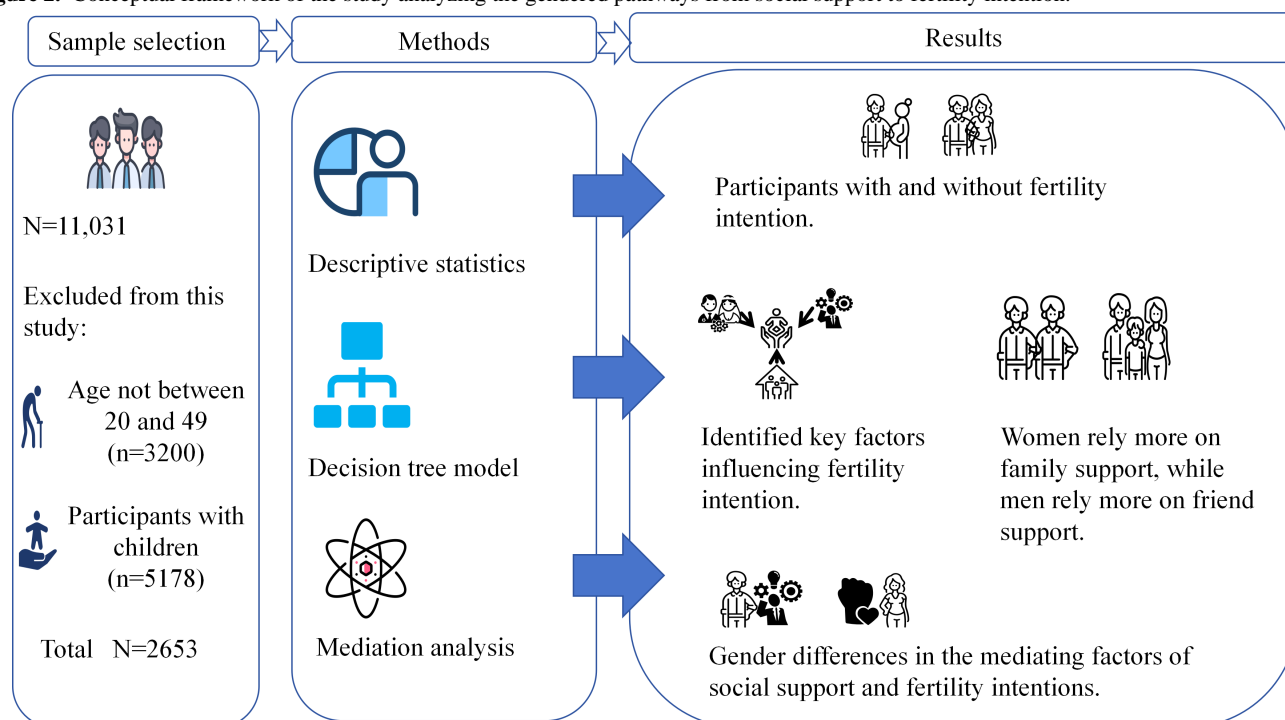


Figure 2. Conceptual framework of the study analyzing the gendered pathways from social support to fertility intention.



Ethical Considerations

This study was reviewed and approved by the institutional review committee of Jinan University (approval number: JNUKY-2021-018). All procedures involving human participants were conducted in accordance with the ethical standards of this committee and with the principles of the WMA Declaration of Helsinki. Prior to participation, informed consent was obtained from all individual participants involved in the

study. The consent process ensured that participants were fully informed of the study's nature, purpose, and procedures, and they were advised that their participation was voluntary. To protect participant privacy, all collected data were anonymized at the point of entry using unique identification codes. No personally identifiable information was stored in the research databases. All electronic data were stored securely on a password-protected server with access strictly limited to authorized members of the research team.

Outcome Variable: Fertility Intention

Fertility intention was measured using a single question, which has been widely accepted and used in demographic surveys and fertility studies [17]. The participants were asked: “How strong is your willingness to have your first child?” The response scale consisted of five options, with 1 indicating “completely unwilling,” 2 indicating “not willing,” 3 indicating “average,” 4 indicating “willing,” and 5 indicating “strongly willing.” For analysis, the fertility intention variable was used as a dichotomized variable. Participants who selected 1 or 2 were categorized as “having no intention to have children,” whereas those who selected 3, 4, or 5 were categorized as “having the intention to have children.” Unlike the descriptive analysis where the outcome was dichotomized, for the mediation analysis, fertility intention was utilized in its original 1-5 Likert scale form. It was treated as a continuous variable to facilitate linear regression modeling.

Explanatory Variable: Social Support

The participants completed the Perceived Social Support Scale (PSSS) developed by Zimet et al [18] to assess social support. This scale comprises 12 items divided into three dimensions: (1) family support, (2) friend support, and (3) significant other support. Each item is rated on a 7-point Likert scale (1=strongly disagree to 7=strongly agree). Total scores from 12 to 36 indicate a low level of social support, scores from 37 to 60 indicate a moderate level, and scores from 61 to 84 indicate a high level of social support. We conducted separate analyses of each dimension, with each dimension consisting of 4 questions. The average score was calculated to determine the level of support for each dimension, with higher scores indicating higher levels of support. The reliability coefficient for the total social support dimension was 0.96, 0.93 for the friend support dimension, 0.90 for the significant other support dimension, and 0.90 for the family support dimension.

Mediating Variables

The mediating variables of interest in this study were self-efficacy level, personality traits, depression symptoms, and anxiety symptoms of the respondents.

The New General Self-Efficacy Scale was used to measure the respondents' self-efficacy level. It consists of 8 items, and each item was scored on a 5-point Likert scale (1=completely disagree, 2=disagree, 3=neutral, 4=agree, and 5=strongly agree) [19]. All items were scored positively, and the total score on the scale was calculated by summing all item scores and ranged from 8 to 40 points. The higher the score, the higher the self-efficacy level of the respondents. The Cronbach α of the scale in this study was 0.94, indicating that the scale had good reliability in this study.

The Big Five Inventory-10 (BFI-10) was used to assess the personality traits of individuals, including extraversion, agreeableness, conscientiousness, neuroticism, and openness [20,21]. This assessment uses a 5-point Likert scale, with responses ranging from 1 (completely disagree) to 5 (completely agree). A higher score in a particular personality trait indicates a stronger presence of that trait in the respondent. Numerous studies have demonstrated that the BFI-10 possesses strong

reliability and validity [22,23]. In our study, the reliability of the BFI-10 was confirmed through Cronbach α analysis, yielding satisfactory results: extraversion (Cronbach α =.80), agreeableness (Cronbach α =.81), conscientiousness (Cronbach α =.86), neuroticism (Cronbach α =.79), and openness to experience (Cronbach α =.90).

The Patient Health Questionnaire-9 (PHQ-9) is a 9-item instrument used to measure the severity of depressive symptoms experienced over the past 2 weeks. Each item is rated on a scale from 0 (not at all) to 3 (nearly every day), with total scores ranging from 0 to 27 [24]. Higher scores indicate more severe depression. The PHQ-9 has been validated and shown to be reliable in various populations [25,26]. In our research, the reliability was 0.94.

The Generalized Anxiety Disorder-7 (GAD-7) tool is a 7-item scale designed to assess the severity of generalized anxiety symptoms over the previous 2 weeks. Items are scored from 0 (not at all) to 3 (nearly every day), with total scores ranging between 0 and 21. Higher scores suggest more severe anxiety [27]. The GAD-7 has demonstrated strong reliability across different groups [28,29]. In our research, the reliability was 0.96.

Control Variables

The control variables included in this study were gender, age, BMI, marital status (married or single), rural or urban residence, number of siblings, education level (primary school or below or middle school or high school or vocational school or junior college or undergraduate or graduate or above), employment status (full-time work or part-time work or no fixed job or retirement), religious beliefs (yes or no), ethnic groups (Han or non-Han), recent medication use (none, 1, 2, 3, 4, or 5 types or more), smoking status (never or current or past), alcohol consumption (never or current or past), and annual per capita household income.

Statistical Analysis

We constructed a decision tree model to identify the key factors influencing fertility intentions. In constructing the decision tree, the splitting criteria were based on minimizing Gini impurity, a standard measure used to quantify node homogeneity. Parameters, such as the minimum number of observations per leaf node (minsplit=20) and the maximum depth of the tree (maxdepth=5), were prespecified to prevent overfitting. These parameters were determined through cross-validation to optimize the trade-off between model complexity and predictive performance. The performance and accuracy of the decision tree model were evaluated using receiver operating characteristic (ROC) curves, which plotted the relationship between the true positive rate and the false positive rate across various classification thresholds. The area under the curve (AUC) of ROC was calculated using the *pROC* package to quantify the model's classification performance, with values closer to 1 indicating better accuracy. We used the *rpart* package in R statistical software (version 4.4.1; R Core Team), which implements the classification and regression tree (CART) algorithm, enabling recursive partitioning of the dataset to generate interpretable decision tree models. We used mediation

analysis using the *mediation* package in R to investigate the mechanisms through which independent variables influence fertility intentions through mediating variables. The parameters for the mediation model were carefully designed. Independent variables and mediators were selected based on theoretical relevance and previous empirical evidence. Continuous variables were standardized to ensure comparability across scales. The significance of the mediating effects was tested using the bootstrap method, providing robust estimates of the indirect effects. These analyses helped to elucidate the pathways through which key variables impact fertility intentions. To account for the complex sampling design and potential deviations from the population benchmarks, all analyses in this study used survey weights. The weights were constructed using a poststratification raking procedure to calibrate the sample to the national population distributions of gender, age group, and urban-rural residence among adults aged 20 - 49 years, based on the 2020 Chinese National Population Census. All descriptive statistics (reported as weighted percentages or means with 95% CIs) and inferential analyses (including χ^2 tests and regression models) were performed using these weights to obtain estimates that are representative of the target national subpopulation. All statistical analyses and graphing were performed using R statistical software. Numerical data were subjected to normality tests.

Continuous data are presented as mean \pm standard deviation, while categorical data are presented as frequency.

Results

Description of the Study Population

Table 1 presents the sociodemographic characteristics of the study participants based on weighted analyses to ensure national representativeness. Among the 2653 childless adults of reproductive age, an estimated 49.2% (95% CI 46.9%-51.5%) were women, and 41.2% (95% CI 38.9%-43.5%) were aged 20 - 25 years. Overall, 71.3% (1892/2653) of respondents reported having fertility intentions. The fertility intention was significantly higher among man participants (weighted 79%, 95% CI 76.5%-81.3%) than among women participants (weighted 64.5%, 95% CI 61.8-67.1; $P<.001$). Marital status was also strongly associated with fertility intention ($P<.001$), with weighted 77.2% of those intending to have children being married. Other characteristics that showed significant differences between the groups with and without fertility intentions included age group ($P=.045$), monthly income ($P=.003$), number of siblings ($P=.02$), BMI ($P<.001$), smoking status ($P=.01$), and alcohol use ($P=.04$). Variables including religion, ethnicity, education, employment status, and place of residence showed no significant associations.

Table . Demographic and sociological characteristics of childless adults of reproductive age in China (N=2653).

Variable	Total (N=2653)		No fertility intention (n=761)	Having fertility intention (n=1892)	P value
	Unweighted n	Weighted n (95% CI)	Unweighted n (weighted %)	Unweighted n (weighted %)	
Sex					<.001
Man	1192	50.8 (48.5-53.1)	245 (33.5)	947 (49.5)	
Woman	1461	49.2 (46.9-51.5)	516 (66.5)	945 (50.5)	
Age group (years)					.045
20- 25	1301	41.2 (38.9-43.5)	388 (45.1)	913 (39.8)	
26 - 30	898	35.7 (33.5-38.0)	249 (34.2)	649 (36.3)	
31 - 35	286	14.1 (12.5-15.9)	63 (11.2)	223 (15.0)	
36 - 40	86	5.3 (4.2-6.7)	29 (6.1)	57 (5.0)	
41 - 45	53	2.5 (1.8-3.5)	23 (3.0)	30 (2.3)	
46 - 49	29	1.2 (0.8-1.8)	9 (0.4)	20 (1.6)	
Marital status					<.001
Married	1930	78.5 (76.4-80.5)	420 (53.1)	1510 (77.2)	
Single	723	21.5 (19.5-23.6)	341 (46.9)	382 (22.8)	
Religion					.72
No	2585	97.5 (96.7-98.1)	744 (97.7)	1841 (97.4)	
Yes	68	2.5 (1.9-3.3)	17 (2.3)	51 (2.6)	
Ethnicity					.89
Han	2498	94.3 (93.2-95.3)	715 (94.1)	1783 (94.4)	
Other	155	5.7 (4.7-6.8)	46 (5.9)	109 (5.6)	
Education					.85
Primary school or low	35	1.5 (1.0-2.2)	13 (1.8)	22 (1.4)	
Secondary school	36	1.5 (1.1-2.1)	9 (1.3)	27 (1.6)	
High school or technical secondary	226	8.7 (7.6-10.0)	62 (8.2)	164 (8.9)	
Junior college or undergraduate	2055	77.0 (75.0-78.9)	588 (76.8)	1467 (77.1)	
Graduate or above	301	11.3 (10.0-12.7)	89 (11.9)	212 (11.0)	
Employment status					.22
Student	1441	52.1 (49.8-54.4)	439 (55.2)	1002 (51.0)	
Retired	4	0.2 (0.1-0.5)	2 (0.3)	2 (0.1)	
Employed	945	36.8 (34.7-39.0)	248 (33.1)	697 (38.1)	
Unemployed	263	10.9 (9.6-12.3)	72 (11.4)	191 (10.8)	
Monthly income, yuan					.003
≤3000	755	29.1 (27.0-31.3)	221 (30.1)	534 (28.7)	
3001 - 6000	967	36.0 (33.9-38.2)	288 (37.1)	679 (35.6)	
6001 - 9000	466	17.3 (15.7-19.0)	121 (15.2)	325 (18.0)	
>9000	465	17.6 (15.9-19.4)	131 (17.6)	354 (17.7)	
Residence					.22
Rural area	661	31.6 (29.4-33.9)	172 (29.8)	489 (32.2)	

Variable	Total (N=2653)		No fertility intention (n=761)	Having fertility intention (n=1892)	P value
	Unweighted n	Weighted n (95% CI)	Unweighted n (weighted %)	Unweighted n (weighted %)	
Urban area	1992	68.4 (66.1-70.6)	589 (70.2)	1403 (67.8)	
Number of siblings					.02
0	1105	40.2 (38.0-42.4)	339 (42.8)	766 (39.2)	
1	1118	42.5 (40.3-44.7)	315 (41.0)	803 (43.0)	
2	284	11.3 (10.0-12.8)	75 (10.1)	209 (11.8)	
≥3	146	6.0 (5.1-7.1)	32 (6.1)	114 (6.0)	
BMI (kg/m ²), mean (95% CI)	2653	21.5 (21.3-21.7)	20.9 (20.6-21.2)	21.7 (21.5-21.9)	<.001
Smoking status					.01
Never	2316	86.5 (84.8-88.0)	685 (89.1)	1631 (85.6)	
Current	242	10.1 (8.9-11.5)	48 (6.7)	194 (11.3)	
Past	95	3.4 (2.8-4.2)	28 (4.2)	67 (3.1)	
Alcohol use					.04
Never	1462	54.3 (52.0-56.6)	438 (56.8)	1024 (53.4)	
Current	773	30.5 (28.5-32.6)	193 (26.1)	580 (32.1)	
Past	418	15.2 (13.7-16.8)	130 (17.1)	288 (14.5)	

All percentages, means, and *P* values are calculated based on survey weights to ensure that the sample is consistent with the distribution of the 20 - 49 age group in the 2020 Chinese National Population Census in terms of gender, age group, and urban-rural distribution. Continuous variables are represented by weighted means and their 95% CIs. The *P* value of categorical variables is based on weighted Rao Scott χ^2 test, while the *P* value of continuous variables is based on weighted linear regression.

Analysis accounting for the complex survey design indicated significant associations between fertility intention and several psychosocial characteristics. Weighted scores for self-efficacy

(28.85, SD 5.51 vs 27.65, SD 5.73; *P*=.001), conscientiousness (6.38, SD 1.50 vs 6.21, SD 1.53; *P*=.002), total social support (61.25, SD 14.02 vs 58.23, SD 13.01; *P*=.001), family support (4.99, SD 1.25 vs 4.85, SD 1.30; *P*=.001), significant other support (4.98, SD 1.20 vs 4.86, SD 1.27; *P*=.002), and friend support (5.09, SD 1.20 vs 5.02, SD 1.28; *P*=.049) were significantly higher in the group with fertility intention. Conversely, weighted scores for life stress (3.13, SD 1.49 vs 3.37, SD 1.46; *P*=.048) and neuroticism (5.78, SD 1.51 vs 6.12, SD 1.59; *P*=.001) were significantly lower in this group. No statistically significant differences were observed for ability to handle stress, depression, anxiety, extraversion, agreeableness, or openness. Complete data are presented in [Table 2](#).

Table . Distribution of psychological factors, personality traits, and social support scores by fertility intention status among childless adults in China (N=2653).

Characteristic	Overall	Fertility intention		<i>P</i> value
	N=2653	Yes (n=1892)	No (n=761)	
Psychological factors				
Life stress	3.20 (1.48)	3.13 (1.49)	3.37 (1.46)	.048
Ability to handle stress	3.12 (1.65)	3.08 (1.67)	3.31 (1.61)	.08
Depression	7.43 (6.35)	7.35 (6.50)	7.72 (6.01)	.44
Anxiety	5.34 (5.26)	5.29 (5.35)	5.55 (5.04)	.60
Self-efficacy	28.48 (5.62)	28.85 (5.51)	27.65 (5.73)	.001
Personality traits				
Extraversion	6.76 (1.55)	6.71 (1.52)	6.91 (1.60)	.10
Conscientiousness	6.31 (1.51)	6.38 (1.50)	6.21 (1.53)	.002
Neuroticism	5.86 (1.54)	5.78 (1.51)	6.12 (1.59)	.001
Agreeableness	6.84 (1.52)	6.88 (1.54)	6.75 (1.48)	.06
Openness	6.19 (1.72)	6.22 (1.69)	6.16 (1.78)	.09
Social supports				
Family dimension score	4.93 (1.27)	4.99 (1.25)	4.85 (1.30)	.001
Friend dimension score	5.05 (1.23)	5.09 (1.20)	5.02 (1.28)	.049
Significant others dimension score	4.92 (1.22)	4.98 (1.20)	4.86 (1.27)	.002
Total social support score	60.38 (13.85)	61.25 (14.02)	58.23 (13.01)	.001

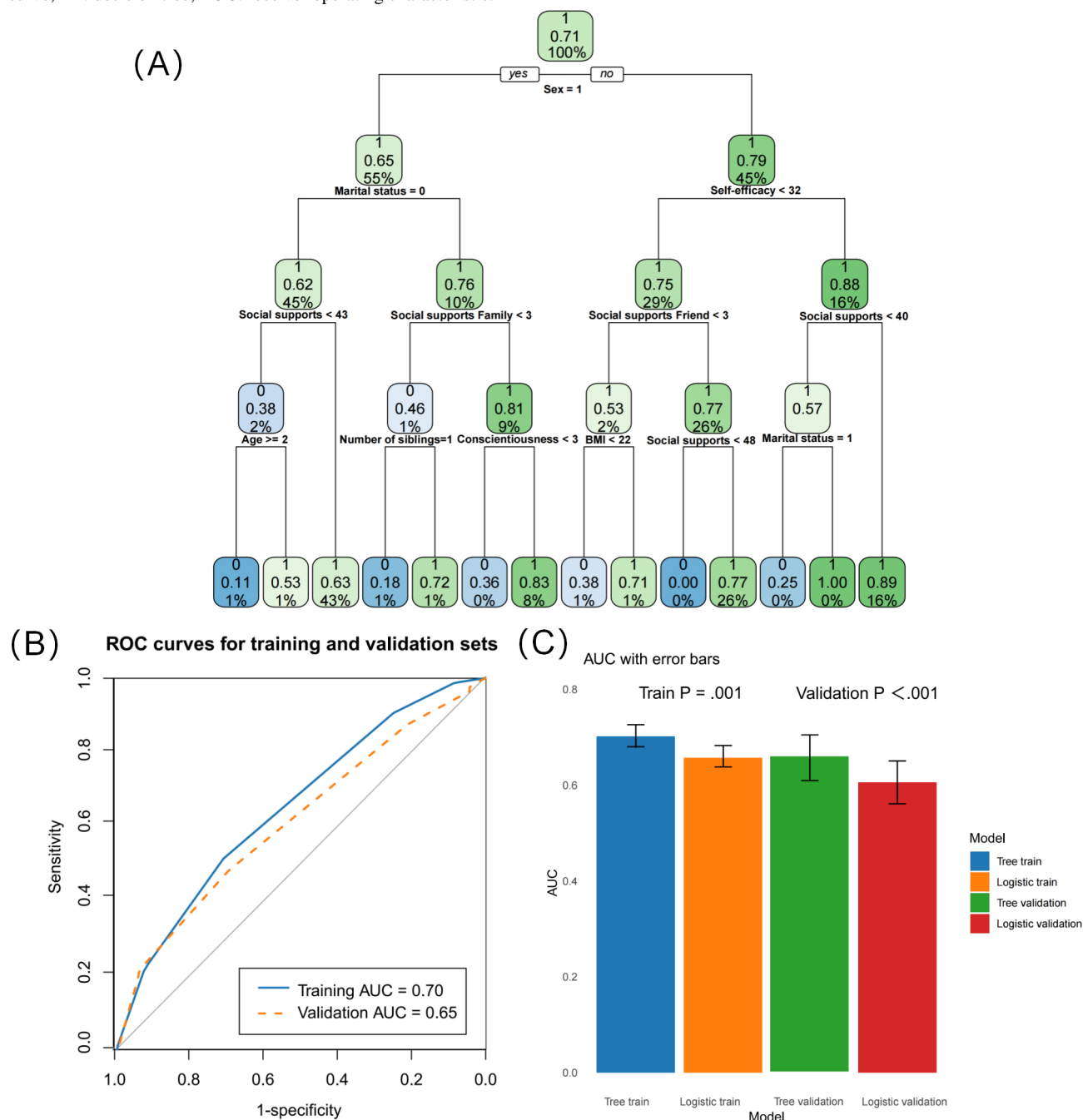
Data are presented as weighted mean (weighted SD). All estimates (means, SDs) and *P* values were derived from analyses that accounted for the complex, multistage sampling design by applying survey weights. The weights were constructed using poststratification raking to calibrate the sample to the national population distributions of gender, age, and urban-rural residence for adults aged 20 - 49 years, based on the 2020 Chinese National Population Census. *P* values for comparisons between groups (Yes vs No fertility intention) were obtained from weighted linear regression models. The sample sizes (n) represent the unweighted number of participants in each group.

Association Between Fertility Intentions and Social Support in the Decision Tree

The fertility intention rate of women was lower than that of men (65% vs 79%, [Figure 3A](#)). The results of our study showed that marital status was the most significant variable associated with

fertility intentions among women. For women, being married and having strong family support (family support >3) was associated with a fertility intention rate of 81%. Additionally, respondents whose marital status=0 (married) and social supports of family >3 and reported Conscientiousness >3 had a higher proportion of fertility intention than married individuals with high family support but low conscientiousness (83% vs 36%). For those whose marital status was 0 but had the support of <4 family members, the proportion of fertility intention increased when the number of siblings was 1 (72% vs 18%). Our study found self-efficacy to be the strongest predictor of fertility intention among men. When self-efficacy >32 and social support >40, there was a high proportion of fertility intention (89%). Respondents with self-efficacy scores of <32, social support of friends >3, and social support >48 also presented high fertility intention rates, at 77%.

Figure 3. Decision tree model for predicting fertility intention and its performance evaluation among childless adults in China. (A) The DT model for predicting fertility intention. (B) ROC curves for training and validation sets. (C) AUC with error bars for training and validation sets. AUC: area under the curve; DT: decision tree; ROC: receiver operating characteristic.



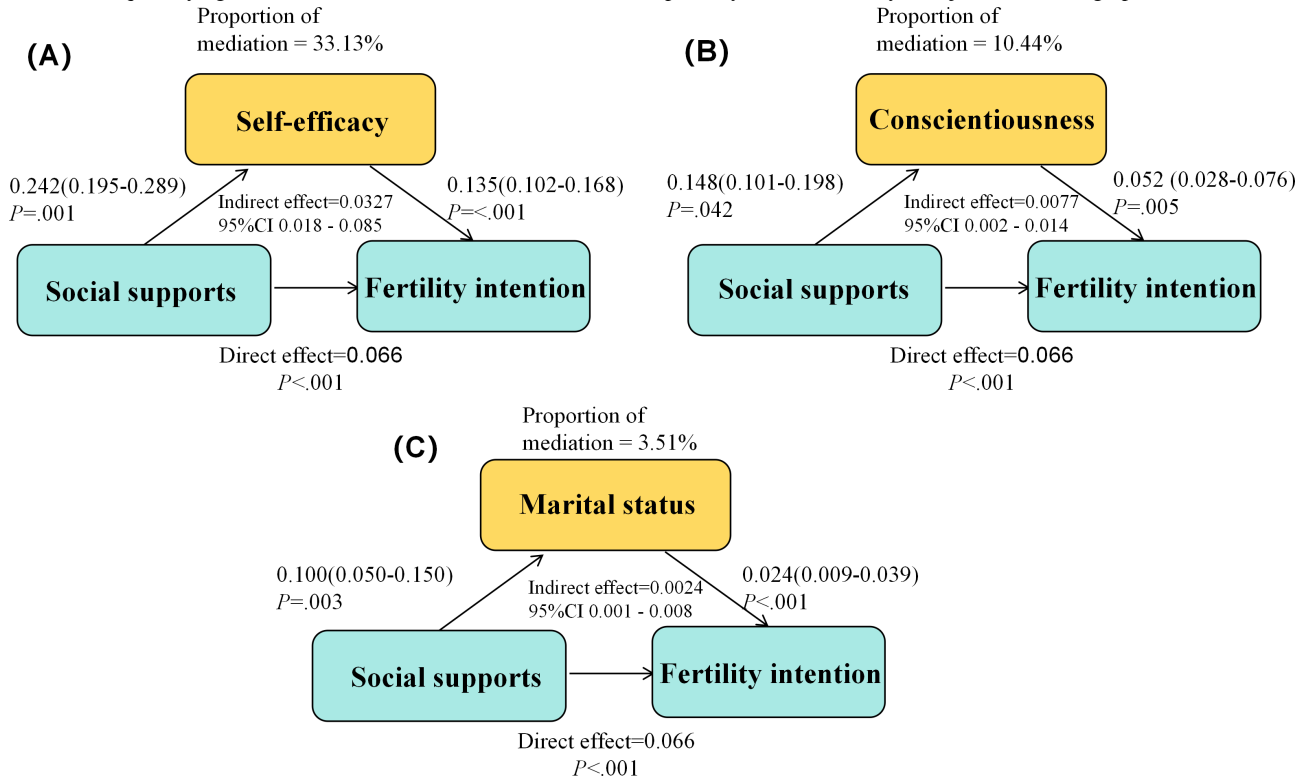
The decision tree model demonstrated strong predictive accuracy for fertility intention, with an AUC of 0.70, indicating good overall model performance. The model showed excellent diagnostic ability in both the training set (AUC=0.70) and test set (AUC=0.65), confirming its ability to generalize across different datasets (Figures 3B and 3C).

Figure 4 indicates that increased social support correlated with higher fertility intentions for both genders, but women generally had lower intentions than men at the same support levels (Figure 4A). For women, family was the most crucial form of social support, while for men, friends held the highest importance (Figures 4B and 4C). Therefore, we explored different mediation pathways for men and women.

Figure 4. Gender differences in fertility intentions and the relative importance of different sources of social support. (A) Line chart of gender differences in fertility intentions. The horizontal axis represents the quartiles of social support, and the vertical axis represents the fertility intention percentage in this population. (B) The importance ranking of the 3 dimensions of fertility intention among men. (C) The importance ranking of the 3 dimensions of fertility intention in women.

The results showed significant indirect effects of conscientiousness (mediation proportion: 10.44%), self-efficacy (mediation proportion: 33.13%), and marital status (mediation proportion: 3.51%) on the association between social support and fertility intention (Figure 5).

Figure 5. Mediation analyses examining the indirect effects of conscientiousness, self-efficacy, and marital status on the relationship between social support and fertility intention. Statistical results from mediation analyses for (A) self-efficacy (B), conscientiousness, and (C) marital status as mediators. Each panel reports the Average Causal Mediation Effect (ACME; ie, the indirect effect), the average direct effect (ADE), and the proportion of the total effect mediated, quantifying the contribution of each factor in the mediation pathway. Mediation analysis adjusted for demographic confounders



The mediation analysis revealed gender differences in the mediating effects of self-efficacy and conscientiousness on fertility intention (Table 3). Specifically, self-efficacy played a significant mediating role in the relationship between social support and fertility intention for men, with a mediation effect of 0.06 (95% CI 0.04 to 0.09; P<.001) and a mediation proportion of 52.54%. In women, self-efficacy did not demonstrate a significant mediation effect (95% CI -0.02 to 0.04; P=.85).

Table . Gender-stratified mediation analysis of the effect of social support on fertility intention through self-efficacy and conscientiousness among childless Chinese adults.

Expo- sure ^a	Media- tor ^b	Outcome	Man					Woman				
			Total ef- fect	Direct ef- fect	Media- tion ef- fect (95% CI)	P value	Media- tion pro- portion, %	Total ef- fect	Direct ef- fect	Media- tion ef- fect (95% CI)	P value	Media- tion pro- portion, %
Social supports	Self-ef- facy	Fertility intention	0.118	0.055	0.062 (0.040 to 0.087)	<.001	52.54	0.100	0.097	0.003 (-0.023 to 0.043)	.85	0
Social supports	Conscien- tiousness	Fertility intention	0.119	0.056	0.001 (-0.014 to 0.011)	.95	0	.100	0.089	0.011 (0.002 to 0.018)	<.001	10.25

^aThe Bootstrap method is used to test the mediating effect, and the 95% confidence interval (95% CI) of the mediating effect is estimated through repeated sampling (with 5000 repetitions).

^bMediation analysis adjusted for demographic confounders.

For conscientiousness, the mediation effect was significant in women, with a mediation effect of 0.011 (95% CI 0.002 to 0.018; P<.001) and a mediation proportion of 10.25%. In men, conscientiousness did not significantly mediate the relationship (95% CI -0.014 to 0.011, P=.95).

Adjustments were made for some confounding factors, including age, ethnicity, the amount of medication taken (excluding health supplements), smoking, BMI, educational level, alcohol consumption, annual income, and marital status.

Discussion

Principal Findings

This study examined the influence of social support on fertility intentions in Chinese adults, focusing on gender differences and the mediating effects of self-efficacy and conscientiousness, and revealed 3 key findings. First, social support was positively linked to fertility intention, suggesting that individuals with higher levels of support are more likely to express a desire to have children. Second, self-efficacy, conscientiousness, and marital status were significant mediators of the relationship between social support and fertility intention. Self-efficacy was especially relevant in men, while conscientiousness was more impactful in women. Third, a gender difference was seen in fertility intention. At the same level of social support, women had lower fertility intentions than men. However, the type of support mattered; family support was more critical for women, while men benefited significantly from friend-based support. This relationship was mediated by self-efficacy in men and conscientiousness in women. The study findings highlight important pathways for enhancing fertility intentions among men and women by enhancing social support, especially in strategy development for gender differences.

Our study revealed a positive relationship between social support and fertility intention, highlighting that individuals with stronger social networks are more likely to express a desire to have children. This finding aligns with previous research indicating that emotional and instrumental support can foster the intention to start or expand a family. Higher levels of social support, including support from family and friends, may provide the psychological and practical resources needed to manage the demands of child-rearing, thus promoting fertility intentions [30–32].

Our study identified self-efficacy, conscientiousness, and marital status as key mediators in the relationship between social support and fertility intention. Self-efficacy, which refers to one's belief in one's ability to achieve goals, was particularly influential for men, whereas conscientiousness, the tendency to be organized and responsible, had a stronger mediating effect in women. This supports earlier findings that personality traits and psychological factors can significantly influence fertility decisions [33]. In addition, marital status moderated this effect, with married individuals showing stronger fertility intentions than single people [30]. Together, these mediators emphasize the importance of both psychological resources and relationship status in shaping fertility intentions, providing critical pathways for interventions aimed at enhancing fertility decisions.

The study findings also highlight important gender differences in fertility intention. At equivalent levels of social support, women demonstrated lower fertility intentions than men. This phenomenon may reflect the potential influence of sociocultural and gender roles on woman fertility decisions, consistent with

other studies [34–36]. Okun et al [35] suggest that Confucian culture profoundly influences China, and women take on traditional family service roles in their households. Therefore, Chinese women shoulder the dual responsibility of social work and family care and face a career fertility dilemma, an essential factor that reduces the fertility intentions of women. Furthermore, the study found that the type of social support mattered. For women, family support emerged as the most influential, while men benefited more from support from friends. These gender-specific differences in the role of support were mediated by self-efficacy in men and conscientiousness in women. These gender differences may stem from the traditional division of gender roles, where women take more responsibility and pressure in the family and, thus, are more dependent on family support when making reproductive decisions. In contrast, men are less involved in the family domain [37–39]. In many cultures, men are often expected to play the role of breadwinner and decision-maker in the family [40]. Thus, their self-efficacy is closely related to their confidence in their abilities. Social support enhances men's sense of self-efficacy and makes them more confident in their fatherly roles and responsibilities. For women, the mediating role of responsibility between social support and fertility intentions may be related to traditional societal role expectations. Women are usually expected to take more responsibility for caring for and educating the children in the family, and therefore, their fertility intentions are closely related to their sense of responsibility [40]. Social support can help women feel more resourceful and emotionally supported, thus enhancing their sense of responsibility and making them more willing to take on the role of motherhood. Although gender roles have diversified and become more flexible with time, traditional gender role expectations still play a role.

In summary, our study findings underscore the critical role of social support in shaping fertility intentions, with self-efficacy, conscientiousness, and marital status identified as significant mediators. Importantly, gender differences were evident in how support influences reproductive decisions, with distinct pathways for men and women. This suggests that future strategies to promote fertility intentions should consider gender-specific needs and personality traits, particularly by enhancing the types of support most relevant to each gender. Policymakers and health professionals could focus on promoting family and friend support in ways that align with individual gender dynamics and personality characteristics, potentially leading to more effective fertility interventions. For example, the fertility intentions of women can be enhanced by strengthening family support and developing a sense of responsibility, whereas for men, fertility intentions can be enhanced by boosting self-efficacy and friend support.

Limitations

However, the study has some limitations. This study has several limitations that should be considered. First, the observational cross-sectional design hinders causal inference regarding the relationships between social support, psychological mechanisms, and fertility intentions. Future longitudinal studies are needed to verify the directionality and temporal dynamics of these associations. Second, while statistically significant, some of the observed effect sizes were modest. Their practical significance

should be interpreted with caution. While social support, self-efficacy, and conscientiousness are significant predictors, they account for limited variance in fertility intentions. This indicates that fertility decisions are heavily influenced by unmeasured factors beyond the psychosocial domain, such as economic constraints (e.g., housing, childcare costs) and public policies. Future research should integrate these macro-level variables to build more comprehensive models. Third, the generalizability of our findings may be limited as the study specifically focused on childless individuals of reproductive age. The applicability of the proposed model to other populations requires further examination. Finally, a key methodological limitation is the use of a single-item measure for fertility intention. Although practical in large-scale surveys, such a measure may not fully capture the complexity and multifaceted nature of reproductive planning (eg, timing and

desired number of children), which could influence the depth and nuance of our conclusions.

Conclusion

The study revealed that individuals with greater support are more likely to want children, with self-efficacy, conscientiousness, and marital status significantly influencing the link between social support and fertility intentions. Additionally, women were generally found to have lower intentions than men at the same level of social support. Family support was more crucial for women, whereas men benefited more from friend-based support. For men, this relationship was influenced by self-efficacy, whereas for women, it was affected by conscientiousness. This study enhances our understanding of gender differences in fertility intentions and offers practical guidelines for policymakers to improve these intentions by increasing social support and psychological factors.

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Data Availability

The datasets analyzed during this study are available in the Psychology and Behavior Investigation of Chinese Residents repository [41].

Authors' Contributions

Conceptualization: XX (lead), PL (equal)

Methodology: XX (lead), PR (equal)

Resources: SL (lead), PL (supporting), WS (supporting)

Formal analysis: XX (lead), PL (equal), PR (supporting), WS (supporting)

Investigation: PR (lead), WS (equal)

Visualization: XX (lead), PR (equal), PL (supporting)

Writing – original draft: XX (lead), PR (equal), WS (supporting)

Writing – review and editing: SL (lead), XX (supporting), PL (supporting), WS (supporting)

Conflicts of Interest

None declared.

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Abbreviations

AUC: area under the curve

BFI-10: Big Five Inventory-10

CART: classification and regression tree

GAD-7: Generalized Anxiety Disorder-7

PBICR: Psychology and Behavior Investigation of Chinese Residents

PHQ-9: Patient Health Questionnaire-9

PSSS: Perceived Social Support Scale

ROC: receiver operating characteristic

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Knowledge, Attitudes, Practices, and Vaccination Willingness Toward Mpox (Monkeypox) Among Chinese Medical Students: Cross-Sectional Study

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Abstract

Background: Mpox (monkeypox) remains a global public health threat. However, data on mpox-related knowledge, attitudes, and practices (KAP) and vaccination willingness among Chinese medical students, who are key future health care practitioners, remain lacking.

Objective: This study aimed to investigate systematically the KAP and mpox vaccination willingness of Chinese medical students and identify the factors influencing their vaccination decisions.

Methods: A nationwide cross-sectional survey was conducted from November 2023 to March 2024. An anonymous self-designed questionnaire was used to assess basic information, KAP toward mpox, vaccination-related behaviors, and willingness. Categorical data were presented as frequency (constituent ratio). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables that did not conform to a normal distribution were presented as median (IQR). Data were analyzed using the chi-square test, 2-tailed *t* test, ANOVA, Kruskal-Wallis *H* test, and multinomial logistic regression.

Results: Among the 4098 participants, 84.63% (*n*=3468) accepted mpox vaccination. The median scores of KAP toward mpox were 43 (IQR 33-50), 33 (IQR 32-36), and 20 (IQR 19-24), respectively, with a median score of 73 (IQR 68-79) for vaccination-related practices. Multinomial logistic regression showed that factors associated with vaccination hesitancy (vs acceptance) included male individuals (odds ratio [OR] 1.416, 95% CI 1.158 - 1.732), being an only child (OR 1.340, 95% CI 1.098 - 1.635), no history of COVID-19 in family or friends (OR 1.520, 95% CI 1.161 - 1.991), no influenza vaccination (OR 1.429, 95% CI 1.146 - 1.783), and low mpox knowledge (OR 0.948, 95% CI 0.941 - 0.955). Factors associated with vaccination rejection (vs acceptance) included male sex (OR 1.641, 95% CI 1.003 - 2.686), high academic grade (OR 1.442, 95% CI 1.154 - 1.802), family or friends working on COVID-19 frontlines (OR 2.243, 95% CI 1.337 - 3.764), no internship experience (OR 2.049, 95% CI 1.076 - 3.901), presence of organic diseases (OR 3.733, 95% CI 1.778 - 7.838), and low mpox knowledge (OR 0.954, 95% CI 0.938 - 0.971). Good self-reported health status was a protective factor against refusal (OR 0.748, 95% CI 0.580 - 0.965).

Conclusions: The high willingness to receive mpox vaccination among Chinese medical students and its determinants, as identified in this study, carry clear implications for both education and policy. These findings inform the design of targeted health education programs for students and guide the development of evidence-based prevention strategies on campuses during public health emergencies.

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KEYWORDS

monkeypox; mpox; mpox vaccination; vaccine hesitancy; determinants; knowledge; attitude; practice

Introduction

Monkeypox (mpox) is a zoonotic infectious disease caused by the mpox virus (MPXV) [1], with universal susceptibility in the human population. Its clinical manifestations are similar to those

of smallpox, including fever, rash, and malaise. A key difference from smallpox is the higher prevalence of lymphadenopathy in mpox cases [2]. The first human case of mpox was identified in the Democratic Republic of the Congo (then known as Zaire) in 1970, after which the virus was primarily endemic in west

and central Africa [3]. Since May 2022, a large-scale mpox outbreak has re-emerged globally [4]. In July 2024, a more virulent new strain of MPXV (clade Ib) began spreading rapidly in the Democratic Republic of the Congo. Initially prevalent among sex workers, this strain has now spread to other populations [5,6]. As of now, a total of 162,785 mpox cases and 424 deaths have been reported across 140 countries worldwide [7]. In China, 767 infections have been documented in 2025 [8]. The mpox epidemic may have catastrophic consequences for public health, socioeconomic factors, and the entire health care system. On July 23, 2022, the World Health Organization declared the mpox epidemic a “Public Health Emergency of International Concern” [9], and reaffirmed this declaration on August 14, 2024 [10]. On September 15, 2023, the National Health Commission of the People’s Republic of China classified mpox as a category B infectious disease for management, which took effect on September 20, 2023 [11]. In accordance with the Law of the People’s Republic of China on the Prevention and Control of Infectious Diseases, category B infectious diseases are subject to strict management [12].

Public health measures to prevent mpox transmission include enhancing public awareness of the disease; however, vaccination remains the core measure. Previous studies have demonstrated that smallpox vaccination provides at least 85% effectiveness in preventing MPXV infection [13]. The World Health Organization recommends vaccination for priority populations, but vaccine hesitancy is widespread globally [14–17]. Previous experience with COVID-19 vaccine hesitancy highlights the need for targeted research on vaccination willingness toward mpox [18,19].

Medical students represent a crucial demographic in epidemic preparedness. As future frontline health care professionals and influential health communicators, their knowledge, attitudes, practices (KAP), and willingness to be vaccinated directly will impact clinical response capacity, the effectiveness of community health education, and public health messaging during outbreaks. While prior research indicates a generally high willingness to receive the mpox vaccine among Chinese health care workers [17], data regarding medical students’ KAP related to mpox and their willingness to receive the vaccine are lacking. This study used a cross-sectional online survey to investigate the mpox-related KAP of Chinese medical students and their willingness to be vaccinated against mpox, as well as the factors influencing their vaccination willingness. These factors may serve as key targets for controlling the current mpox outbreak and rapidly responding to future epidemic outbreaks. Therefore, this study provides a basis for policy decisions regarding targeted educational interventions and vaccination strategies, thereby enhancing preparedness for potential mpox outbreaks.

Methods

Study Design

A nationwide population-based cross-sectional survey was conducted from November 2023 to March 2024, and the snowball sampling method was adopted to recruit participants. Data were collected through an anonymous, self-administered questionnaire designed to assess Chinese medical students’

demographic characteristics and KAP related to mpox, as well as vaccination-related behaviors and willingness. The study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Checklist 1).

Study Objects

The study population met the following inclusion criteria: (1) full-time medical students in mainland China, (2) currently enrolled in a degree program, and (3) willing to complete a questionnaire. A total of 4320 students participated in the survey, among whom 4098 valid questionnaires were collected, with an effective response rate of 94.86%.

Survey Methods

An anonymous online survey was conducted via the Wenjuanxing platform, a professional online survey platform in China, and snowball sampling was used to recruit participants. All the questionnaires were edited, and an electronic 2D code for the survey was generated through the Wenjuanxing online platform. The process was initiated by the research team contacting academic advisors and student leaders from various medical schools. These initial contacts were provided with a standardized recruitment package, which included a brief study description, eligibility criteria, and the unique 2D code link to the questionnaire. The initial contacts distributed the recruitment package to potential participants via QQ (Tencent), a popular instant messaging software in China, and WeChat (Tencent), a multifunctional social media and messaging app. Specifically, dissemination occurred through a combination of private messages, academic group chats, and institutional social media channels. Additionally, participants were encouraged to assist in recruiting other study individuals by sharing the electronic 2D code of the questionnaire.

Students scanned the 2D code of the questionnaire using electronic devices, participated in the survey voluntarily, and completed the questionnaire. All items in the questionnaire were set as mandatory to ensure data integrity. Each IP address was restricted to submitting the questionnaire only once to prevent duplicate submissions. Furthermore, the time spent completing the questionnaire was automatically monitored by the Wenjuanxing platform; responses were considered invalid if the completion time was less than 180 seconds.

Survey Instruments

A self-designed questionnaire was used to investigate medical students’ KAP regarding mpox, their willingness to receive mpox vaccination, and the influencing factors thereof. The questionnaire was developed on the basis of the *Technical Guidelines for Mpox Prevention and Control* (2022 version) [20]. To ensure its content validity, the initial draft was reviewed by 4 experts in public health and health education, after which it was revised. Subsequently, a pilot survey was conducted to test the clarity and feasibility of the instrument, leading to the final version used in the study.

The questionnaire consisted of 6 sections with a total of 81 items, including basic information (20 items), knowledge (23 items), attitude (11 items), practice (5 items), vaccination-related

behaviors (21 items), and vaccination willingness (1 item). For the knowledge section, 2 points were awarded for each correct answer to single-choice questions, and no points for incorrect answers; for multiple-choice questions, 1 point was given for each correctly selected option. The attitude, practice, vaccination-related behaviors, and vaccination willingness sections were scored using a 5-point Likert scale, with response options of “Strongly disagree,” “Disagree,” “Neutral,” “Agree,” and “Strongly agree,” corresponding to scores of 1, 2, 3, 4, and 5, respectively. Respondents were required to rate each question. The total score of the questionnaire was 245 points. The maximum scores for the 4 sections, knowledge, attitude, practice, and vaccination-related behaviors, were 60, 55, 25, and 105 points, respectively. The Cronbach α coefficient of the questionnaire was 0.915, indicating good reliability of the questionnaire.

Statistical Methods

SPSS (Statistical Package for the Social Sciences) 24.0 software (IBM Corp) was used for data analysis. Categorical data were presented as frequency (constituent ratio), and comparisons between groups were performed using the chi-square test or the Fisher exact test. The Kolmogorov-Smirnov test was used to test the normality of continuous variables. Continuous variables that conformed to a normal distribution were expressed as mean (SD), and comparisons between groups were conducted using the 2-tailed t test or ANOVA. Continuous variables that did not conform to a normal distribution were presented as median [IQR], and comparisons between groups were performed using the Kruskal-Wallis H test. Multinomial logistic regression was performed to identify the factors correlated with the willingness to receive the mpox vaccine. The willingness to receive the mpox vaccine was taken as the dependent variable, which included 3 categories: acceptance, hesitancy, and rejection. In the multinomial logistic regression model, the status of the acceptance group served as the reference category for the dependent variable. Variables with $P < .10$ in univariable analyses were considered as independent variables in the multinomial logistic regression model. A stepwise selection method (entry and removal criteria: $P = .05$) was used for predictor selection. The risks of the factors were displayed as odds ratios (OR) and the corresponding 95% CIs. The P value $< .05$ (2-sided) was considered statistically significant.

Ethical Considerations

This study was approved by the ethics committee of Qiqihar Medical University (approval: 202371). This study adhered to the Declaration of Helsinki. Participants in this research participated voluntarily and were conducted anonymously

through an online platform. The questionnaire did not include any identifying or sensitive content. All participants provided online informed consent. Participants did not receive any financial or nonfinancial compensation for their participation.

Results

Demographic Characteristics of Medical Students and Their Willingness to Receive Mpox Vaccination

A total of 4098 participants were included in the study, which included 1739 male participants and 2359 female participants. Among them, 3468 individuals accepted mpox vaccination, accounting for 84.63%; 550 individuals expressed hesitancy, representing 13.42%; and 80 individuals refused, making up 1.95%.

The willingness of medical students to receive mpox vaccination showed significant differences between sex ($\chi^2_2=42.5$; $P < .001$), grade ($\chi^2_8=23.8$; $P = .003$), being an only child ($\chi^2_2=8.2$; $P = .02$), the reason for choosing medicine ($\chi^2_2=11.1$; $P = .004$), having parents or relatives who worked in the frontline during the COVID-19 outbreak ($\chi^2_2=10.0$; $P = .007$), self-health status ($\chi^2_8=59.4$; $P < .001$), chronic disease ($\chi^2_2=14.1$; $P < .001$), allergic constitution ($\chi^2_2=8.6$; $P = .01$), organic disease ($\chi^2_2=26.0$; $P < .001$), having family members or friends who had experienced COVID-19 ($\chi^2_2=40.6$; $P < .001$), having received the influenza vaccination ($\chi^2_2=24.2$; $P < .001$), having received the COVID-19 vaccination ($\chi^2_2=47.6$; $P < .001$), and having considered the reason for receiving COVID-19 vaccination ($\chi^2_2=35.4$; $P < .001$). The details are presented in [Multimedia Appendix 1](#).

KAP Status Regarding Mpox Among Medical Students and Their Willingness to Receive Mpox Vaccination

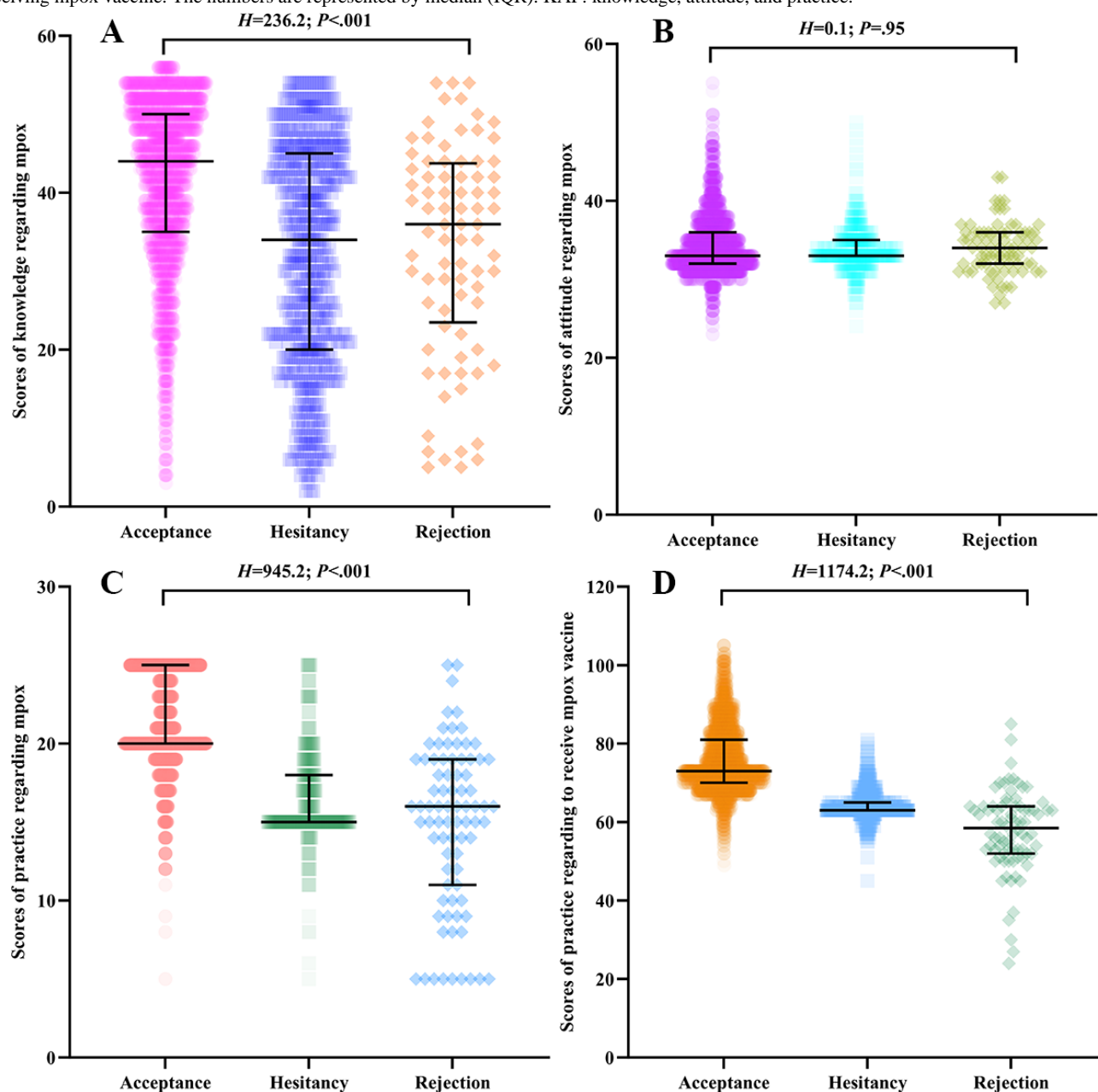
The maximum scores for the 4 sections—knowledge, attitude, practice, and vaccination-related behaviors—were 60, 55, 25, and 105 points, respectively. The median scores for KAP status regarding mpox among medical students were 43 (IQR 33-50), 33 (IQR 32-36), and 20 (IQR 19-24), respectively. The median for practice status regarding receiving the mpox vaccine among medical students was 73 (IQR 68-79). A significant difference was found between willingness to receive mpox vaccination and knowledge level regarding mpox ($H=236.2$; $P < .001$), practice status regarding mpox ($H=945.2$; $P < .001$), and practice status regarding receiving mpox vaccine ($H=1174.2$; $P < .001$). [Table 1](#) outlines the details, and [Figure 1](#) illustrates the results.

Table . Knowledge, attitude, and practice (KAP) status regarding monkeypox (mpox) among Chinese medical students and its association with their willingness to receive mpox vaccination.

Variables	All participants, median (IQR)	Willingness to receive mpox vaccine, median (IQR)			<i>H</i> value ^a	<i>P</i> value
		Acceptance	Hesitancy	Rejection		
Knowledge status regarding mpox	43 (33-50)	44 (35-50)	34 (20-45)	36 (24-43.5)	236.2	<.001 ^b
Attitude status regarding mpox	33 (32-36)	33 (32-36)	33 (33-35)	34 (32-36)	0.1	.95
Practice status regarding mpox	20 (19-24)	20 (20-25)	15 (15-18)	16 (11-19)	945.2	<.001 ^b
Practice status regarding receiving mpox vaccine	73 (68-79)	73 (70-81)	63 (63-65)	58.5 (52-64)	1174.2	<.001 ^b

^aKruskal-Wallis *H* test.^b*P*<.05 and the difference was statistically significant.

Figure 1. KAP status regarding monkeypox (mpox) and practice status regarding receiving mpox vaccination among Chinese medical students: (A) scores of knowledge regarding mpox; (B) scores of attitude regarding mpox; (C) scores of practice regarding mpox; and (D) scores of practice regarding receiving mpox vaccine. The numbers are represented by median (IQR). KAP: knowledge, attitude, and practice.




Multinomial Logistic Regression for Identification of the Factors Correlated With the Willingness to Receive Mpox Vaccination

Compared with the acceptance group, factors such as sex, only-child status, history of COVID-19 infection among students or their relatives and friends, prior influenza vaccination, and knowledge level regarding mpox were significantly correlated with hesitancy to receive the mpox vaccine. Male sex was a risk factor for vaccine hesitancy, with a 1.416-fold risk than female

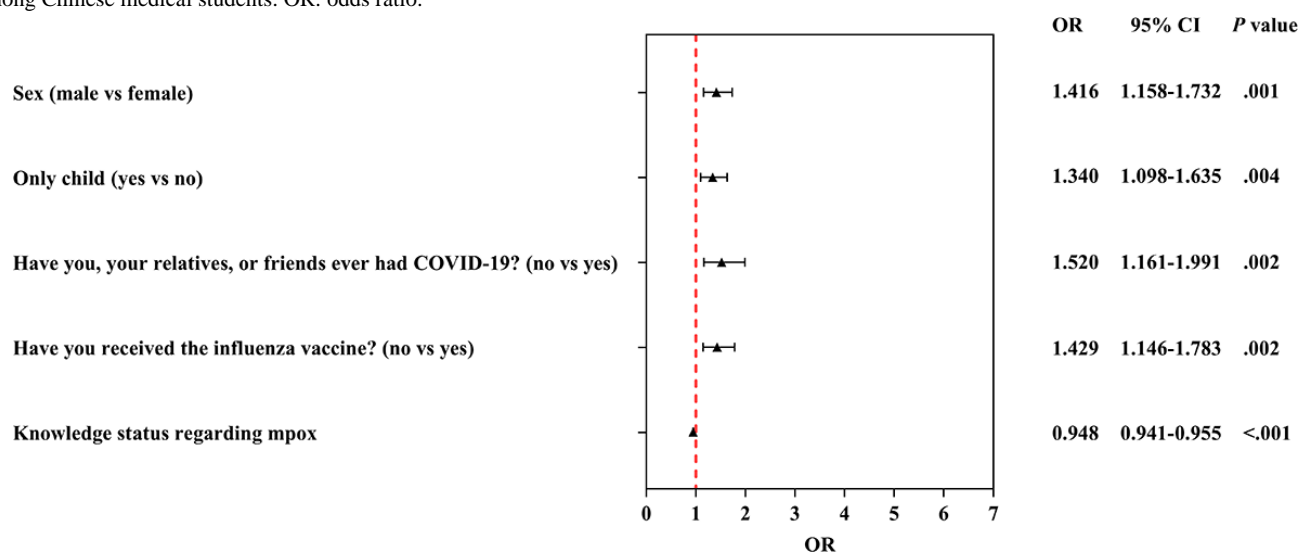
sex (OR 1.416, 95% CI 1.158-1.732). Compared with their counterpart groups, participants who were the only child in their family (OR 1.340, 95% CI 1.098 - 1.635), those who had never contracted COVID-19 with their relatives or friends (OR 1.520, 95% CI 1.161-1.991), those who had not received the influenza vaccine (OR 1.429, 95% CI 1.146 - 1.783), and those with low knowledge level regarding mpox (OR 0.948, 95% CI 0.941 - 0.955) displayed an increased hesitancy to receive mpox vaccination. Table 2 outlines the details, and Figure 2 illustrates the results.

Table . Multivariable analysis of factors correlated with monkeypox (mpox) vaccination willingness among medical students in China^a.

Variables	β		Wald chi-square (df)	P value	OR ^b (95% CI)
Hesitancy					
Sex (reference: female)					
Male	0.3481	0.1028	11.5 (1)	.001	1.416 (1.158 - 1.732)
Only child (reference: no)					
Yes	0.2928	0.1016	8.3 (1)	.004	1.340 (1.098 - 1.635)
Have you, your relatives, or friends ever had COVID-19? (reference: yes)					
No	0.4190	0.1376	9.3 (1)	.002	1.520 (1.161 - 1.991)
Have you received the influenza vaccine? (reference: yes)					
No	0.3573	0.1127	10.1 (1)	.002	1.429 (1.146 - 1.783)
Knowledge status regarding mpox	-0.0537	0.0039	194.5 (1)	<.001	0.948 (0.941 - 0.955)
Rejection					
Sex (reference: female)					
Male	0.4955	0.2513	3.9 (1)	.049	1.641 (1.003 - 2.686)
Grade	0.3662	0.1137	10.4 (1)	.001	1.442 (1.154 - 1.802)
Do your parents or relatives engage in frontline work during the COVID-19 outbreak? (reference: no)					
Yes	0.8079	0.2640	9.4 (1)	.002	2.243 (1.337 - 3.764)
Do you have internship experience? (reference: yes)					
No	0.7174	0.3285	4.8 (1)	.03	2.049 (1.076 - 3.901)
Self-health status	-0.2898	0.1298	5.0 (1)	.03	0.748 (0.580 - 0.965)
Organic disease (reference: no)					
Yes	1.3171	0.3785	12.1 (1)	.001	3.733 (1.778 - 7.838)
Knowledge status regarding mpox	-0.0467	0.0090	27.3 (1)	<.001	0.954 (0.938 - 0.971)

^aThe willingness to receive the mpox vaccine was used as the dependent variable, which included 3 categories: acceptance, hesitancy, and rejection. In the multinomial logistic regression model, the status of the acceptance group served as the reference category for the dependent variable.

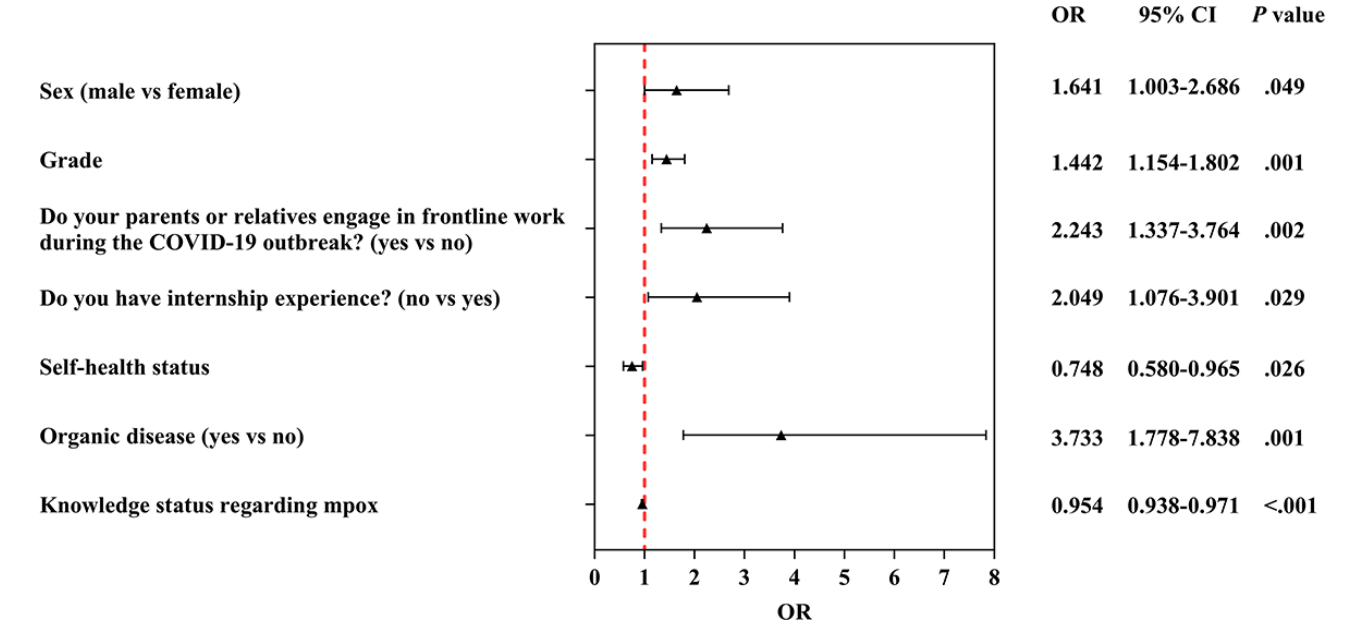
^bOR: odds ratio.

Figure 2. Multinomial logistic regression analysis of the determinants significantly associated with hesitancy to receive monkeypox (mpox) vaccination among Chinese medical students. OR: odds ratio.

Compared with the acceptance group, factors such as sex, grade, parents’ or relatives’ engagement in frontline work during the COVID-19 outbreak, internship experience, self-reported health status, presence of organic disease, and knowledge level regarding mpox were significantly correlated with rejection of mpox vaccination. Male sex was the risk factor for rejection status, with a 1.641-fold risk compared to the female sex (OR 1.641, 95% CI 1.003 - 2.686). Grade was the risk factor for rejection status with a 1.442-fold risk as grade increased (OR 1.442, 95% CI 1.154 - 1.802). Self-health status was the protective factor for rejection status as the health scores

increased (OR 0.748, 95% CI 0.580 - 0.965). Compared with their counterpart groups, participants whose parents or relatives engaged in frontline work during the COVID-19 outbreak (OR 2.243, 95% CI 1.337 - 3.764), those who had no internship experience (OR 2.049, 95% CI=1.076 - 3.901), those who had organic disease (OR 3.733, 95% CI 1.778 - 7.838), and those with low knowledge level regarding mpox (OR 0.954, 95% CI 0.938 - 0.971) displayed an increased rejection to receive mpox vaccination. Table 2 outlines the details, and Figure 3 visualizes the results.

Figure 3. Multinomial logistic regression analysis of the determinants significantly associated with rejection to receive monkeypox (mpox) vaccination among Chinese medical students. OR: odds ratio.



Discussion

Principal Findings

This study conducted a nationwide cross-sectional online survey, targeting 4098 full-time medical students in mainland China to investigate their KAP regarding mpox and their willingness to receive the mpox vaccination systematically. As the first study to focus on Chinese medical students, a group poised to become core public health practitioners, this research fills a critical gap in domestic data on mpox-related health literacy and vaccine acceptance. The findings reveal high overall vaccine acceptance among medical students, alongside clear demographic, health-related, and KAP-associated factors influencing vaccine hesitancy and rejection. These results are not only timely, given the ongoing global mpox epidemic (with 162,785 cases and 424 deaths across 140 countries) and China’s classification of mpox as a class B notifiable disease, but also provide actionable evidence for formulating targeted educational interventions and vaccine distribution strategies. By identifying modifiable determinants of vaccine willingness, this study supports enhanced preparedness for potential future mpox outbreaks and strengthens the role of medical students as frontline communicators of public health knowledge.

The results of this study showed that 84.63% of Chinese medical students were willing to accept mpox vaccination, with 13.42%

expressing hesitancy and only 1.95% refusing. This acceptance rate is remarkably higher than that reported in most studies on health care–related populations or college students. For example, a study in the Democratic Republic of the Congo involving health care workers found that the willingness rate to receive vaccines was 61% [21]; in a Saudi Arabian study, 52.7% of health care workers were willing to receive vaccines [22]; in Pakistan, the vaccine acceptance rate among college students was 67.7% [23]; while a meta-analysis conducted by Yappalparvi et al [24] showed that only 58.6% of college students were willing to receive the mpox vaccine. Another cross-sectional multinational study targeting health care providers found that the acceptability of the mpox vaccine was just over half of the participants (54.5%) [25]. Notably, the acceptance rate in our study is slightly lower than the 90.1% reported for Chinese health care workers in a 2023 systematic review by Lounis and Riad [17] but remains among the highest globally. The high vaccine acceptance among Chinese medical students can be attributed to three key factors. First, their professional medical background enables them to gain a deeper understanding of the pathogenesis of mpox, transmission risks, and the 85% protective efficacy of smallpox vaccines against mpox [13]. Furthermore, they are more capable of comprehending the high-efficiency protective mechanism of mRNA vaccines developed by scholars, which is achieved through the synergistic activation of “humoral immunity +

cellular immunity” [26,27]. This knowledge reserve mitigates doubts arising from information asymmetry. Second, differences in the policy environment are equally critical. China’s strict category B management of mpox, coupled with targeted health education conducted via official guidelines, such as *Monkeypox Prevention and Control Technology* (2022 Edition) [20], has established a clear public health narrative regarding the necessity of vaccines. In addition, the experience accumulated from large-scale COVID-19 vaccination has led to a remarkably higher recognition of vaccines as public health intervention tools among Chinese medical students [28,29]. The marginal gap between medical students and practicing health care workers likely reflects differences in direct clinical exposure risk; health care workers face immediate occupational exposure, while medical students’ risk perception is more knowledge-based than experiential.

Multivariate logistic regression identified five independent factors associated with vaccine hesitancy: male sex, being an only child, no personal or familial COVID-19 history, no influenza vaccine uptake, and low mpox knowledge levels. Male participants were 1.416-fold more likely to be hesitant than female participants (OR 1.416, 95% CI 1.158 - 1.732). This result is consistent with the findings of a study on COVID-19 vaccines among Saudi university students, where male individuals often exhibit low health-seeking behavior and a great tendency to downplay infectious disease risks [30]. The observed association in our study may reflect a similar pattern of risk underestimation, which could be a particularly relevant factor in decision-making regarding nonhighly lethal infectious diseases such as mpox. Only children had a 34.0% higher hesitancy risk (OR 1.340, 95% CI 1.098 - 1.635). This unique finding is closely associated with the characteristics of family structures shaped by the long-term impact of China’s family planning policy. Only children often face greater parental caution regarding medical interventions, and family decision-making may prioritize avoiding potential, even rare, vaccine risks over mpox prevention. Furthermore, only children may have less exposure to collective health narratives compared with those with siblings, reducing perceived personal responsibility for vaccination. Participants without a history of COVID-19 in themselves or relatives were 1.520-fold more hesitant (OR 1.520, 95% CI 1.161 - 1.991). A study in Arab countries also found that experiencing COVID-19 firsthand or through family members likely reinforces awareness of infectious disease severity and the value of preventive measures [31]. By contrast, those without such experience may perceive mpox as a “distant threat,” weakening motivation to accept vaccination. Nonrecipients of influenza vaccines had a 42.9% higher hesitancy risk (OR 1.429, 95% CI 1.146 - 1.783). Influenza vaccine uptake reflects established trust in routine immunization. Nonrecipients may hold persistent doubts about vaccine safety or effectiveness, attitudes that generalize to novel vaccines such as mpox. This result suggests that routine vaccine adherence is a strong predictor of willingness to accept emerging vaccines. The level of correct knowledge about mpox among medical students was associated with vaccine willingness: each unit decrease in knowledge score increased hesitancy (OR 0.948, 95% CI 0.941 - 0.955). This finding echoes the conclusion from a Nigerian study that “knowledge gaps lead to barriers in

prevention and control” [32]. Medical students with incomplete knowledge may misunderstand transmission routes or overestimate vaccine side effects, resulting in hesitation. Within the KAP framework, these factors do not exist in isolation. Knowledge of emerging infectious diseases, as an identified influencing factor, may affect individuals’ vaccination attitudes, and such attitudes may further impact vaccination willingness. Past vaccination practices may consolidate vaccination attitudes, which is supported by our single-factor analysis results showing that previous influenza and COVID-19 vaccination history strengthened mpox vaccination willingness. These findings indicate that vaccine hesitancy may arise from the interaction of knowledge, attitudes, and practices.

Vaccine refusal was associated with 6 factors: male sex, high academic year, having relatives or friends who worked on the COVID-19 frontline, no internship experience, presence of organic diseases, and low mpox knowledge. Conversely, good self-reported health status was a protective factor. Male participants were 1.641-fold more likely to refuse (OR 1.641, 95% CI 1.003 - 2.686), and each increase in academic year raised refusal risk by 44.2% (OR 1.442, 95% CI 1.154 - 1.802). The sex effect is more pronounced for refusal than hesitancy, suggesting male individuals may hold more entrenched skepticism, possibly due to overconfidence in clinical knowledge or exposure to niche medical debates about vaccine use. Higher-year students, while more knowledgeable about clinical practice, may also be more exposed to anecdotal reports of vaccine adverse events, which could foster increased skepticism toward public health guidelines. This skepticism may manifest as deliberate rejection rather than indecision. Studies on American medical students also found that 25.1% of the students believed that vaccine education was insufficient, and 8.6% refused to encourage patients to receive the COVID-19 vaccine [33]. Such findings suggest that clinical training should strengthen education on “the dialectical relationship between individual cases and population data.” Participants with relatives or friends on the COVID-19 frontline had a 2.233-fold higher refusal risk (OR 2.233, 95% CI 1.337 - 3.764). This counterintuitive finding may stem from unique knowledge sources and consequent attitude shifts. Their proximity to frontline workers provides them with first-hand, often stressful, knowledge regarding systemic challenges, health care worker overwork, and rare adverse events. This direct or relayed knowledge can critically shape attitudes, eroding trust in official vaccine recommendations, which is consistent with the research findings on high vaccine hesitancy toward the COVID-19 vaccine in health care workers and health care students worldwide [34]. This finding also aligns with the conclusion that pandemic fatigue among the Chinese public in the postpandemic era may hinder the conversion of vaccine uptake willingness into actual behavior [35], suggesting that authorities must rebuild the trust of professional groups by enhancing transparency in epidemic prevention and control processes. Students without internships were 2.049-fold more likely to refuse (OR 2.049, 95% CI 1.076 - 3.901). Clinical internships expose students to real-world cases and reinforce vaccine use through direct observation of patient outcomes. Without this experiential learning, vaccine refusal may stem from abstract, theoretical skepticism rather than evidence-based reasoning.

Individuals with organic diseases had the highest refusal risk (OR 3.733, 95% CI 1.780 - 7.838). This result is clinically rational: those with chronic conditions may fear vaccine-disease interactions or adverse effects exacerbating their condition. Even with medical training, concerns about individual health vulnerability likely override general preventive benefits, highlighting the need for personalized vaccine counseling [36,37]. Concerns about vaccine safety are also reflected in surveys conducted among college students in southwest China [38]. Low knowledge increased refusal (OR 0.954, 95% CI 0.938 - 0.971), while good health reduced it (OR 0.748, 95% CI 0.580 - 0.965). Healthy students may perceive fewer barriers to vaccination and more benefits. By contrast, knowledge deficits amplify misconceptions [39]; for example, conflating mpox with low-prevalence diseases, leading to active rejection.

Limitations

The following limitations should be acknowledged. First, the snowball sampling in this study was a nonprobability sample, as all participants enrolled on a voluntary basis. Therefore, the recruitment networks may have over-represented students with stronger social connections or a pre-existing interest in public health, which could introduce selection bias. Second, 4 experts in public health and health education reviewed the questionnaire for content validity, while factor analysis results were lacking. Third, self-reported vaccination willingness may be subject to social desirability bias, which may have been heightened by mandatory response items, regulated minimum response time, and the participants' identity as medical students. Fourth, the

study sample was confined to medical students, which limits the generalizability of the findings to nonmedical students or other populations. Finally, the use of a self-designed questionnaire may limit comparability with other studies.

Conclusions

This study demonstrates high mpox vaccination acceptance among Chinese medical students. Factors associated with vaccination hesitancy included male sex, being an only child, no history of COVID-19 in family or friends, no influenza vaccination, and low mpox knowledge. Factors associated with vaccination rejection included male sex, high academic grade, family or friends working on COVID-19 frontlines, no internship experience, and presence of organic diseases. Good self-reported health status was a protective factor against refusal. The identified influencing factors provide actionable insights for policymakers, offering a reference for future risk assessment, emergency response, and management during similar public health emergencies. For medical education, the findings point to specific, operational measures: integrating mpox education into medical curricula to address knowledge gaps; designing targeted messaging for higher-risk subgroups such as male individuals and senior students; leveraging medical students as trusted community health advocates; and rebuilding trust through transparent communication, particularly among those affected by pandemic fatigue. These measures not only contribute to controlling current mpox outbreaks but also strengthen long-term public health resilience against future zoonotic disease threats.

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Data Availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

JC and YL contributed to conceptualization, project management, resources, supervision, writing, and review. YJ and JG analyzed the data and reviewed the manuscript. HL, YH, and ZX were responsible for data curation, investigation, supervision, and software. JC acquired funding. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Demographic characteristics of Chinese medical students and their willingness to receive monkeypox (mpox) vaccination. [DOC File, 114 KB - [publichealth_v12i1e86981_app1.doc](#)]

Checklist 1

STROBE checklist.

[DOCX File, 45 KB - [publichealth_v12i1e86981_app2.docx](#)]

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Abbreviations

KAP: knowledge, attitudes, and practices

mpox: monkeypox

MPXV: monkeypox virus

OR: odds ratio

SPSS: Statistical Package for the Social Sciences

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Original Paper

Digital Exclusion Among People Experiencing Homelessness and Residents of Urban Communities in Brazil: Cross-Sectional Study

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Abstract

Background: The COVID-19 pandemic amplified digital divides in Brazil, restricting vulnerable groups' online access to health information and preventive guidance, with limited intersectional analyses of these inequities.

Objective: This study aimed to investigate inequalities in digital exclusion and access to online COVID-19 information among people experiencing homelessness and residents of urban communities in Brazil by using an intersectional multilevel analysis.

Methods: A cross-sectional study (2021-2023) involving 2652 participants (n=1353, 51% experiencing homelessness and n=1299, 49% from urban communities across 26 state capitals) was conducted using the adapted COVID-19 Social Thermometer questionnaire administered via face-to-face interviews. Multilevel analysis of individual heterogeneity and discriminatory accuracy examined 115 intersectional strata (gender, race and ethnicity, schooling, income, and Brazilian Unified Health System use) with online COVID-19 information seeking as the binary outcome; multilevel logistic models estimated additive effects and between-strata variance.

Results: Most participants were men (1600/2652, 60.3%), self-identified as Black or Brown individuals (1942/2652, 73.2%), and were Unified Health System users (2433/2652, 91.7%) without private insurance (2469/2652, 93.1%). Over one-third (905/2652, 34.1%) had no formal schooling; 62.4% (1655/2652) reported low income. A total of 39.2% (1040/2652) sought online COVID-19 information. Being a woman (odds ratio [OR] 1.49, 95% CI 1.13-1.97), higher schooling (OR 1.78-5.59, 95% CI 3.52-8.88), and higher income (OR 2.37-4.54, 95% CI 2.59-7.93) showed a stronger association with online COVID-19 information seeking; public health system use was not associated with the outcome (OR 0.92, 95% CI 0.64-1.33). Predicted probabilities ranged between 14% and 85% across 115 strata, with the lowest among Black or Brown men (no schooling or low income) and the highest among women and higher schooling or income. The intersectional analysis (n=2405) null model showed 24% between-strata variance; the full additive model reduced it to 1% (proportional change in variance=97%).

Conclusions: Intersectional analysis reveals structural informational exclusion driven by additive disadvantages in schooling, income, and gender among participants, calling for digital inclusion policies, critical health literacy programs, and equitable multichannel communication strategies to address persistent COVID-19 information seeking disparities.

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KEYWORDS

digital health; intersectionality; COVID-19; information-seeking behavior; internet

Introduction

The COVID-19 pandemic exacerbated structural inequalities in health and information systems, highlighting barriers to accessing reliable content [1,2]. In Brazil, the unequal distribution of digital infrastructure, combined with low health literacy, a phenomenon known as the digital divide, undermined the ability of vulnerable social groups to access and apply relevant information for adopting preventive measures [3,4].

Digital exclusion refers to the inability of individuals or groups to fully participate in digital society due to barriers in access, skills, or use, resulting in limited benefits from online services such as health information [5].

In the COVID-19 context, it manifested as restricted access to online pandemic guidance, exacerbated by 3 layers: physical or material access (device or internet costs), skills (digital literacy), and outcomes (effective information seeking) [5]. During lockdowns, services shifted online, excluding people in vulnerable situations without smartphones (eg, 22% of UK adults lacked basic digital skills before the pandemic), creating “informational exclusion” in which low-income, low-literacy groups missed preventive advice, worsening health inequities [6].

Despite growing evidence of the digital divide in Brazil, most studies focus on the general population or on socioeconomically disadvantaged households and rarely include people experiencing homelessness or residents of urban communities as specific populations of interest [4-9]. Furthermore, previous work has typically analyzed social dimensions such as gender, race, educational level, income, and use of health services separately rather than examining how these characteristics intersect to shape digital exclusion and access to online COVID-19 information.

By applying an intersectional multilevel analysis to people experiencing homelessness and residents of urban communities in Brazil, this study addresses this gap and provides new evidence on how overlapping social positions jointly influence inequalities in digital exclusion.

From a methodological perspective, few studies have used multilevel analysis of individual heterogeneity and discriminatory accuracy (MAIHDA), a statistical approach that estimates the effects of specific social combinations on outcomes and can overcome several limitations of traditional additive models [10,11]. Grounded in Black feminist scholarship, this approach provides robust tools for measuring structural inequality [12-14].

In this context, the COVID-19 pandemic presents a critical opportunity to identify patterns of digital and informational exclusion that, if not addressed, are likely to persist and deepen in future public health emergencies. Therefore, this study aimed to investigate inequalities in digital exclusion and access to online COVID-19 information among people experiencing homelessness and residents of urban communities in Brazil using an intersectional multilevel analysis to examine how overlapping social characteristics jointly shape these disparities.

Methods

Study Design

This was a cross-sectional study guided by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [15,16].

Study Setting

This study was conducted in all 26 Brazilian state capitals and the Federal District, covering the 5 major regions of the country: north, northeast, central-west, southeast, and south. This geographic coverage was defined to encompass diverse urban and regional contexts considering Brazil's socioterritorial diversity and the deep structural inequalities that characterize the country [17,18].

Brazil has a total area of approximately 8.5 million km² and an estimated population of 203 million [19]. The target population of this study included people experiencing homelessness and residents of urban communities to capture their experiences and vulnerabilities during the COVID-19 pandemic.

The selection of these groups is justified by historical inequalities in access to basic rights, including health care, housing, and information, which were exacerbated during the pandemic [20,21]. It is estimated that the country has approximately 281,400 individuals experiencing homelessness and approximately 16.4 million residents of urban communities, representing 8.1% of the national population [22,23].

Study Population and Sample

Inclusion criteria were Brazilian nationality, age of ≥18 years, and either residence in an urban community or living in a situation of homelessness. For the intersectional analysis, participants who did not provide responses to key variables, namely, gender, race and ethnicity, income, place of residence, use of the Unified Health System (SUS; *Sistema Único de Saúde* in Portuguese), and information-seeking behavior related to COVID-19, were excluded. This represented 9.3% (247/2652) of the total sample.

Urban communities refer to densely populated territories characterized by unregulated growth and inadequate infrastructure. In contrast, people experiencing homelessness are those without conventional housing, living in public spaces such as sidewalks, squares, and abandoned buildings and exposed to multiple forms of vulnerability [24].

Sampling was sequential, where participants were invited to take part as they were approached in public spaces, shelters, hostels, boarding houses, and urban communities provided they were willing to take part and gave informed consent [25].

Due to the unique characteristics of each of Brazil's macroregions, the sample did not have a fixed size for each subgroup. Therefore, we applied the standard formula for simple random sampling with finite populations following classic references for opinion polls, epidemiological research, and surveys [26]. Specifically, the Cochran formula for infinite populations is as follows:



The adjusted Cochran formula for finite populations is as follows:



In these formulas, z is the percentile of the standard normal distribution, ϵ is the margin of error, N is the population size, and \hat{p} is the estimated population proportion. On the basis of the calculation for finite populations, a minimum sample size of 385 individuals was adopted for the vulnerable population considering a random margin of error of 5%, a confidence level of 95%, a statistical power of 80%, and a variance of 50%. Additionally, a 10% increase was calculated to account for possible sample losses [26,27].

Data Collection Instrument

The instrument used for data collection was the COVID-19 Social Thermometer: Social Opinion questionnaire, originally developed by the National School of Public Health at NOVA University Lisbon and later adapted and validated for the Brazilian context using the Delphi method. The questionnaire comprises 141 variables, including structured questions formatted as checklists, multiple-choice items, and Likert-scale responses [28].

To ensure data integrity and security, the questionnaire was hosted on REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, web-based platform widely used by academic institutions worldwide for the collection and management of clinical and epidemiological research data. The REDCap version used in this study was installed at the University of São Paulo (USP) Ribeirão Preto campus and includes features that ensure response traceability and internal consistency [29].

Data Collection

Data collection was conducted between 2021 and 2023 across multiple urban settings characterized by high social vulnerability. Participant mobilization took place through a coordinated network of professionals from research institutions, universities, civil society organizations, and social movements, which facilitated access to different territories and ensured broad geographic coverage.

Participants were recruited as they were encountered in the field following predefined routes and schedules established by the research team in collaboration with local partners. Recruitment took place in public spaces (such as parks, squares, and streets), shelters, social assistance centers, hostels, boarding houses, and urban communities.

Among people experiencing homelessness, interviewers circulated through designated areas previously identified by local teams familiar with the territory and the population. Recruitment followed a standardized protocol: individuals were approached individually, informed about the study, and invited to participate if they met the eligibility criteria and demonstrated willingness to participate. This procedure also ensured participant safety and adherence to ethical standards.

In urban communities, recruitment occurred with the support of local partners in each city, who acted as intermediaries. These groups identified the most appropriate locations and times for conducting interviews, facilitated safe entry into the territory, and guided the research team toward areas with greater resident flow. This collaboration contributed to a systematic recruitment approach and enhanced both the feasibility and safety of fieldwork.

All interviews were conducted face-to-face using mobile devices (tablets or smartphones) by interviewers who were previously trained and exclusively assigned to the project. Training emphasized consistent administration of the questionnaire, standardized participant approach techniques, and the reduction of potential measurement bias. Each interview lasted approximately 20 to 30 minutes and was conducted only once, a strategy necessary due to the high mobility of people experiencing homelessness.

Study Variables

The outcome variable in this study was the search for information about COVID-19 on the internet, operationalized as a dichotomous variable (“yes” or “no”). In the questionnaire, the question used was as follows: “Which sources of information do you use to stay informed about covid-19?” Among the 8 available response options, the category “internet” was isolated as the main outcome indicator. Participants who selected this option were classified as “yes,” and those who did not select it were classified as “no.”

The internet was selected as the outcome variable due to its central role as a mediator of access to information during public health crises. During the pandemic, the web became the primary channel for disseminating health-related content. However, its use depends on physical access, connectivity, digital literacy, and information seeking skills. Thus, internet use constitutes not only an informational practice but also an indirect marker of structural inequality. By analyzing this variable in isolation, the aim was to identify social profiles with a lower propensity to rely on this resource, particularly among vulnerable populations in territories historically marked by digital exclusion.

To examine differences in information-seeking behavior across dimensions, five socioeconomic characteristics were used to construct intersectional strata: (1) gender (man, woman, or other); (2) race or ethnicity (White; Black or Brown; or other, comprising East Asian and Indigenous identities); (3) household income (low income [no income and less than 1 minimum wage per month], 1 to 2 minimum wages per month, 2 to 3 minimum wages per month, and more than 3 minimum wages per month); (4) schooling (no schooling, basic education, secondary education, and higher education); and (5) use of the SUS (yes and no), the Brazilian public and universal health system, constitutionally guaranteed and responsible for comprehensive health care delivery to the population [30]. Race/ethnicity was self-reported and categorized according to the Brazilian Institute of Geography and Statistics (IBGE) as White, Black, Brown (parda), Asian, and Indigenous.

For race and ethnicity, the categories “other,” “East Asian,” and “Indigenous” were grouped into a single category due to their very low frequency in the sample. This procedure resulted in 3 analytically robust categories: White, Black or Brown, and “other.” A similar limitation occurred for the gender variable, which was collected through self-identification with the response options “woman,” “man,” and “other,” the latter allowing participants to specify another gender identity, including transgender identities. However, no participant selected the “other” option in the final dataset. Consequently, although the study design allowed for the identification of gender diversity, the empirical distribution did not include respondents outside the “woman” or “man” categories.

Furthermore, it is important to highlight that the minimum wage in Brazil varied between R\$1100 (US \$197.68) and R\$1320 (US \$237.22) over the course of the study. These variables (sex, race/ethnicity, schooling, household income, and use of the public health system) were selected based on the literature on inequalities in access to information with the goal of analyzing differences in information-seeking behavior across distinct social groups.

Data Analysis

We used the MAIHDA approach within an intersectional framework [11]. Following the 2-model intersectional MAIHDA approach described by Evans et al [10], the analysis was designed to estimate inequalities across social strata, quantify the role of additive main effects, and detect potential intersectional interaction effects.

An intersectional strata matrix was constructed based on the combination of 5 sociodemographic and health-related dimensions: gender (2 categories), race and ethnicity (3 categories), schooling (4 categories), family income (4 categories), and use of the public health system (2 categories).

This resulted in 192 possible intersectional strata ($2 \times 3 \times 4 \times 4 \times 2$) [10,11,31-33]. Among these, 115 intersectional strata were represented in the study sample and constituted the analytical strata. The selection of these combinations was constrained by data availability but achieved the maximum feasible level of intersectional detail.

Variable selection was guided by the premise that inequalities may exist in access to information relevant to coping with COVID-19. On the basis of the matrix, an intersectional MAIHDA model was conducted, with individual-level data nested within intersectional strata. To estimate the probability of seeking COVID-19-related information, we applied a sequence of 2 multilevel logistic regression models [10,11].

The null model (model 1) included only a random intercept for each intersectional stratum with no fixed covariates. From this model, the between-stratum variance (σ^2) was estimated, and the variance partition coefficient (VPC) was calculated on the latent scale assuming a fixed residual variance (approximately $\sigma^2=3.29$) according to the latent response approach for logistic models. The VPC represents the proportion of the total variance attributable to differences between strata. We also calculated the area under the receiver operating characteristic curve (AUC)

to assess the discriminatory accuracy of the strata in predicting internet use [10,11,31-33].

The second model (model 2) included all variables defining the intersectional strata (race and ethnicity, schooling, family income, and use of the public health system) as fixed effects at level 2 while retaining the stratum random intercept. This model allowed us to break down the between-stratum variance into a component explained by additive main effects and a residual component attributable to intersectional interaction effects [10,11,31-33].

The proportional change in variance (PCV) was calculated to quantify the reduction in between-stratum variance relative to the null model. Its complement ($1-PCV$) represents the portion of residual variance that may be attributed to intersectional interactions. Additionally, predicted probabilities were estimated for each stratum and broken down into an additive component (based on fixed effects) and an interaction component (the difference between the total predicted probability and the additive component). This allowed for the identification of strata with meaningful deviations from additivity [10,11,31-33].

The AUC was interpreted following the work by Axelsson Fisk et al [11]. In MAIHDA models, the AUC is treated as a comparative measure of the strata's ability to discriminate the outcome, avoiding conventional absolute thresholds for predictive classification. The AUC ranges from 50% (no discriminatory accuracy) to 100% (perfect discriminatory accuracy), reflecting how well intersectional strata distinguish between individuals with and without the outcome [10,11,31-33].

All models were estimated using the maximum likelihood estimation method via the *lme4* package (*lmer* and *glmer* functions) in the R software (version 4.4.0; R Foundation for Statistical Computing) [34].

Ethical Considerations

This study was approved by the Research Ethics Committee of the Ribeirão Preto School of Nursing at USP, with certificate of submission for ethical appraisal (57933622.4.1001.5393). The entire investigation was conducted in accordance with resolution 466 of December 12, 2012, of the National Health Council considering the relevant ethical and scientific foundations. Before participation, all individuals were informed about the purpose of the study, their rights, and the voluntary nature of participation. Participants received no compensation for participation. The informed consent form was read and explained to participants, and only those who agreed and provided written informed consent were interviewed. For participants who were unable to read or write, consent was obtained verbally and documented through a fingerprint signature. Participant confidentiality was ensured throughout the study. Personal information obtained during data collection was stored securely in encrypted REDCap servers hosted at USP, with access limited to authorized members of the research team. Before any analytical procedures were performed, all datasets were anonymized, and any variables that could identify individuals were removed. Statistical analyses were conducted exclusively with deidentified data, and no results are presented

in a manner that could allow for the reidentification of participants.

Results

Descriptive Analysis

A total of 2652 individuals participated in the study (Table 1), of whom 1353 (51%) self-identified as people experiencing

homelessness and 1299 (49%) were residents of urban communities. Most participants were men (1600/2652, 60.3%), self-identified as Black or Brown individuals (1942/2652, 73.2%), were uninsured (2469/2652, 93.1%), and used the Brazilian SUS (2433/2652, 91.7%). A considerable proportion of participants had no formal education (905/2652, 34.1%) and reported low income (1655/2652, 62.4%). Regarding the use of the internet to seek information about COVID-19, most (1612/2652, 60.8%) stated that they did not use this source.

Table 1. Socioeconomic characteristics of vulnerable populations seeking online information about COVID-19 (Brazil, 2021-2023; N=2652).

Variable	Values, n (%)
Participant category	
People experiencing homelessness	1353 (51)
People residing in urban communities	1299 (49)
Gender	
Man	1600 (60.3)
Woman	1001 (37.7)
No answer	51 (1.9)
Race or ethnicity	
Black or Brown	1942 (73.2)
White	601 (22.7)
Other	109 (4.1)
Schooling	
No schooling	905 (34.1)
Basic education	726 (27.4)
Secondary education	871 (32.8)
Higher education	148 (5.6)
Family income	
Low income	1655 (62.4)
1 to 2 minimum wages	570 (21.5)
2 to 3 minimum wages	157 (5.9)
More than 3 minimum wages	94 (3.5)
Did not know	176 (6.6)
Use of the public health system	
Yes	2433 (91.7)
No	219 (8.3)
Health insurance	
Yes	172 (6.5)
No	2469 (93.1)
No answer	11 (0.4)
Seeking COVID-19 information online	
Yes	1040 (39.2)
No	1612 (60.8)

MAIHDA Analysis

For the intersectional analysis using the MAIHDA approach, 2405 participants were included after applying eligibility criteria.

Table 2 presents the results from the hierarchical logistic models used to estimate the likelihood of seeking information about COVID-19 on the internet based on intersectional strata defined by sociodemographic characteristics.

Table 2. Intersectional multilevel analysis of individual heterogeneity and discriminatory accuracy results with parameter estimates from logistic models predicting seeking online information about COVID-19 among vulnerable populations in Brazil (2021-2023).

	Model 1	Model 2
Fixed effects: regression coefficients, OR^a (95% CI)		
Intercept	1.02 ^b (0.78-1.31)	0.19 ^b (0.14-0.25)
Gender		
Man (reference)	— ^c	—
Woman	—	1.49 ^b (1.13-1.97)
Race or ethnicity		
Black or Brown	—	—
White (reference)	—	1.05 (0.82-1.34)
Other	—	1.35 (0.82-2.24)
Schooling		
No schooling (reference)	—	—
Basic education	—	1.78 ^b (1.32-2.41)
Secondary education	—	3.37 ^b (2.53-4.49)
Higher education	—	5.59 ^b (3.52-8.88)
Family income		
Low income (reference)	—	—
1-2 minimum wages	—	2.37 ^b (1.84-3.06)
2-3 minimum wages	—	2.85 ^b (1.87-4.34)
More than 3 minimum wages	—	4.54 ^b (2.59-7.93)
Use of the public health system		
Yes (reference)	—	—
No	—	0.92 (0.64-1.33)
Summary statistics		
Variance partition coefficient (%)	24	1
Proportional change in variance (%)	—	97
Area under the receiver operating characteristic curve	0.74	0.73

^aOR: odds ratio.

^bStatistically significant at $P < .05$.

^cNot applicable.

Model 1 (null) showed a VPC of 24%, indicating that nearly a quarter of the total variation in information-seeking behavior lay between social strata; that is, between-group inequality was substantial. The AUC was 0.74.

Model 2, which included the individual components of the strata as additive effects, reduced the VPC to 1%, with a PCV of 97%. This means that almost all the inequality observed between strata can be explained by additive effects of gender, race, educational level, income, and age. The AUC remained

practically unchanged (0.73), suggesting that incorporating additive effects did not significantly improve the predictive capacity of the model.

Women were more likely to seek information online than men (odds ratio [OR] 1.49, 95% CI 1.13-1.97), representing a 49% increase in odds relative to the reference group.

Schooling was positively associated with the outcome. Compared to individuals with no formal schooling, those with primary schooling had a 78% higher likelihood of seeking

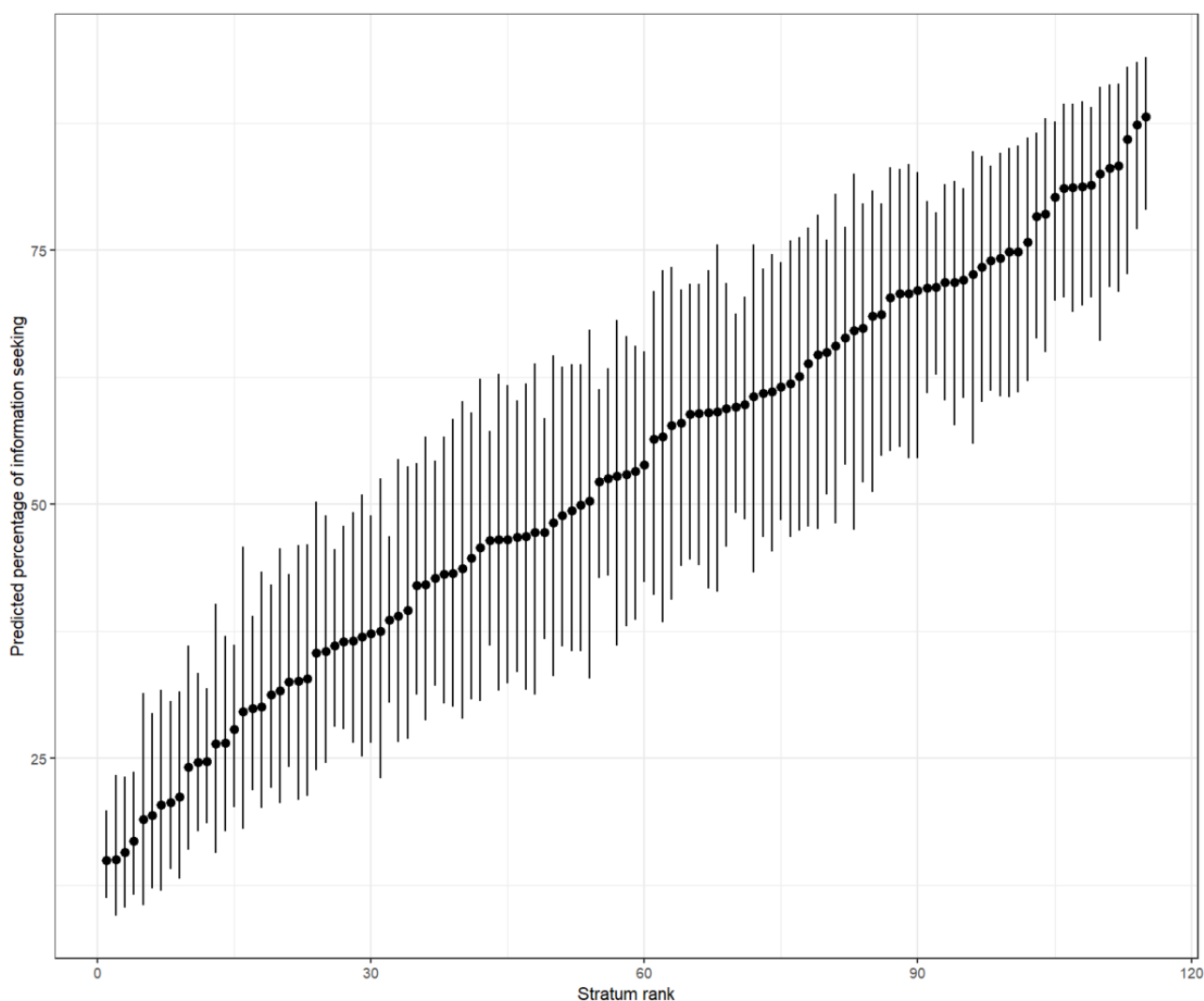
information (OR 1.78, 95% CI 1.32-2.41), those with secondary schooling had a 237% increase (OR 3.37, 95% CI 2.53-4.49), and those with higher education had a 459% increase (OR 5.59, 95% CI 3.52-8.88).

Household income was also positively associated with information seeking. Compared to participants in the lowest income category, those earning between 1 and 2 minimum wages had an OR of 2.37 (95% CI 1.84-3.06), those earning between 2 and 3 minimum wages had an OR of 2.85 (95% CI 1.87-4.34), and those who earned more than 3 minimum wages had an OR of 4.54 (95% CI 2.59-7.93). Use of the public health system was not significantly associated with the outcome (OR 0.92, 95% CI 0.64-1.33).

Comparison between models revealed a substantial reduction in between-strata variance: the VPC dropped from 25% in the null model to 0.01% in the full model, resulting in a PCV of 97%. The VPC of 25% indicates that one-quarter of the variance in information-seeking behavior was attributable to intersectional groupings. This finding suggests that most of the explained variance was due to the additive effects of individual variables rather than intersectional interactions. The AUC for model 2 was 0.73, maintaining a similar discriminatory performance to that of the null model.

Figure 1 shows the predicted probabilities of seeking COVID-19 information across intersectional strata (null model). Strata are ranked from the lowest to the highest predicted probability. Predicted values range from approximately 15% to nearly 90%, revealing a wide gradient of intersectional inequality.

Figure 1. Predicted probabilities of seeking COVID-19 information across intersectional strata (null model) in Brazil in 2021-2023.



The continuous distribution—without discrete clusters—suggests cumulative and overlapping disadvantage. Wider CIs for some strata reflect smaller sample sizes and greater estimation uncertainty. Because the null model captures both additive and interactive components, this distribution represents the overall pattern of intersectional heterogeneity in information-seeking behavior.

Table 3 presents the 5 intersectional strata with the lowest and highest predicted probabilities of seeking information about COVID-19 online based on estimates from the null model (model 1). The strata are organized in ascending order of predicted probability.

Table 3. Classification of strata by predicted probability levels (highest and lowest) of seeking online information about COVID-19 among vulnerable populations (null model; Brazil, 2021-2023).

Rank	Stratum ID	Gender	Race or ethnicity	Schooling	Family income	Use of the public health system	n (participants per stratum)	Predicted probability of seeking online information about COVID-19 (95% CI)
Five strata with the lowest information seeking								
1	12111	Man	Black or Brown	No schooling	Low income	Yes	335	14.26 (9.20-23.13)
2	13111	Man	Other	No schooling	Low income	Yes	19	18.31 (10.80-31.78)
3	23111	Woman	Other	No schooling	Low income	Yes	8	18.40 (10.80-31.78)
4	21111	Woman	White	No schooling	Low income	Yes	38	19.48 (11.71-23.84)
5	12112	Man	Black or Brown	No schooling	Low income	No	53	19.61 (9.91-23.86)
Five strata with the highest information seeking								
110	21321	Woman	White	High schooling	1-2 minimum wages	Yes	35	79.17 (69.54-90.65)
111	22421	Woman	Black or Brown	Higher education	1-2 minimum wages	Yes	11	79.17 (69.54-90.65)
113	12421	Man	Black or Brown	Higher education	1-2 minimum wages	Yes	12	80.32 (73.28-93.25)
114	11441	Man	White	Higher education	More than 3 minimum wages	Yes	8	81.80 (76.58-92.86)
115	11331	Man	White	Higher education	2-3 minimum wages	Yes	11	84.82 (73.28-93.25)

Among the 5 strata with the lowest predicted probabilities, there was a predominance of men; Black, Brown, or other race or ethnicity; no formal education; low-income households; and use of the public health system. The lowest predicted probability was 14.26% (95% CI 9.2%-23.13%).

In contrast, the 5 strata with the highest predicted probabilities showed an opposite profile: most were women or men with higher education, middle to high income (1-3 minimum wages), and users of the public health system. The predicted probabilities of information seeking in these strata ranged from 79.17% (95% CI 69.54%-90.65%) to 84.82% (95% CI 73.28%-93.25%).

These findings highlight the coexistence of significant intersectional disparities in health information seeking during the pandemic associated with structural markers of vulnerability such as race or ethnicity, educational attainment, income, and access to public health services

Discussion

Principal Findings

This study aimed to investigate inequalities in digital exclusion and access to online COVID-19 information among people experiencing homelessness and urban community residents in Brazil using intersectional multilevel analysis. Key findings show that only 39.2% (1040/2652) sought online COVID-19 information, with being a woman, higher schooling, and income strongly linked to higher access across 115 intersectional strata.

The findings also revealed predicted probabilities ranging from 14% (Black or Brown men, no schooling, and low income) to 85% (higher educated, higher income groups), with 97% of the between-strata variance (VPC=24% to 1%) explained by additive effects rather than interactions. The findings confirm structural digital exclusion driven by overlapping gender, schooling, income, race or ethnicity, and SUS use disadvantages, fulfilling the study's goal of mapping how social positions jointly shaped informational inequities during the pandemic [10,11,32].

The association between higher levels of education and greater use of the internet as a source of health information reflects not only technical access but also, more importantly, the possession of cognitive and informational competencies that support autonomy in health care [35]. Income, in turn, functions as a proxy for time availability, connectivity, access to digital devices, and overall stability, factors that are all essential for sustained online engagement. This underscores the structural nature of digital exclusion [36,37].

The absence of an association between the use of the SUS and online health information seeking suggests that the public health care system still lacks effective digital strategies for informational mediation targeting vulnerable populations. This finding offers a critical lesson for future public health emergencies: institutional digital channels alone are not sufficient. Health communication requires multichannel, territory-based approaches supported by community-based mediation [38].

Notably, all 5 of the strata with the lowest predicted probability of seeking COVID-19 information online were users of the SUS, whereas among the strata with the highest predicted probability, SUS users also predominated. This suggests that the inequality does not lie between those who do or do not use the public health system but rather in how intersectional social characteristics moderate digital engagement even within the same health care system.

By identifying that men with low levels of education and income exhibit the lowest rates of health information seeking online, this study highlights a social group that remains systematically overlooked in communication strategies. This population profile embodies multiple layers of exclusion (informational, economic, and institutional), placing them at constant risk in the face of misinformation and informational disengagement [20,21].

The relationship between gender and health information seeking observed in this study contrasts with international findings that identified greater male engagement in COVID-19–related communicative uses of the internet. While the international study assessed online communication practices such as content sharing and interaction on social networks, our focus was on the active search for health information.

This distinction suggests that gender differences in the digital sphere are not homogeneous but vary according to the type of activity analyzed. These findings also point to an expanded understanding of digital exclusion, which is not limited to physical access but involves symbolic and functional disconnections from the networks through which knowledge circulates. The greater tendency among women to seek health information may be associated with their central role in care networks, indicating the potential for future strategies anchored in female and community leadership [39–41].

This pattern is not exclusive to the Brazilian context. Both national and international studies have shown that groups with lower educational levels and those residing in marginalized or racialized territories consistently exhibit reduced access to and critical use of digital health information [6,7,37,42,43]. In the United States, Suh et al [37] found that communities facing greater socioeconomic vulnerability showed limited increases in online information seeking even during a global crisis. This suggests that exclusion patterns are not only resistant to exceptional circumstances but may, in fact, be exacerbated by them [37].

Moreover, research has shown that overcoming digital exclusion requires more than infrastructure expansion. Public policies must address informational competencies and invest in effective symbolic mediation channels, especially in vulnerable contexts [31,41]. In Brazil, qualitative studies indicate that community leaders and public health agents remain the primary bridges between the population and health information, suggesting that trust and accessibility are as crucial as connectivity [44].

These results engage with international debates on digital health inequities, which highlight how structurally marginalized groups face not only limited physical access but also a drastically reduced capacity to translate information into health action [4]. Such processes intensify during public health emergencies,

when the infodemic rather than democratizing access often amplifies existing asymmetries by demanding complex digital literacies and continuous connectivity, 2 factors profoundly shaped by class, gender, and race [37].

Corroborating this picture, studies show that older adults, people with lower educational attainment, and those with low traditional literacy are precisely those who were least able to obtain positive outcomes from internet use during the COVID-19 pandemic [4].

Such identification is strategically valuable for the formulation of proactive public policies that can mitigate disparities before they become irreversible in future crises. Thus, the trends observed during the pandemic should be interpreted as early warnings of chronic vulnerabilities. The adoption of exclusively digital solutions without territorial grounding or community mediation tends to reproduce and even amplify the very asymmetries this study reveals.

Therefore, promoting informational equity is not a peripheral goal but a central tenet of health justice. It is essential to ensure that all social groups not only have access to information but are also able to understand, contextualize, and use it to make informed care decisions. Tackling the infodemic demands integrated approaches that combine digital inclusion, critical literacy, trust networks, and communication strategies sensitive to territorial diversity [2,4].

These findings underscore the urgency of territorialized strategies to combat infodemics, as evidenced by studies in Brazilian favelas in which digital divides during COVID-19 amplified misinformation uptake among low-income residents lacking community mediation [45–47]. Literature on health communication highlights how ungrounded digital interventions exacerbate asymmetries in rural and indigenous groups, reducing trust and engagement due to cultural mismatches [45–47]. Taken together, these findings suggest that future research and interventions should further explore how territorially grounded and socially mediated communication strategies can mitigate informational inequalities during public health emergencies.

This study has limitations. Its cross-sectional design does not allow for causal inferences, and using a single question to measure the outcome may not fully capture the complexity of information-seeking behaviors. In addition, self-reported data are vulnerable to recall and social desirability bias, although the use of a validated instrument, face-to-face data collection, and trained interviewers strengthens the reliability of the findings [28].

There were also important constraints related to measuring gender and race and ethnicity. Although the questionnaire allowed for self-identification beyond binary gender and included detailed racial and ethnic categories, no participant identified as gender diverse or transgender, and very few identified as Indigenous, East Asian, or “other.” This underrepresentation is consistent with evidence that gender and racial and ethnic minority groups are often less visible in surveys involving socially vulnerable populations because of stigma, safety concerns, and structural barriers to participation [48].

From a methodological perspective, the absence of participants outside the “woman” and “man” categories prevented exploration of gender diversity within the intersectional MAIHDA framework. Very small cell sizes in some strata also required grouping categories to preserve statistical stability and confidentiality, which reduced the granularity of intersectional comparisons [10].

Finally, the analysis was limited to participants with complete data for all intersectional variables. While this complete-case strategy was necessary to construct comparable strata, it may have disproportionately excluded individuals in more vulnerable situations, introducing potential selection bias.

We highlight the need for future studies using mixed methods approaches to investigate the meanings attributed to information, the relationship between formal and informal sources, and the impact of community mediation on the development of informational attitudes. Research that integrates qualitative and quantitative methods may offer new insights into the information behavior of vulnerable populations and help guide more

inclusive, effective, and sustainable health communication policies.

Conclusions

Beyond mapping intersectional patterns, this analysis reveals how overlapping social positions (gender, race and ethnicity, schooling, and income) drive structural disparities in online COVID-19 information seeking among people experiencing homelessness and urban community residents in Brazil. These patterns underscore additive disadvantages as the primary mechanism of digital exclusion rather than synergistic interactions, highlighting the cumulative impact of vulnerability markers even within the public health system. Identifying these extreme social profiles enables policymakers to prioritize territory-based digital inclusion strategies, advancing informational equity and health justice in future public health crises. These intersectional disparities reveal that, even within Brazil’s constitutionally guaranteed SUS, a fundamental right under Article 196 of the 1988 Federal Constitution, no vulnerable group should be left behind in accessing essential health information.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: AFT and RAA

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Formal analysis: AFT, DG, and RAA

Funding acquisition: AFT and RAA

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Conflicts of Interest

None declared.

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Abbreviations

AUC: area under the receiver operating characteristic curve

MAIHDA: multilevel analysis of individual heterogeneity and discriminatory accuracy

OR: odds ratio

PCV: proportional change in variance

REDCap: Research Electronic Data Capture

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

SUS: Unified Health System (Sistema Único de Saúde in Portuguese)

USP: University of São Paulo

VPC: variance partition coefficient

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Original Paper

Drug-Facilitated Sexual Assault Pornography and Sexual Violence While Partying: Cross-Sectional Study

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Abstract

Background: Drug-facilitated sexual assaults (DFSAs) in youth partying contexts represent a growing public health concern, affecting approximately half of women and 1 in 4 men. These assaults often occur in environments where alcohol and other psychoactive substances are consumed, leading to impaired consent and increased vulnerability. At the same time, young people are increasingly exposed to pornography, often using it as a primary source of sexual information. However, pornography can disseminate misleading or harmful messages about sexuality and consent. Of particular concern is a subtype of pornographic material (hereafter referred to as DFSA pornography) that depicts nonconsensual sexual acts involving individuals who are asleep, unconscious, or under the influence of psychoactive substances, including alcohol and other drugs.

Objective: This study aimed to examine the prevalence of DFSA pornography consumption among young adults in Spain and analyze its association with self-reported DFSA perpetration and victimization in party settings.

Methods: A cross-sectional online survey (computer-assisted web interviewing) was conducted among individuals aged 18 to 35 years residing in Spain. Participants (N=1601; n=1534, 95.8% valid responses) were recruited from a certified online panel using quota sampling stratified by sex, age group, and region to ensure national representativeness. The questionnaire was adapted from the Sexual Experiences Survey–Short Form Victimization and the Spanish Macro-Survey on Violence Against Women. It assessed DFSA perpetration and victimization in partying contexts under the influence of alcohol or drugs. A specific variable, DFSA pornography, was created to measure intentional viewing of explicit sexual content depicting unconscious or intoxicated individuals. Additional sociodemographic variables included sex, age, educational level, sexual orientation, political ideology, nationality, and socioeconomic level. Descriptive, bivariate, and binary logistic regression analyses were performed, estimating associations between DFSA experiences and both general and DFSA pornography consumption.

Results: Among respondents (800/1593, 50.2% female participants; mean age 27.0, SD 5.1 years), 78.4% (1233/1572) identified as heterosexual, and 52% (825/1587) held a university degree. Overall, 66.6% (1013/1521) reported consuming pornography in the previous year, with higher prevalence among male participants (638/753, 84.7%) than among female participants (370/762, 48.6%). DFSA pornography consumption was reported by 22.2% (167/753) of male participants and 11.3% (86/762) of female participants, and increased with overall pornography use frequency. Multivariate logistic regression indicated that DFSA perpetration (adjusted odds ratio 3.78, 95% CI 1.72-8.28; $P<.001$) and victimization (adjusted odds ratio 1.86, 95% CI 1.24-2.78; $P=.003$) were associated with DFSA pornography consumption.

Conclusions: The findings reveal an association between exposure to DFSA pornography and both DFSA perpetration and victimization among young people in Spain. These results underscore the need for comprehensive sexual education that critically addresses pornography as a source of misinformation, emphasizing accurate understanding of consent and substance-impaired sexual activity. Public health strategies should integrate media literacy and consent education to mitigate the normalization of sexual violence depicted in pornography.

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KEYWORDS

drug-facilitated sexual assault; drugs; sexual assault; pornography consumption; sexual violence

Introduction

Sexual violence is a pervasive public health concern that demands immediate attention [1]. According to the World Health Organization, sexual violence encompasses unwanted sexual acts, comments, or insinuations, from verbal harassment to forced penetration [1,2]. Drug-facilitated sexual assault (DFSA) is a specific form of sexual violence in which perpetrators take advantage of individuals who are incapacitated by psychoactive substances, including alcohol, illicit drugs, or medications, consumed either voluntarily or involuntarily [1,3]. DFSA episodes particularly affect partying, dating, and hookup contexts, where alcohol and other drug use is often combined with high expectations for sexual interaction [3,4]. This type of violence occurs across diverse settings worldwide, including Europe, within which Spain has shown particular concerns [5]. A recent study showed that 1 in 2 women and 1 in 4 men among young people in Spain have experienced DFSA at least once while partying [6]. The relationship between nightlife partying and DFSA has been a focus of intense research in Spain in recent years [7-11]. Multiple studies have highlighted how rape culture leads young people of both sexes to normalize sexually violent practices such as nonconsensual sex, thereby rendering sexual violence invisible and minimizing its impact [12-16].

Pornography consumption is widespread among the young population, especially men, with prevalence of consumption in the last year ranging between 60% and 80% in Spain and other high-income countries [17-21]. In addition, this consumption has significantly increased in recent years, driven by its growing accessibility online [19,21,22]. One of the main problems related to the consumption of pornography is that many young people perceive it as a source of sexual education, turning to it for information in the absence of reliable and quality guidance; in Spain, just over 10% of young people express satisfaction with the sexual education they have received, whereas approximately half report that pornography helps them better understand and learn about sex and acknowledge using it as a source of inspiration [19]. Similar figures have been observed in other countries [23], highlighting how particularly young men incorporate practices depicted in pornography into their sexual lives [24,25].

Pornography can be a source of misinformation about sex [26,27]. Violent content in pornography can encompass a wide range of physical, verbal, and sexual violence. Numerous studies have highlighted that mainstream pornography often portrays violent scenes featuring practices characterized by aggression that demean and sexually objectify people [23,28,29]. This type

of pornographic content also includes scenes of nonconsensual sexual activity while someone is asleep, unconscious, or under the influence of alcohol or other drugs [29,30]. This pornographic content resembles DFSA situations, where individuals are rendered incapacitated by the psychoactive effects of licit or illicit substances, including alcohol, other drugs of abuse, and medications. There are no data available on the consumption of this type of pornography with DFSA content. Nevertheless, as a proxy, in Spain, at least 18.2% of men and 14.5% of women among young people admit to consuming pornography classified as highly violent, particularly degrading, or humiliating [18]. These are particularly concerning figures considering that numerous studies indicate that some young people do not distinguish between pornography and real-life sexual behaviors, potentially leading to the normalization of degrading acts or extreme violence [31]; 31% of young people in Spain agree that pornography shapes sexual fantasies involving either the perpetration or reception of violence, which they perceive as a harmful effect of pornography on its consumers [18]. Therefore, given the high prevalence of DFSA in party contexts, combined with the widespread use of pornography as a sexual education source and the accessibility of violent content, this study aimed to examine the prevalence of DFSA pornography consumption and its relationship with having either experienced or perpetrated DFSA while partying.

Methods

Design and Participants

This was a cross-sectional study using an anonymized, self-administered online survey for sexual victimization and perpetration (computer-assisted web interviewing). The study population consisted of individuals aged 18 to 35 years residing in Spain, totaling 9,250,779 people in 2022, with 50.85% being men [32]. A minimum sample size of 1537 individuals was required, assuming 50% prevalence, 95% confidence, and a 2.5% margin of error, with a prevalence of 0.5 due to the lack of prior data as recommended by statistical guidelines [33]. Participants were recruited from an online panel managed by a research company certified under ISO 20252, which provides verified samples for social and health research. The panel includes more than 100,000 registered members residing in Spain. Panelists are recruited through paid social strategies and undergo a validation process, with sociodemographic profiles periodically updated to ensure data accuracy.

Quota sampling was applied to ensure proportional representation by sex, age group (18-24 and 25-35 years), and region (17 autonomous communities) according to the

demographic distribution of the Spanish population. Study participants were selected through a routing system designed to minimize self-selection bias and received personalized invitations via email and mobile notifications. To maintain quota compliance, invitations were dynamically adjusted based on response and dropout rates.

Survey access included duplicate checks, captcha verification, and validation of self-reported gender and age. Standard quality controls, such as attention-check questions, a minimum completion time threshold, and mandatory responses, were applied to ensure data integrity.

Of the 1707 invited individuals, 106 (6.2%) declined participation or did not complete the questionnaire, resulting in a final sample of 1601 respondents.

The questionnaire was specifically tailored by an interdisciplinary team, drawing on sources such as the Sexual Experiences Survey–Short Form Victimization [34] and the 2019 Macro-Survey on Violence Against Women [35]. At the time this study was conducted, to the authors' knowledge, no fully validated instruments existed to specifically assess DFSA perpetration and victimization or the use of pornography depicting DFSA content. A pretest assessed clarity, reliability, and validity, including cognitive debriefing with over 100 participants to address any understanding issues and ensure clarity. Questions were designed to avoid identifiable information and social desirability biases. IP addresses and cookies were not collected.

Variables

Two main variables provided information about DFSA perpetration or victimization experiences while partying. Sexual violence included unwanted sexual touching, kissing, masturbation by another person, oral sex, or penetration. DFSA perpetration was defined as “having engaged in any of these sexual behaviors non-consensually with someone who was under the influence of alcohol or other drugs and, because of that, was unable to communicate their sexual consent, while partying or immediately afterwards” (“no” or “yes”). DFSA victimization was defined as “having experienced any of these sexual acts non-consensually when you were under the influence of alcohol or other drugs, while partying or immediately afterwards” (“no” or “yes”).

Variables concerning pornography use were pornography consumption frequency, defined as “how often one intentionally seeks out and views videos or photographs containing explicit sexual content” (“no consumption,” “Yes, between every day and two to three times per week,” “Yes, between once per week and two to three times per month,” and “Yes, less than once per month”) and DFSA pornography consumption, defined as “seeking out and intentionally viewing videos or photographs containing explicit sexual content in which a person is asleep, unconscious, or under the influence of alcohol or other drugs (including sedation or other effects)” (“no” or “yes”). The item assessing DFSA pornography consumption was developed and reviewed by the research team to ensure conceptual clarity. During the pilot questionnaire, all participants completed the item, and only 1 reported discomfort, indicating good

comprehension and acceptability. Other independent variables were sex; age; educational level (university or nonuniversity); sexual orientation (heterosexual or nonheterosexual); political ideology (left or right), originally measured on a scale from 1 to 10 and dichotomized into 1 to 5 for “left” and 6 to 10 for “right”; nationality (Spanish or Spanish and/or other); and socioeconomic level (family income [net per month in €]; low and low to medium: \leq €2000 [US \$2357.44]; medium to high or high: $>$ €2000 [US \$2357.44]). Details on variable measurement and the full list of items are provided in the questionnaire in [Multimedia Appendix 1](#).

Statistical Analysis

A descriptive analysis of pornography use focusing on the overall and gender-specific prevalence rates of pornography consumption frequency and DFSA pornography consumption was conducted. Relationships between the 2 main variables (DFSA perpetration and DFSA victimization) and covariates were examined using the chi-square and Fisher exact tests for categorical variables and ANOVA for continuous variables. Binary logistic regression models were performed to explore the relationship between DFSA perpetration and DFSA victimization and pornography use including all sociodemographic variables, with $P<.05$ in the bivariate analysis. Odds ratios and their corresponding 95% CIs were provided. Data analyses were conducted using Stata (version 19; StataCorp).

Ethical Considerations

Ethics approval was granted by the Research Ethics Committee of the University of Alcalá (approval code CEIP2022/2/040) on March 31, 2022. Informed consent was obtained from all participants before taking part. Participation was voluntary, and participants were free to decline or withdraw at any time. Privacy and confidentiality were ensured through the use of an anonymous survey. No personal identifiers were collected, and all data were analyzed in aggregate form. Consequently, individual participants cannot be identified from the dataset.

As a result of their participation in the surveys, panelists receive incentive points that can be redeemed through a catalog of gifts, prize draws, and even donations to nongovernmental organizations. These incentives are flexible and tailored to the specific conditions of each survey, taking into account factors such as survey duration, and are designed to reward panelists according to their level of commitment and effort. The incentive system allows for variations to be defined according to the survey process, ensuring that panelists receive appropriate compensation for their time and contributions. This approach not only motivates panelists to participate actively in surveys but also encourages them to provide thoughtful and comprehensive responses, resulting in higher-quality data by optimizing participant engagement and maximizing response rates.

Results

Among the 1601 respondents, (800/1593, 50.2%) were female participants, the mean age was 27.0 (SD 5.1) years, 78.4% (1233/1572) were heterosexual, 51.9% (825/1587) had a

university degree, 54.6% (689/1262) had a low to medium or low socioeconomic status, 91.4% (1446/1583) were Spanish, and 75.8% (1213/1601) had a left-wing political ideology. Ages ranged from 18 to 35 years for both male and female participants (Table 1).

The prevalence of pornography consumption in the last year was 66.6% (1013/1521), with 24.5% (373/1521) consuming it daily or 2 to 3 times a week. Among male participants, 84.7% (638/753) had consumed pornography, with 44.2% (333/753) consuming it daily or 2 to 3 times a week and 28.2% (212/753) consuming it between once a week and 2 to 3 times a month. Among female participants, 27.2% (207/762) reported consuming pornography less than once a month, whereas 16.3% (124/762) consumed it between once a week and 2 to 3 times a month. Regarding the type of pornography consumed, 22.2% (167/753) of male participants and 11.3% (86/762) of female participants reported consuming pornography with DFSA content (Table 2). The higher the frequency of pornography use, the greater the consumption of DFSA pornography. A total of 30.8% (115/373) of those who consumed pornography more frequently acknowledged having seen DFSA pornography (Figure 1).

The results of the bivariate analysis showed that the odds of having perpetrated DFSA at least once while partying were 6.27 times higher among those who consumed DFSA pornography ($P<.001$), whereas they were 3.01 times higher among those who had more frequent pornography consumption (daily or 2-3 times a week; $P<.001$). However, the results of the multivariate analysis model, adjusted for both variables and other sociodemographic characteristics, revealed that perpetrating DFSA while partying appeared only in relation to the type of pornography consumed, not its frequency. The odds of having perpetrated DFSA while partying were 3.78 times higher among people who reported consuming DFSA pornography than among those who did not ($P<.001$). Regarding other factors, in the multivariate analysis, DFSA perpetration was higher among male participants (adjusted odds ratio [aOR] 2.03, 95% CI 1.17-3.51; $P=.01$), nonheterosexual individuals (aOR 2.10, 95% CI 1.33-3.32; $P<.001$), and individuals of foreign origin (aOR 2.55, 95% CI 1.40-4.62; $P=.002$). The logistic model ($\chi^2_{8}=88.8$; $P<.001$; McFadden pseudo- $R^2=0.123$) fit the data well (Hosmer-Lemeshow $\chi^2_{8}=7.5$; $P=.48$; Table 3).

Table 1. Sociodemographic characteristics of the studied sample, overall and stratified by sex (N=1601).^a

	Global	Female (n=800)	Male (n=793)
Age (y), mean (SD; 95% CI)	27.0 (5.1; 26.8-27.3)	26.1 (4.9; 25.7-26.4)	28.0 (5.2; 27.7-28.4)
Sexual orientation, n (%; 95% CI)			
Heterosexual	1233 (78.4; 76.3-80.4)	623 (79.6; 76.6-82.2)	608 (77.8; 74.7-80.5)
Nonheterosexual	339 (21.6; 19.6-23.7)	160 (20.4; 17.8-23.4)	174 (22.3; 19.5-25.3)
Political ideology, n (%; 95% CI)			
Left	1231 (75.8; 73.6-77.8)	635 (79.4; 76.4-82.0)	571 (72.0; 68.8-75.0)
Right	388 (24.2; 22.2-26.4)	165 (20.6; 18.0-23.6)	222 (28.0; 25.0-32.1)
Nationality, n (%; 95% CI)			
Spanish	1446 (91.4; 89.9-92.6)	719 (90.9; 88.7-92.7)	723 (92.2; 90.1-93.9)
Spanish and/or other	137 (8.7; 7.4-10.1)	72 (9.1; 7.3-11.3)	61 (7.8; 6.1-9.9)
Socioeconomic level, n (%; 95% CI)			
Low to medium low	689 (54.6; 51.8-57.3)	358 (57.9; 54.0-61.8)	329 (51.3; 47.4-55.2)
Medium high to high	573 (45.4; 42.7-48.2)	260 (42.1; 38.2-46.0)	312 (48.7; 44.8-52.6)
Educational level, n (%; 95% CI)			
University	825 (52.0; 49.5-54.4)	406 (51.2; 47.7-54.7)	414 (52.7; 49.2-56.1)
Nonuniversity	762 (48.0; 45.6-50.5)	387 (48.8; 45.3-52.3)	372 (47.3; 43.9-50.8)

^aTotals do not equal 1601 because 8 (0.5%) participants preferred not to specify their sex.

Table 2. Prevalence of pornography consumption categorized by use frequency and type of pornography consumed based on whether drug-facilitated sexual assault (DFSA) pornography was used (N=1521).

	Global, n (%; 95% CI)	Female, n (%; 95% CI)	Male, n (%; 95% CI)
Total responding “yes”	1013 (66.6; 64.2-68.9)	370 (48.6; 45.0-52.1)	638 (84.7; 82.0-87.1)
Daily to 2 to 3 times per week	373 (24.5; 22.4-26.8)	39 (5.1; 3.8-6.9)	333 (44.2; 40.7-47.8)
Once per week to 2 to 3 times per month	339 (22.3; 20.3-24.5)	124 (16.3; 13.8-19.1)	212 (28.2; 25.1-31.5)
Less than once per month	301 (19.8; 17.9-21.9)	207 (27.2; 24.9-29.5)	93 (12.4; 10.2-14.9)
Pornography without DFSA	759 (49.9; 47.4-52.4)	284 (37.3; 33.9-40.8)	471 (62.6; 59.0-65.9)
Pornography with DFSA	254 (16.7; 14.9-18.7)	86 (11.3; 9.2-13.7)	167 (22.2; 19.3-25.3)
No pornography use	508 (33.4; 31.1-35.8)	392 (51.4; 47.8-55.0)	115 (15.3; 12.9-18.0)

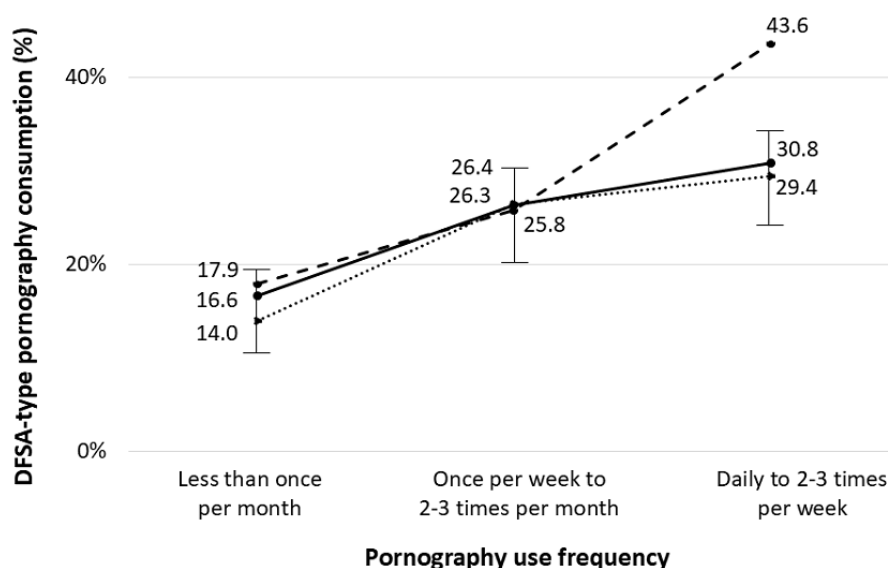
Figure 1. Relationship between drug-facilitated sexual assault (DFSA)–type pornography consumption and pornography use frequency (low, medium, and high), overall and by gender. The solid line represents the overall group, the dotted line represents men, and the dashed line represents women. The 95% CIs are shown for the overall group ($P<.001$).

Table 3. The relationship between lifetime drug-facilitated sexual assault (DFSA) perpetration while partying and the type of pornography consumed and frequency of consumption (N=1482).^a

Sociodemographic and behavioral variables	Perpetrated DFSA at any point in their life while partying		P value	Crude OR ^b (95% CI)	Adjusted OR (95% CI)
	Yes	No			
Type of pornography consumed, n (%)			<.001		
No consumption	18 (3.6)	485 (96.4)		Reference	Reference
Without DFSA	35 (4.6)	719 (95.4)		1.31 (0.73-2.34)	0.91 (0.43-1.95)
With DFSA	47 (18.9)	202 (81.1)		6.27 (3.55-11.06) ^c	3.78 (1.72-8.28) ^d
Frequency of pornography consumption, n (%)			<.001		
Never to less than once per month	33 (4.1)	770 (95.9)		Reference	Reference
Once per week to 2 to 3 times per month	25 (7.5)	310 (92.5)		1.88 (1.10-3.22) ^d	1.01 (0.49-2.06)
Daily to 2 to 3 times per week	42 (11.4)	326 (88.6)		3.01 (1.87-4.83) ^c	1.30 (0.65-2.59)
Sex, n (%)			<.001		
Female	32 (4.1)	757 (95.9)		Reference	Reference
Male	72 (9.2)	711 (90.8)		2.40 (1.56-3.68) ^c	2.03 (1.17-3.51) ^d
Age (y), mean (SD)	27 (5)	27 (5)	.79	0.99 (0.96-1.03)	1.00 (0.98-1.05)
Sexual orientation, n (%)			<.001		
Heterosexual	61 (5.0)	1162 (95.0)		Reference	Reference
Nonheterosexual	42 (12.6)	292 (87.4)		2.74 (1.81-4.14) ^c	2.10 (1.33-3.32) ^d
Nationality, n (%)			<.001		
Spanish	81 (5.7)	1351 (94.3)		Reference	Reference
Spanish and/or other	20 (14.8)	115 (85.2)		2.90 (1.72-4.90) ^c	2.55 (1.40-4.62) ^d
Educational level, n (%)			.68		
University	56 (6.9)	759 (93.1)		Reference	— ^e
Nonuniversity	48 (6.4)	707 (93.6)		0.92 (0.62-1.37)	—

^aThe multivariate model included as covariates those variables that showed a *P* value of <.05 in the bivariate analysis.

^bOR: odds ratio.

^c*P*<.001.

^d*P*<.05.

^eVariables not included in the multivariate model according to the results of the bivariate analysis.

Regarding DFSA victimization while partying, the results of the bivariate analysis were largely consistent with those of the multivariate analysis. In this model, the probability was 1.86 times higher among DFSA pornography users (95% CI 1.24-2.78, *P*=.003). This association was also 3.36 (95% CI 2.53-4.46) times higher among female participants (*P*<.001), 1.67 (95% CI 1.28-2.20) times higher among nonheterosexual

individuals (*P*<.001), 1.65 (95% CI 1.10-2.47) times higher among individuals of foreign origin (*P*=.01), and 1.36 (95% CI 1.09-1.71) times higher among those with lower educational levels (*P*=.008). The overall model ($\chi^2_9=128.4$; *P*<.001) explained 6.6% of the variance (McFadden pseudo-*R*²=0.066) and showed good fit to the data (Hosmer-Lemeshow $\chi^2_8=4.5$; *P*=.81; Table 4).

Table 4. The relationship between lifetime drug-facilitated sexual assault (DFSA) victimization while partying and the type of pornography consumed and frequency of consumption (N=1470).^a

Sociodemographic and behavioral variables	Experienced DFSA at any point in their life while partying		P value	Crude OR ^b (95% CI)	Adjusted OR (95% CI)
	Yes	No			
Type of pornography consumed, n (%)			.07		
No consumption	190 (37.8)	313 (62.2)		Reference	Reference
Without DFSA	275 (36.5)	478 (63.5)		0.95 (0.75-1.20)	1.26 (0.92-1.72)
With DFSA	109 (44.7)	135 (55.3)		1.33 (0.98-1.81)	1.86 (1.24-2.78) ^c
Frequency of pornography consumption, n (%)			.02		
Never to less than once per month	319 (39.9)	481 (60.1)		Reference	Reference
Once per week to 2 to 3 times per month	137 (41.4)	194 (58.6)		1.06 (0.82-1.38)	1.28 (0.90-1.82)
Daily to 2 to 3 times per week	118 (32.0)	251 (68.0)		0.71 (0.55-0.92)	1.12 (0.77-1.64)
Sex, n (%)			<.001		
Male	210 (27.0)	567 (73.0)		Reference	Reference
Female	381 (48.4)	406 (51.6)		2.53 (2.05-3.13) ^d	3.36 (2.53-4.46) ^d
Age (y), median (SD)	27 (5)	27 (5)	.88	1.00 (0.98-1.02)	1.03 (1.00-1.05) ^c
Sexual orientation, n (%)			<.001		
Heterosexual	430 (35.3)	790 (64.8)		Reference	Reference
Nonheterosexual	156 (47.7)	171 (52.3)		1.68 (1.31-2.15) ^d	1.67 (1.28-2.20) ^d
Nationality, n (%)			.002		
Spanish	521 (36.5)	905 (63.5)		Reference	Reference
Spanish and/or other	66 (50.0)	66 (50.0)		1.74 (1.21-2.48) ^c	1.65 (1.10-2.47) ^c
Educational level, n (%)			.001		
University	274 (34.0)	532 (66.0)		Reference	Reference
Nonuniversity	319 (42.2)	437 (57.8)		1.42 (1.15-1.74) ^c	1.36 (1.09-1.71) ^c

^aThe multivariate model included as covariates those variables that showed a *P* value of <.05 in the bivariate analysis.

^bOR: odds ratio.

^c*P*<.05.

^d*P*<.001.

Discussion

This study confirms the widespread use of pornography among young people, indicating that those who use it more frequently are also more likely to consume sexually violent pornography. Additionally, evidence was provided regarding the relationship between the use of sexually violent pornography and both DFSA perpetration and victimization.

In this study, 2 out of 3 young people (1013/1521, 66.6%) admitted to consuming pornography, with consumption being almost twice as high in male participants compared to female participants. These results align with a recent nationwide study in Spain, according to which 6 out of 10 young people aged 16 to 29 years admitted to using pornography, with 72.1% being men and 59.3% being women [19]. Similarly, other studies have

found that approximately 70% of men and 30% of women use pornography in high-income countries [17,18]. Regarding frequency, in our study, almost half (333/753, 44.2%) of all male participants consumed pornography daily or 2 to 3 times a week. Among female participants, consumption was much less frequent. These figures are slightly higher than those reported in similar studies conducted in Spain [19] and Europe [36]. The data from our study are more up-to-date and are based on more representative samples. Therefore, they may reflect current consumption, especially considering that pornography consumption has been growing in recent years [22,37].

In terms of type of pornography, more than 20% of male participants (167/753, 22.2%) and 10% of female participants (86/762, 11.3%) in our study reported consumption of pornography featuring scenes in which a person is asleep, unconscious, or under the influence of alcohol or other drugs

(referred to as DFSA pornography). These figures cannot be directly compared as there is currently no scientific literature providing prevalence data on the consumption of violent pornographic content specifically depicting DFSA situations. As such, comparisons could be made with broader data on the consumption of violent pornography. Some studies indicate that 10% of adolescents have been exposed to violent pornography, with a gradual increase in violent themes as age progresses [38]. In this regard, a study in New Zealand highlighted how easily young people can be exposed to nonconsensual sexual behavior in online pornography, including scenes of sexual activity while someone is sleeping [39], findings similar to those described by other authors [30,31]. In Spain, 40.2% of individuals have viewed pornographic content classified as high in violence, particularly degrading, or humiliating, and 16.6% acknowledge doing so with high or moderate frequency (18.2% of men and 14.5% of women) [19]. Additionally, 5.2% of men and 6.9% of women indicate that the presence of violence is the factor that influences them the most when selecting pornographic material [19]. These results show the magnitude of pornography consumption of this type. There are many related considerations, but these are beyond the scope of this study. What we must emphasize again is that many young people acquire their sexual education through pornography (in the absence of other forms of education) [19,40], with a significant portion of this pornography being of a violent nature.

According to our study, using DFSA pornography is related to approximately fourfold higher odds of perpetrated DFSA while partying. Similarly, other researchers have observed a connection between sexual assault perpetration and the use of violent pornography [23,41]. Models explaining this relationship suggest that the risk of perpetration correlates with male pornography users who have high levels of hostility and sexual promiscuity [42]. Exposure to violent pornography also shapes sexual behavior by reinforcing scripts that are perceived as normative, acceptable, and gratifying, which are then activated and applied in dating and sexual relationships [43]. This correlation was obtained in analyses adjusting for other factors. In addition to the type of pornography consumption, it was noted in this study that there were more perpetrators among male participants, foreigners, and nonheterosexual individuals. The presence of men in these studies is nothing new [23,44], hence the importance of adjusting the results by gender. Regarding country of origin and sexual orientation, these categories encompass highly diverse populations. These groups are heterogeneous and shaped by intersecting social determinants that may influence risk and experiences in complex ways [45]. Further research is needed stratifying by country of origin and other relevant factors [46,47].

Concerning victimization, experiencing DFSA while partying was twice as frequent among users of DFSA pornography content. Although various studies have indicated a link between sexual victimization and exposure to pornography [44,48,49], there is currently no known research specifically addressing DFSA. On the one hand, many studies on violence against women suggest that conventional pornography often depicts violent scenes that sexually degrade and objectify women [23,28,29,40]. It is noted that female sexual objectification in

pornography is linked to a higher likelihood of sexual victimization in young women due to the normalization of or desensitization to violent sexual behaviors [50]. On the other hand, studies linking violence using psychoactive substances and pornography primarily focus on alcohol, consistently finding an increased risk of sexual victimization among women who consume pornography [48]. While it is difficult to infer a cause, it has been suggested that increased exposure to violent pornography and its normalization, combined with the effects of alcohol, may impair the initial ability to detect an aggression [51]. At the same time, considering the absence of temporality in cross-sectional designs, the observed relationship between having experienced DFSA and DFSA pornography consumption leads us to hypothesize that, in the absence of adequate social support, some DFSA survivors may resort to viewing such content to understand the episode even at the risk of revictimization. However, this hypothesis is not supported by empirical data, suggesting directions for future research. Regardless, this highlights the imperative to strengthen support systems for survivors of DFSA. Consequently, it is essential to conduct longitudinal studies that establish causal relationships and qualitative research that explores DFSA survivors' experiences in depth. In the same way, related adjustment variables indicate that this is an issue in which global messages must be accompanied by other messages particularized according to gender, educational level, or country of origin.

Considering the high prevalence of DFSA experiences in youth party settings [6] and the fact that many young people turn to pornography as a source of sexual education [19], the influence of DFSA-themed pornography in normalizing this form of sexual violence among young people is deeply concerning. While we cannot establish a causal relationship, there is a clear correlation between DFSA—whether perpetration or victimization—and the consumption of this specific type of pornography. This correlation does not emerge when considering the overall quantity of pornography consumed. Although higher levels of consumption are related to the consumption of violent porn, it is specifically this violent content that shows a significant correlation with DFSA. Consequently, we should not wait for causal evidence to implement the necessary sexual health promotion interventions. Preventive action is essential, particularly to ensure that the normalization of sexual behaviors is not shaped primarily by the content of the pornography that young people consume.

This study's findings contribute to addressing some global challenges highlighted by the United Nations Sustainable Development Goals, particularly those aimed at ending violence and fostering just societies. As DFSA is a paradigmatic example of how violence affects the most vulnerable individuals, this study reinforces the commitment to "leave no one behind" in achieving sustainability.

This study has several limitations. First, the cross-sectional design precludes causal inference. Second, although quota sampling approximated the demographic distribution of the Spanish population in terms of age, gender, and region, participation was voluntary and based on an online panel, which may have introduced self-selection bias and limited generalizability. Social desirability bias cannot be entirely ruled

out despite assurances of anonymity. In addition, the representation of sexually diverse and gender-diverse groups was limited, and the sample size did not allow for analyses by DFSA subtype or level of invasiveness. Third, although the questionnaire was piloted, some constructs—such as the use of DFSA-related pornographic content—were assessed using nonvalidated items, which may affect measurement precision. Finally, no psychological support was available for participants who might have experienced discomfort. Despite these limitations, this study provides novel and valuable evidence on DFSA-related pornographic content and its association with sexual violence perpetration and victimization in party contexts.

The use of pornography depicting nonconsensual sex involving individuals who are asleep, unconscious, or under the influence of alcohol or other drugs correlates with experiences of DFSA perpetration and victimization in youth party settings. This

association emphasizes the importance of addressing the impact of pornography as a primary source of sexual knowledge for young people, particularly in a context in which the widespread use of pornography intersects with insufficient sexual education and a lack of effective mechanisms to control consumption among minors. Future public health strategies may include ongoing research regarding the implications of pornography for sexual violence. From a public health policy perspective, it is recommended to provide training programs for educators and clinicians to enhance their skills in sex education considering the realities of pornography and its influence on young people. Accurate information on these realities should also be integrated into comprehensive sexual education initiatives and educational materials aimed directly at youth. Finally, legal responsibilities should be expanded, and the obligations of online pornography distribution platforms should be strengthened to improve the monitoring, filtering, and removal of violent content.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

PP-M took the lead in writing the manuscript and performing the analytic calculations with support from LS. Both authors designed and planned the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaire used in the study.

[[DOCX File, 24 KB](#) - [publichealth_v12i1e80110_app1.docx](#)]

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Abbreviations

aOR: adjusted odds ratio

DFSA: drug-facilitated sexual assault

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Original Paper

Problematic Alcohol Use Among Adolescents in Germany: Representative Cross-Sectional Study

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Abstract

Background: Alcohol is a widely used psychoactive substance, and its use constitutes a major public health challenge due to its immediate and long-term adverse effects on various health-related outcomes. Adolescence has been identified as a particularly vulnerable phase regarding alcohol use. Although consumption rates in this age group have declined in Germany over the past decades, a plateau has been reached, and there is a continued need for interventions to further reduce consumption rates.

Objective: This study aimed to assess problematic alcohol use among adolescents in Germany and explore associations with sociodemographic and psychosocial characteristics, particularly with health literacy, to inform future interventions tailored to the specific needs of this target group.

Methods: In a cross-sectional quota-based survey, 2006 adolescents (aged 12-17 years) completed an online survey (n=1406) or face-to-face interview (n=600) assessing the frequency of weekly alcohol use, the presence of problematic alcohol use (German version of the Car-, Relax-, Alone-, Forget-, Friends-, Trouble- questionnaire [CRAFT-d]), sociodemographic information, and health literacy (European Health Literacy Survey instrument [HLS-EU-Q16]). Based on their CRAFT-d and HLS-EU-Q16 scores, participants were identified as exhibiting problematic alcohol use (vs no problematic alcohol use) and inadequate or problematic health literacy levels (vs adequate health literacy levels), respectively. Chi-square tests were computed to analyze differences between different groups (as defined by the sociodemographic factors, weekly alcohol consumption frequency, and health literacy) in terms of problematic alcohol use (binary CRAFT-d outcome).

Results: Approximately 20% (390/2006) of the participants reported consuming alcohol on at least 1 day per week, and 12.7% (255/2006) of the sample met the CRAFT-d screening criterion for problematic alcohol use. Problematic alcohol use was significantly associated with gender ($\chi^2_1=20.96$, $V=0.10$; $P<.001$), age ($\chi^2_2=85.88$, $V=0.21$; $P<.001$), subjective social status ($\chi^2_2=8.23$, $V=0.06$; $P=.02$), and migration background ($\chi^2_1=5.60$, $V=0.05$; $P=.02$), but there were no significant associations with level of education ($\chi^2_1=3.43$, $V=0.04$; $P=.06$), and health literacy ($\chi^2_1=1.54$, $V=0.03$; $P=.21$). In addition, participants who reported more frequent alcohol consumption per week, also met the screening criterion for problematic alcohol consumption more frequently ($\chi^2_7=698.65$, $V=0.59$; $P<.001$).

Conclusions: The findings demonstrate that problematic alcohol use is more common in boys than girls, in older vs younger adolescents, in those with high or low (vs intermediate) social status, in individuals with (vs without) a migration background, and in those who drink alcohol more frequently. These results emphasize the necessity of implementing targeted prevention strategies that address the specific risk profiles of adolescents concerning alcohol consumption.

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KEYWORDS

adolescents; alcohol, Germany; health literacy; problematic alcohol use; representative survey

Introduction

Background

Alcohol use poses a major public health challenge [1,2], and adolescence has emerged as a particularly vulnerable period for its detrimental short- and long-term effects [3-5]. This study addresses the problematic use of alcohol among adolescents in Germany and how this problematic use relates to psychosocial and sociodemographic factors with cross-sectional data.

Public Health Relevance of Alcohol Use

Alcohol is one of the most widely used psychoactive substances worldwide [6,7]. At the same time, more than 3 million deaths worldwide are attributable to alcohol, corresponding to 5.3% of all deaths [2]. This effect is exacerbated in younger age, with 18.4% of all deaths in men aged 25-29 years attributed to alcohol. Women are less affected than men but also experience a substantial health burden due to alcohol [2]. While there is some evidence that alcohol might have beneficial effects when consumed in smaller quantities [8-10], this position has been challenged in recent years and might be attributed to methodological artifacts [11-13]. Importantly, it is undisputed that health effects are detrimental when alcohol is consumed in large quantities [10,14-16]. These harmful effects on health can be observed in the short and long term [11]. Short-term effects refer to the immediate consequences of alcohol consumption, including acute alcohol intoxication as well as decreased visuomotor coordination, increased reaction times, and increased impulsivity [11,17,18]. These may lead to more severe consequences, such as injuries or deaths, for example, from falls, traffic accidents, or drowning [11,19]. The arguably most apparent long-term effects of excessive alcohol consumption are clinically relevant alcohol abuse and dependence, which are highly prevalent worldwide, and also in many European countries, including Germany [1,20]. These effects are associated with a significant decline in physical and mental health and a loss of quality of life [21,22]. Other long-term effects of alcohol consumption on health-related outcomes include, but are not limited to, cancer, cardiovascular, gastrointestinal, and neuropsychiatric conditions, which may result in premature mortality [11,16]. In addition to these individual consequences, alcohol consumption has also been associated with substantial direct and indirect economic costs at a societal level [23].

Alcohol Use Among Adolescents

Given the detrimental effects of alcohol consumption on various health outcomes, more recent nutritional policies in Germany recommend abstaining from alcohol entirely [11]. However, alcohol consumption remains at a high level in Germany compared to other Western-European countries [24,25]. Critically, alcohol is consumed from a young age [26]. Recent evidence from representative samples estimates the prevalence of regular alcohol use, defined as consumption of alcoholic beverages at least weekly in the past 12 months, at about 9.7% in those aged 12-17 years, with substantially higher rates in boys (12.4%) than girls (6.9%). In addition, 63% of all adolescents in that age group report lifetime alcohol use, and about 4% show risky drinking behaviors, exceeding established

thresholds for risky alcohol consumption in adults (equivalent to drinking more than 12 grams of pure alcohol for women and 24 grams of pure alcohol for men daily). However, a decrease in general and risky alcohol consumption over the past decades has also been observed in adolescents [26]. Crucially, this decline appears to have plateaued in the last few years, showing only minimal variation [26].

Problematic Alcohol Use Among Adolescents and Its Correlates

The stagnation in alcohol use in recent years underscores the need for renewed public health strategies to address the persistent harm associated with alcohol consumption from a young age. A particular focus should be placed on problematic alcohol use in adolescents as this has been associated with severe consequences, including functional and structural brain damage and increased risks for developing alcohol use disorders [3-5,27]. A recent investigation with data from a representative sample from Germany found that 11.3% of the participants aged 12-17 years met the criteria for problematic alcohol use on a standardized screening tool. Moreover, it was shown that problematic alcohol use was associated with greater psychopathology, lower mindfulness, and lower quality of life, even when potentially confounding factors were controlled for [28]. In order to develop interventions that are specifically tailored to societal needs, particularly for adolescents, it is necessary to collect more detailed data on the associations between problematic alcohol use and other factors.

In particular, there is currently insufficient data on the relationship between problematic alcohol consumption and specific sociodemographic and psychosocial factors. For example, the association with health literacy has not yet been adequately explored. Health literacy encompasses the knowledge, motivation, and competencies in the process of accessing, understanding, appraising, and applying health information [29]. Health-literate individuals are more likely to successfully take care of their own health and navigate the health care system [29]. As a consequence, individuals with greater health literacy often exhibit healthier lifestyles (eg, adequate medication intake, less sedentary behavior), have a better overall health status, and lower mortality than individuals with lower health literacy levels [29-32]. This might also give them an advantage when making decisions regarding their alcohol consumption [33,34]. For example, greater levels of health literacy may help individuals to understand and appraise content, units, strengths, and harms of alcohol and make healthier choices regarding their alcohol intake [35,36].

Furthermore, while some relevant sociodemographic correlates (eg, gender) of (problematic) alcohol use among adolescents have already been obtained [26], there is still insufficient data on other possible associations and a strong need for replication of prior findings. Particularly, some associations have not been found consistently, for example, concerning levels of education and social status [37-40].

Study Aims

Therefore, the aim of this study was to assess the frequency of alcohol use and the prevalence of individuals with problematic

alcohol use among adolescents in Germany, and to explore associations between problematic alcohol use and various sociodemographic and psychosocial characteristics, including health literacy.

Methods

Participants, Recruitment, and Survey Methodology

The target population for this study was adolescents aged 12-17 years living in Germany with sufficient knowledge of the German language to participate in the study. We aimed to recruit 2000 individuals in order to allow precise estimates of prevalences of problematic drinking, to test for differences between the sociodemographic and psychosocial groups, and to allow representativeness of the sample for the characteristics described below (more information is given in the Data Weighting section). For example, an a priori power analysis for a chi-square test of independence for comparing the prevalences of problematic drinking across different age groups yielded a minimum sample size of 1283 participants (input parameters: 80% power, $\alpha=.05$, $df=5$, effect size $\omega=0.1$ [41]). Recruitment of the participants, study administration, and data acquisition were carried out by the German market research institute Gesellschaft für Innovative Marktforschung mbH and took place from November 2024 to January 2025. Only complete datasets without missing data were provided by the market research institute. A total of 2006 individuals participated in the study. Data were collected both online via web-based surveys ($n=1406$ participants, 70.1% of all participants) and via in-person face-to-face interviews ($n=600$ participants, 29.9% of all participants). Online participants were recruited from 3 online-access panels via personalized e-mail invitation links. Face-to-face participants were recruited from validated and regularly updated address pools of private households in Germany with known household composition. All participants aged 15 and younger were recruited via their parents. A quota-based sampling strategy was used, with quotas for 3 age categories (12-13 years, 14-15 years, and 16-17 years), gender, type of school, and federal state. Quotas were based on current data from the MA Audio (agma) study and the Federal Statistical Office (Statistisches Bundesamt). The MA Audio study is a large nation-wide and representative study with more than 66,000 yearly interviews. Detailed descriptive statistics for the final sample are in Table 1.

Data Weighting

Despite careful quota-based recruitment, some disparities between the sample and the reference population regarding relevant sociodemographic characteristics remain, for example, because some sociodemographic characteristics, such as level of education, negatively correlate with the willingness to participate in online surveys. Therefore, the data were weighted by the market research institute to match the target distribution of relevant reference studies (again using the latest MA Audio study and specifications of the Federal Statistical Office). The reference population for the weighting procedure is the German-speaking population living in Germany aged 12 years and older. The following weighting variables and combinations were used: age \times gender; education (operationalized as type of

school); and federal state. The calculation method involved using an iterative process in which all weighting variables of the sample are used simultaneously to inform the weighting with the aim of achieving minimal weights. This procedure resulted in a single weighting factor per individual.

Measures

Sociodemographic Information

We collected sociodemographic information concerning gender (boys, girls, and diverse), age, level of education, subjective social status, and migration background. For further analyses, participants were categorized into 3 age groups (12-13 years, 14-15 years, and 16-17 years).

To assess levels of education, participants were asked to indicate the type of school they currently attend. They were grouped into 2 categories: those participants attending the most advanced type of secondary school (Gymnasium, equivalent to grammar schools where a university entrance qualification can be obtained) were assigned a high level of education, and all other participants were assigned a low level of education.

Subjective social status was assessed using the German version of the MacArthur scale [42,43]. The scale uses the analogy of a ladder to represent social status, with the top rung (10) symbolizing the highest social status and the bottom rung (1) denoting the lowest social status. Participants are asked to identify the rung that best represents their individual position relative to other members of society. In total, 3 categories of subjective social status were determined: low subjective social status (scores 1-4), intermediate subjective social status (scores 5-7), and high subjective social status (scores 8-10).

Finally, participants were asked to specify whether they had a migration background, which was defined as having at least 1 parent who was not born in Germany or having been born outside of Germany themselves.

Health Literacy

The German translation of the short version of the European Health Literacy Survey instrument (HLS-EU-Q16) was administered to assess health literacy [44-46]. Participants were asked to indicate perceived difficulty in accessing, understanding, appraising, and applying information in the domains of health care, disease prevention, and health promotion. A total of 16 items was presented with a 4-point Likert scale ("very easy," "fairly easy," "fairly difficult," and "very difficult"). Individual data points were preprocessed by dichotomizing item responses, that is, by assigning one point to any "fairly easy" and "very easy" responses and zero points to any "fairly difficult" and "very difficult" responses. Then, a total score was calculated by summing up points across these dichotomized items (possible range 0-16). Finally, participants were grouped according to their overall score, for example, those with inadequate or problematic health literacy (scores 0-12) and those with adequate health literacy (scores 13-16) [47]. The HLS-EU-Q16 questionnaire was originally developed from a more comprehensive questionnaire with 47 items. It has been thoroughly validated and analyzed regarding its reliability in samples of the (adult) general population [45,46]. In addition,

the 16-item version of the questionnaire was found to be both valid and reliable in studies of adolescents [48,49].

Frequency of Alcohol Use and Problematic Alcohol Use

Two relevant statistics were collected regarding the alcohol use of the participants. First, to assess the frequency of alcohol consumption, participants were asked to indicate in a closed-response format with 8 response options (0-7 days) on how many days they consume alcohol in an average week. Second, to assess problematic alcohol use, the German version of the Car-, Relax-, Alone-, Forget-, Friends-, Trouble- (CRAFFT-d) questionnaire [50,51] was administered. The questionnaire's name is an acronym for its 6 items used to assess problematic alcohol use. The original questionnaire was developed as a screening instrument for both alcohol and drug misuse in adolescents [51], but the German CRAFFT-d only assesses alcohol use [50]. In 6 items the participants are asked to indicate whether they have ever ridden in a car with a driver (including themselves) who had consumed alcohol, whether they ever drink to relax, feel better about themselves or fit in, whether they have ever drunk by themselves, whether they have ever forgotten things while using alcohol, whether they were ever told by friends or family to cut down drinking, and whether they had ever gotten into trouble while drinking [51]. Each item is a simple yes-no question, and an overall score can be calculated as the number of positive answers to these questions. The outcome of the questionnaire is binary: if the overall score of an individual is equivalent to or exceeds 2, these individuals are classified as having potentially problematic alcohol consumption; a score lower than 2 indicates no problematic alcohol consumption [50-53]. The German CRAFFT-d has been validated with a sensitivity of 88.8% and a specificity of 66.2% [53].

Statistical Analysis

Data preprocessing and all statistical analyses were conducted with the statistical software SPSS (version 29.0.2.0; IBM Corp). All inferential statistical analyses are reported for the weighted data (Data Weighting for details on the weighting procedures). Internal consistencies of the CRAFFT-d and HLS-EU-Q16 were calculated as Cronbach α . To test for significant associations

between the sociodemographic and psychosocial factors and problematic alcohol consumption according to the CRAFFT-d screening criterion, chi-square tests of independence were calculated with Cramer V as a measure of effect size. Cramer V assesses the strength of the association between 2 nominal variables, for example, when analyzing contingency tables. It can be interpreted according to the following rule of thumb: 0.10 small, 0.30 medium, and 0.50 large [54].

Ethical Considerations

The ethics committee of the Berlin Medical Association did not raise any ethical or professional objections to the study protocol (reference number Eth-SB-24-047). Informed consent was obtained from all participants before data collection was initiated. For all participants aged 15 and younger, informed consent was also provided by a parent or legal guardian. The market research institute provided only anonymized data to the Stiftung Gesundheitswissen. Confidentiality was maintained throughout the study. Participants were not directly compensated by the Stiftung Gesundheitswissen. They received panel-specific compensation or credits that can be redeemed for bank transfers, vouchers, or raffle entries. In face-to-face settings, compensation is handled individually by the interviewers and typically involves direct cash payments or small gifts. This study was part of a larger study that assessed several different health-related constructs and behaviors (eg, anxiety and eating habits) with a specific focus on health literacy in 2 independent samples of the adult general population and adolescents in a cross-sectional study design. Further analyses focusing on other thematic areas are ongoing and are expected to result in additional publications.

Results

Sample Characteristics and Descriptive Statistics

A total of 2006 individuals aged 12-17 years (mean 14.47, SD 1.70 years) participated in the study. Detailed descriptive statistics of the sample across the relevant sociodemographic and psychosocial categories before and after the weighting process are presented in Table 1.

Table 1. Sample characteristics of weighted and unweighted data from a cross-sectional survey (2024-2025) of N=2006 adolescents (aged 12-17 years) in Germany.

Variables ^a	Unweighted sample, n (%)	Weighted sample, n (%)
Gender		
Boys	1025 (51.1)	1035 (51.6)
Girls	975 (48.6)	964 (48.1)
Diverse	6 (0.3)	6 (0.3)
Age groups (years)		
12-13	657 (32.8)	676 (33.7)
14-15	688 (34.3)	681 (34)
16-17	661 (33)	649 (32.4)
Level of education		
Low	1167 (58.2)	1370 (68.3)
High	839 (41.8)	636 (31.7)
Social status		
Low	248 (12.4)	258 (12.9)
Intermediate	1324 (66)	1329 (66.3)
High	434 (21.6)	419 (20.9)
Migration background		
Yes	292 (14.6)	295 (14.7)
No	1714 (85.4)	1711 (85.3)
Health literacy		
Inadequate or problematic	1180 (58.8)	1203 (60)
Adequate	826 (41.2)	803 (40)

^aCumulative percentages and absolute numbers may exceed or fall below 100% due to weighting and rounding.

Reliability of the Measures

Internal consistency of the CRAFFT-d overall score to assess problematic alcohol use was $\alpha=.75$, and internal consistency of the HLS-EU-Q16 to assess health literacy was $\alpha=.86$.

Descriptive Findings on Frequency of Alcohol Consumption

On average, participants drank alcohol on a mean of 0.35 (SD 0.89) days per week, with the majority of the participants (1615/2006, 80.5%) reporting not drinking at all across an average week. Details of the frequency of alcohol consumption are presented in [Table 2](#).

Table 2. Frequency of weekly alcohol consumption across the sample of 2006 adolescents (aged 12-17 years) from a cross-sectional survey (2024-2025) in Germany.

How many days per week, on average, do you consume alcohol? ^a	Values, n (%)
0	1615 (80.5)
1	221 (11)
2	91 (4.6)
3	46 (2.3)
4	15 (0.8)
5	7 (0.4)
6	6 (0.3)
7	4 (0.2)

^aNote: Cumulative percentages and absolute numbers may exceed or fall below 100% due to weighting and rounding.

Across the entire sample, $n=255$ (12.7%; 95% CI 11.2%-14.2%) individuals reported problematic alcohol consumption according to the CRAFFT-d screening questionnaire, and $n=1751$ (87.3%) individuals did not. Response frequencies for each CRAFFT-d item are reported in Table 3. The items referring to drinking to relax, forgetting things when drinking, and getting into trouble

while drinking were affirmed more frequently (ie, by more than 10% of the sample) than the items on drunk driving, drinking alone, and being told to cut down drinking, which were affirmed by less than 10% of the sample. On average, participants reached a sum score of mean 0.50 (SD 1.11) in the CRAFFT-d questionnaire.

Table 3. Individual item responses for the German version of the Car-, Relax-, Alone-, Forget-, Friends-, Trouble- questionnaire to assess problematic alcohol use across the sample of $N=2006$ adolescents (aged 12-17 years) from a cross-sectional survey (2024-2025) in Germany.

Item number	Items ^a	Yes, n (%)	No, n (%)
1	Have you ever ridden in a car driven by someone (including yourself) who had been using alcohol?	113 (5.6)	1893 (94.4)
2	Do you ever use alcohol to relax, feel better about yourself, or fit in?	209 (10.4)	1797 (89.6)
3	Do you ever use alcohol when you are by yourself (alone)?	104 (5.2)	1902 (94.8)
4	Do you ever forget things you did while using alcohol?	209 (10.4)	1797 (89.6)
5	Do your family or friends ever tell you that you should cut down on your drinking?	166 (8.3)	1840 (91.7)
6	Have you ever gotten into trouble while you were using alcohol?	205 (10.2)	1801 (89.8)

^aIn contrast to the original English version, the German CRAFFT-d only assesses alcohol consumption and does not refer to drug consumption [50,51]. Therefore, the items are reported with adjusted wording to match the German version, which was presented to the participants in this study. Cumulative percentages and absolute numbers may exceed or fall below 100% due to weighting and rounding.

Prevalences of Problematic Alcohol Use According to the CRAFFT-d Questionnaire and Associations With Sociodemographic and Psychosocial Variables

Table 4 presents the descriptive results regarding rates of problematic and nonproblematic alcohol use according to the CRAFFT-d questionnaire across the sociodemographic and psychosocial categories.

Boys reported significantly more problematic alcohol consumption than girls ($\chi^2_1=20.96$, $V=0.10$; $P<.001$). Participants with diverse genders were not included in this analysis because cell frequencies were too low to allow testing.

Problematic alcohol consumption significantly increased with increasing age ($\chi^2_2=85.88$, $V=0.21$; $P<.001$). Participants aged 12-13 years had the lowest frequency of problematic alcohol consumption (34/676, 5%), and those aged 16-17 years had the highest frequency of problematic alcohol consumption (142/649, 21.9%), with participants aged 14-15 years falling in between these 2 groups (79/681, 11.6%).

Problematic alcohol consumption was not significantly associated with level of education ($\chi^2_1=3.43$, $V=0.04$; $P=.06$), with a descriptively marginally higher frequency in those with a low (187/1370, 13.6%) compared to a higher level of education (68/636, 10.7%).

Participants who reported low subjective social status had the highest frequency of problematic alcohol consumption (46/258, 17.8%), followed by participants with high subjective social

status (56/418, 13.4%) and intermediate subjective social status (152/1329, 11.4%). This association was significant ($\chi^2_2=8.23$, $V=0.06$; $P=.02$).

Problematic alcohol consumption was also significantly associated with migration background, with a higher rate of problematic alcohol consumption in individuals with a migration background (50/295, 16.9%) compared to those without a migration background (205/1711, 12%; $\chi^2_1=5.60$, $V=0.05$; $P=.02$).

Problematic alcohol consumption was not significantly associated with levels of health literacy ($\chi^2_1=1.54$, $V=0.03$; $P=.21$). There was a descriptively higher rate of problematic alcohol consumption in individuals with inadequate or problematic health literacy (162/1203, 13.5%) than in those with adequate health literacy (93/803, 11.6%).

Participants who reported more frequent alcohol consumption per week also showed more frequent problematic alcohol consumption ($\chi^2_7=698.65$, $V=0.59$; $P<.001$). Rates of problematic alcohol consumption were lowest in those who reported drinking on average on zero days per week (57/1614, 3.5%), and highest in those who drank every day (4/4, 100%), with those drinking on 2 to 6 days per week falling in between these 2 extremes (Table 4). However, in some cells, total frequencies were very low, which should be kept in mind when interpreting the results.

A summary of the key significant findings is presented in Figure 1.

Table 4. Proportions of positive and negative screens obtained with the German version of the Car-, Relax-, Alone-, Forget-, Friends-, Trouble-questionnaire indicating problematic alcohol use across the sociodemographic and psychosocial categories in a sample of N=2006 adolescents (aged 12-17 years) from a cross-sectional survey (2024-2025) in Germany.

Categories ^a	Problematic alcohol use, n (%)	No problematic alcohol use, n (%)
Overall	255 (12.7)	1751 (87.3)
Gender		
Boys (n=1035)	165 (15.9)	870 (84.1)
Girls (n=964)	88 (9.1)	876 (90.9)
Age groups (years)		
12-13 (n=676)	34 (5)	642 (95)
14-15 (n=681)	79 (11.6)	602 (88.4)
16-17 (n=649)	142 (21.9)	507 (78.1)
Level of education		
Low (n=1370)	187 (13.6)	1183 (86.4)
High (n=636)	68 (10.7)	568 (89.3)
Social status		
Low (n=258)	46 (17.8)	212 (82.2)
Intermediate (n=1329)	152 (11.4)	1177 (88.6)
High (n=418)	56 (13.4)	362 (86.6)
Migration background		
Yes (n=295)	50 (16.9)	245 (83.1)
No (n=1711)	205 (12)	1506 (88)
Health literacy		
Inadequate or problematic (n=1203)	162 (13.5)	1041 (86.5)
Adequate (n=803)	93 (11.6)	710 (88.4)
Frequency of weekly alcohol consumption		
Zero days (n=1614)	57 (3.5)	1557 (96.5)
One day (n=221)	88 (39.8)	133 (60.2)
Two days (n=91)	48 (52.7)	43 (47.3)
Three days (n=46)	34 (73.9)	12 (26.1)
Four days (n=15)	13 (86.7)	2 (13.3)
Five days (n=7)	5 (71.4)	2 (28.6)
Six days (n=6)	4 (66.7)	2 (33.3)
Seven days (n=4)	4 (100)	0 (0)

^aCumulative percentages and absolute numbers may exceed or fall below 100% due to weighting and rounding.

Figure 1. Visual summary of the key findings regarding problematic alcohol use in a sample of N=2006 adolescents (aged 12-17 years) from a cross-sectional survey (2024-2025) in Germany.



Discussion

Principal Findings

The aim of this study was to assess current data on the rates of problematic alcohol use and the frequency of alcohol use among adolescents aged 12-17 years in Germany, and to explore how problematic alcohol use relates to sociodemographic and psychosocial factors as well as frequency of alcohol use. Approximately 20% (390/2006) of all participants reported drinking alcohol on at least 1 day per week, and 12.7% (255/2006) of the sample met the CRAFFT-d screening criterion for problematic alcohol use. Problematic alcohol use was significantly associated with gender, age, subjective social status, migration background, and frequency of weekly alcohol consumption. However, there were no significant associations between problematic alcohol consumption and level of education or health literacy.

The fact that about 20% (390/2006) of the sample reported alcohol consumption on at least 1 day in an average week is concerning, as dose-response relationships between levels of alcohol use and alcohol use disorder incidence and mortality have been found in previous studies [55]. Consistent with this line of evidence, the frequency of alcohol consumption was associated with problematic alcohol use in our data, with higher rates of problematic use observed in those individuals who consumed alcohol more frequently across an average week. As a recent meta-analysis using longitudinal data suggests that even small doses of alcohol are associated with an increased risk of developing an alcohol use disorder and increased mortality [55], there is a clear public health interest in further reducing alcohol consumption. Regarding the prevalence of problematic alcohol use, our findings obtained with the CRAFFT-d questionnaire (255/2006, 12.7%) are comparable to recent findings that found

a rate of 13.6% (using a liberal threshold) or 11.3% (using a more conservative threshold) of problematic alcohol use with a different screening instrument in a sample of more than 4000 adolescents from Germany [28], highlighting the validity of our approach. Moreover, when compared to data from 2015 from slightly older samples (CRAFFT-d baseline means of 0.95, SD 1.19 and 1.10, SD 1.29 in 2 groups), we obtained lower CRAFFT-d mean scores (mean 0.50, SD 1.11). This pattern of results converges with our finding of higher scores in older individuals and with a decline in the frequency of adolescent drinking in recent years [26]. Overall, our findings demonstrate that there is still a substantial proportion of adolescents (255/2006, 12.7%) who show problematic drinking patterns. Examining the CRAFFT-d items individually reveals that approximately 1 in 10 adolescents have experienced trouble because of drinking, have forgotten things due to alcohol use, and have drunk to relax, feel better, or fit in. The other items concerning drunk driving, having been told to cut down on drinking, and drinking alone were affirmed less frequently, but still had prevalence rates exceeding 5% in the sample. These results emphasize the need for continued and intensified evidence-based efforts to reduce alcohol consumption and problematic drinking among adolescents in Germany.

When analyzing the reasons why adolescents drink alcohol, 3 major motives emerge in the literature: social enhancement (eg, to obtain social rewards), coping (eg, to attenuate negative affect), and dominance (eg, to obtain respect) [56]. In addition, on a neurobiological level, adolescents might be particularly sensitive to the rewarding effects of alcohol and less sensitive to its sedative effects [57]. Crucially, adolescence is characterized as a period of rapid changes in various areas of life, including physical, social, hormonal, and mental transitions, during which individuals have to cope with multiple

developmental tasks [58,59]. These transitions also manifest in concrete behaviors, such as tendencies to take more risks, which might be explained by immature self-regulation competencies and changes in personality factors such as sensation seeking and impulsivity. Of note, these factors have been found to influence alcohol use in longitudinal studies [60-62]. Moreover, alcohol expectancies, that is, the individual beliefs about alcohol effects, have been shown to change in young adolescence and to predict alcohol use in that age group. Environmental factors (eg, influences from parents and peers) play an important role in the development of these expectancies [63], and there is first evidence that programs that include peer groups might be effective when tackling alcohol use in adolescents [64]. Taken together, the findings on predictors of alcohol use among adolescents suggest that psycho-educative and other efforts to reduce alcohol use in that age group might be more effective when they involve the social environment of the targeted population and when they particularly target alcohol expectancies and individual motives to drink [56,63,64], but more research is needed to make causal claims on these relationships.

Problematic alcohol use was associated with some—but not all—sociodemographic factors assessed in our study. For example, problematic alcohol use was found to be more prevalent among boys than girls, consistent with the finding that boys generally consume alcohol more frequently than girls [26]. This finding suggests that gender-specific prevention strategies may be a viable option that should be further investigated in the future [65].

Problematic alcohol consumption was more frequent in the older (16-17 years) compared to the intermediate (14-15 years) and the younger age groups (12-13 years). In the oldest adolescents, problematic alcohol use was observed in more than 1 in 5 participants. Although problematic drinking rates were lower in the youngest age group (5%), the reported frequency in these individuals is still concerning, as alcohol consumption is associated with detrimental developmental consequences [3,4]. Moreover, early adolescence is a particularly vulnerable period as drinking patterns in early adolescence predict problematic alcohol consumption later in life [66,67]. Therefore, prevention strategies specifically targeting both young and older adolescents should be further developed and evaluated [68].

Concerning subjective social status, frequency of problematic alcohol use followed a V-shaped pattern, with the most frequent problematic use in those with the lowest and highest subjective social status and the least frequent problematic consumption in those with intermediate subjective social status. However, problematic drinking was not associated with the level of education in our sample. This pattern of results is only partly in line with evidence that demonstrates that general alcohol consumption is typically higher in adolescents with lower compared to higher socioeconomic status [37] and that it is more often harmful (eg, leading to more frequent hospitalizations) in these individuals [38]. However, other studies point to opposite associations and higher alcohol consumption in individuals with higher socioeconomic status [39] or, in the case of binge drinking, do not find any clear association [40]. Increased problematic consumption among

adolescents from higher socioeconomic levels might be explained by cultural differences, financial resources to buy alcohol, and the availability of alcohol at home [39], whereas more harmful alcohol consumption in individuals with a lower socioeconomic background might be attributed to a lack of parental support or monitoring alongside increased distress among the adolescents [38,69]. When interpreting these results, it should be kept in mind that the evidence comes from studies in different samples, from different cultural backgrounds, in different age groups, and using different modes to assess social or socioeconomic status, which makes it difficult to compare these findings. Our results add to the literature by demonstrating that among adolescents aged 12-17 years in Germany, both low and high subjective social status are associated with higher problematic alcohol use. Furthermore, the level of education was not associated with problematic alcohol use.

More frequent problematic alcohol use was observed in individuals with a migration background compared to those without a migration background. These findings can be further elucidated with the help of evidence from a recent study assessing both risky alcohol consumption (exceeding hazardous dose thresholds concerning total alcohol content) and binge drinking (exceeding thresholds for the number of drinks consumed on a single occasion) in a sample similar to ours. The study found that there are interindividual differences between individuals from various cultural backgrounds concerning their drinking patterns [26]. Risky use rates were similar in individuals with no migration background and those from Western Europe, Eastern Europe, and Turkey or Asia, but significantly lower in individuals from other regions. In contrast, binge drinking was more prevalent in individuals from Western Europe compared to those with no migration background, but less prevalent (compared to those with no migration background) in individuals from Eastern Europe and other countries, while there was no difference between those with no migration background and individuals from Turkey or Asia. Future studies need to investigate more comprehensively how problematic drinking is associated with specific cultural backgrounds and how this information can be used to develop culturally sensitive prevention strategies.

Interestingly, problematic alcohol use was not associated with general health literacy. This finding is surprising, given that health literacy predicts many other health-related behaviors [31,70] and has been shown to be associated with alcohol-related behaviors in adult populations [33,34]. It is possible that the administered instrument to measure general health literacy was too broad to capture its specific facets that more closely apply to the use of alcohol. In this context, recently, the term “alcohol health literacy,” or “alcohol literacy,” has been introduced and conceptualized. While its precise definition is still subject to ongoing debate, it appears to closely relate to general health literacy and more specifically focuses on the “capacity to obtain, process, and understand knowledge about alcohol content, units, strengths, and harms” [35,36]. First attempts to measure alcohol health literacy have been made in adults, but to date, there is no data on levels in adolescents, which should be addressed in future research [71]. Recently, new recommendations have been published to increase alcohol health literacy and reduce alcohol

consumption in Germany [35]. These recommendations include action on the levels of education and information, in the health care system, and concerning alcohol control policy. One important pillar concerning education and information is the implementation of effective alcohol prevention programs in schools and the provision of easily accessible information about alcohol, especially for adolescents and young adults [35,72].

Limitations

When interpreting the results of this study, it is important to bear in mind the following limitations. First, as noted above, we used a measure of general health literacy that might not be specific enough to measure relevant aspects of alcohol-related health literacy in the present sample [35,36]. Second, this was a cross-sectional study, which means that the observed associations cannot be interpreted as causal relationships [73]. Third, problematic alcohol use was assessed with a short screening questionnaire, which does not replace a formal clinical diagnosis for alcohol misuse or dependence. However, importantly, the questionnaire has been validated thoroughly with high sensitivity and specificity scores and therefore provides good estimates for problematic drinking [51-53,74]. Fourth, problematic alcohol use was assessed with a self-report questionnaire. As there is some level of stigma concerning alcohol use, especially among minors who are not legally allowed to drink, there is always a risk of bias due to social desirability and impression management even in anonymous surveys [75]. This might have led to an underestimation of the actual prevalence of problematic drinking in our sample [75].

Fifth, we only collected data on the frequency of drinking and on potential problematic drinking, but not on drinking quantity, which would have allowed us to conduct more in-depth analyses. Finally, the proportion of individuals with a migration background was lower than the most recent census data from Germany indicates. This discrepancy might be attributed to insufficient knowledge of the German language and the more challenging recruitment of this population segment. Therefore, our results concerning migration background should be interpreted cautiously.

Conclusions

This study presents data on problematic alcohol consumption among adolescents in Germany in addition to examining its associations with various psychosocial and sociodemographic factors. The findings show that problematic alcohol use is more prevalent among boys than girls, among older age groups than younger ones, among individuals with a higher or lower subjective social status than those with an intermediate subjective social status, among participants with a migration background than those without, and among those who consume alcohol more frequently on a weekly basis. However, there were no significant associations between problematic alcohol use and levels of education or health literacy. These results underscore the importance of targeted prevention strategies that address the specific risk profiles of adolescents. By tailoring interventions to individuals with a higher risk, policymakers might be able to more successfully mitigate problematic alcohol use and promote healthier life choices.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to copyright restrictions, but are available from the corresponding author on reasonable request.

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Authors' Contributions

Conceptualization, formal analysis, methodology, writing – original draft: R Schröder

Conceptualization, validation, writing, review, and editing: TH

Writing – review and editing: R Suhr

Conceptualization, supervision, methodology, writing – review and editing: LK

Conflicts of Interest

All authors are employees of the independent, nonprofit foundation Stiftung Gesundheitswissen.

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Abbreviations

CRAFFT-d: German version of Car-, Relax-, Alone-, Forget-, Friends-, Trouble- questionnaire to assess problematic alcohol use

HLS-EU-Q16: European Health Literacy Survey instrument

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Developmental Trajectories of Positive Expectancies of Cannabis Use Effects Among Early Adolescents: Longitudinal Observational Study Using Latent Class Growth Analysis

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Abstract

Background: Positive expectancies of cannabis use effects, which are the beliefs about the anticipated positive effects of cannabis, are robust cognitive precursors of adolescent cannabis initiation and escalation. However, little is known about how sociodemographic, familial, and psychopathological factors predict positive expectancies of cannabis use effects or how these expectancies evolve across early adolescence.

Objective: This study aimed to identify distinct developmental trajectories of positive expectancies of cannabis use effects among early adolescents, as well as the longitudinal effects of familial factors on positive expectancies of cannabis use effects over time.

Methods: This study used latent class growth analysis with 3 waves of longitudinal data from the Adolescent Brain Cognitive Development Study (ABCD Study) to identify distinct trajectories of positive expectancies of cannabis use effects among a large, demographically diverse cohort of early adolescents (aged 10 - 13 years). Multinomial logistic regression was used to examine whether baseline sociodemographic and policy-level factors were associated with class membership. Time-varying effects of familial factors (ie, parental monitoring, family cannabis use rules, and family conflict) and adolescents' psychopathology were examined within and across trajectory classes using class-specific and common effects models.

Results: Four distinct trajectories of positive expectancies of cannabis use effects emerged with different profiles: moderate-increasing (3118/7409, 42.1%), high-increasing (2111/7409, 28.5%), low-increasing (1496/7409, 20.2%), and high-decreasing (684/7409, 9.2%) trajectories. Parental monitoring and strict family cannabis use rules consistently predicted lower positive expectancies of cannabis use effects, particularly in the moderate- and high-increasing groups, while family conflict emerged as a robust risk factor. Psychopathological symptoms became increasingly predictive of positive expectancies of cannabis use effects at later ages, suggesting a developmental shift in vulnerability.

Conclusions: The development of positive expectancies of cannabis use effects in early adolescence is heterogeneous and shaped by the interplay among sociodemographic, familial, and psychopathological factors. These findings highlight the critical window for early, family-based prevention and underscore the importance of tailoring intervention strategies to specific developmental and risk profiles.

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KEYWORDS

positive cannabis use expectancy; latent class growth analysis; family dynamics; early adolescents; parental monitoring; family cannabis use rules; family conflict

Introduction

Background

Adolescent cannabis use is a significant public health concern in the United States. Despite its federally illegal status [1], it is estimated that 11.2% (2.9 million) of US adolescents (aged 12 - 17 years) used cannabis during the past 12 months [2]. Prior research has shown that early initiation, frequent use, and escalating cannabis use during adolescence are associated with a range of adverse developmental outcomes, including academic underachievement, impaired social functioning, increased risks for depression and suicidality, elevated likelihood of developing substance use disorders, and poorer psychosocial and occupational functioning in later adulthood [3-6]. Understanding cognitive antecedents of cannabis use, particularly positive expectancies of cannabis use effects, is critical for effective prevention.

Substance use expectancies are beliefs about the anticipated effects of using a particular substance, which can serve as critical proximal cognitive mechanisms determining whether an individual will initiate the use of a substance or continue substance use later in life [7-12]. Furthermore, substance use expectancies serve as a core construct in various psychological theories explaining substance use behavior [13], including social learning theory [14-16]; expectancy theory [17]; and plans, responses, impulses, motives, and evaluations (PRIME) theory [18]. Social learning theory emphasizes that substance-related cognitions are acquired through observational learning, modeling, and reinforcement in salient social contexts, such as the family. Expectancy theory and PRIME theory expand on this by conceptualizing that expectancies form as part of a broader evaluative cognitive network that guides motivation, decision-making, and dynamic behavioral choices, which precedes and organizes actual substance use behavior.

Guided primarily by social learning theory, this study focuses on examining how early adolescents, who are particularly sensitive to familial cues, are likely to form positive expectancies of cannabis use effects in response to familial factors. In this context, defining trajectories of positive expectancies of cannabis use effects and identifying family factors (eg, household rules, parental monitoring, and family conflict) that predict membership in different trajectories of positive expectancies of cannabis use effects are essential for informing early interventions and refining theoretical models of cannabis use during early adolescence.

Positive Expectancies of Cannabis Use Effects

Positive expectancies of cannabis use effects include anticipated feelings of relaxation, enhanced creativity, and social connection when using cannabis [19,20], and have been consistently identified as key cognitive drivers of cannabis use behaviors [21-28]. Adolescents who hold more positive beliefs about the anticipated effects of cannabis use are significantly more likely to initiate cannabis use at an earlier age and engage in sustained and/or escalating use over time, even after controlling for other known established risk factors [29,30]. This underscores the unique etiological role of positive expectancies of cannabis use effects in shaping the developmental trajectories of future

cannabis initiation. More importantly, positive expectancies of cannabis use effects are modifiable, making them compelling targets for early interventions, before beliefs become firmly entrenched.

Despite growing concerns surrounding adolescent cannabis use and the need for prevention, research has largely focused on behaviors emerging in late adolescence, often neglecting early adolescence (ages 10 - 14 years), a critical period when expectancies develop before direct cannabis experimentation [31,32]. During this period, there is rapid cognitive, emotional, and social development, and environmental influences play formative roles in shaping substance-related expectancies. Among these, family factors, such as parental monitoring, household rules, and family conflict, are particularly influential as they structure adolescents' early views of substance use [33,34].

Family Influences on Positive Expectancies of Cannabis Use Effects

Family rules regarding substance use, parental monitoring, and family conflict all have robust influences on shaping adolescents' substance-related expectancies but have yet to be examined relative to positive expectancies of cannabis use effects. Substantial research has demonstrated that parental alcohol and tobacco rules influence alcohol and tobacco expectancies and subsequent use [35,36]. Empirical studies focusing on cannabis use have shown that clear, well-defined family rules on cannabis use serve as protective factors for cannabis use, whereas the absence or ambiguity of such rules is linked to increased cannabis use [37]. However, research has yet to examine the influence of family rules on positive expectancies of cannabis use effects. It may be that parents who clearly communicate the risks of substance use and enforce explicit household rules indirectly cultivate lower positive expectancies of cannabis use effects in their children, whereas permissive or neutral parental attitudes on substance use may promote more favorable expectancies about cannabis effects. Notably, findings from broader literature on substance use expectancies may not fully extend to positive expectancies of cannabis use effects. The distinct social, legal, and perceived medicinal aspects of cannabis use may lead adolescents to form unique expectancies that differ from those observed for alcohol or tobacco.

Parental monitoring, defined as active supervision and awareness of adolescents' activities [38], represents another critical protective factor across various domains of adolescent risk behavior. Parental monitoring has been consistently associated with reduced alcohol, cannabis, and nicotine use across diverse demographic groups [39-42]. In addition to deterring actual use behaviors, higher levels of parental monitoring are associated with a lower intention to initiate substance use [43]. Given the demonstrated impact on behavioral intentions and decision-making, higher levels of parental monitoring may also reduce adolescents' positive expectancies of cannabis use effects, although direct empirical evidence remains limited.

Family conflict has been robustly associated with an increased risk of substance use and more favorable expectancies of alcohol use [44-47]. Mechanistically, conflict may undermine parental

authority, increase psychological distress, and elicit maladaptive coping strategies, thereby engendering positive attitudes toward substance use [48,49]. While most research has centered on alcohol, the underlying mechanisms are likely applicable to cannabis, warranting extension of these findings to positive expectancies of cannabis use effects. Thus, family rules, parental monitoring, and family conflict represent key proximal determinants of the formation and trajectory of positive expectancies of cannabis use effects. Understanding their dynamics provides important leverage points for targeted interventions that may disrupt adolescent cannabis risk trajectories.

Of note, previous studies on substance use expectancies have relied on conventional growth models to examine developmental trajectories [11,50]. These variable-centered approaches assume that all individuals within a population follow a single average growth trajectory and posit that covariates influencing growth factors affect all individuals uniformly [51]. These variable-centered approaches overlook the possibility of distinct subgroups with divergent developmental pathways, limiting the ability to capture the complexity of early adolescent development [52]. To address this limitation, we used latent class growth analysis (LCGA), a person-centered alternative that classifies individuals into distinct subgroups following similar trajectories, thereby capturing unobserved variation in adolescent development [53,54].

Our Study

In this study, we used LCGA to identify distinct developmental trajectories of positive expectancies of cannabis use effects and examine how parental monitoring, family cannabis use rules, and family conflict are associated with trajectories of positive expectancies of cannabis use effects both within and across trajectory classes while adjusting for demographic characteristics. By integrating a person-centered, longitudinal approach, this study seeks to advance our understanding of how familial factors shape the formation and progression of positive expectancies of cannabis use effects during this critical developmental period.

Methods

Data and Study Sample

The data were drawn from the Adolescent Brain Cognitive Development Study (ABCD Study), the largest ongoing longitudinal investigation of development and health among early adolescents in the United States. Funded by the National Institutes of Health (NIH) and conducted across 21 research sites using a rigorous multistage sampling design, the ABCD Study provides a unique opportunity to understand the factors shaping adolescent development, substance use behaviors, and mental health outcomes [55,56]. Recruitment was carried out between 2016 and 2018 using a systematic school-based sampling approach designed to approximate the demographic composition of the national population of 9- and 10-year-old children [57]. Schools were selected through probability sampling methods stratified by geographic region, race and ethnicity distributions, and socioeconomic characteristics. ABCD Study teams coordinated with school administrators to

distribute study information, conduct on-site presentations, and invite families to participate [57]. Additional information regarding study design, methodology, and data accessibility can be found on the study website [58]. The present analysis included data from the 1-year (mean age 10-11 years), 2-year (mean age 11-12 years), and 3-year (mean age 12-13 years) follow-up waves. The 1-year follow-up was designated as baseline (T1), with subsequent waves designated as time 2 (T2) and time 3 (T3) for this study.

Participants who had valid data on the outcome variables at T1 were included, yielding an initial analytic sample of 8841 participants. Between T1 and T2, 418 participants were lost to follow-up, and an additional 606 participants were lost between T2 and T3. Furthermore, 408 cases were excluded due to missing poststratification weights, which are required for population-representative estimates. These exclusions led to a final analytic sample of 7409 participants.

Ethical Considerations

This is a secondary analysis of data collected by the ABCD Study. The ABCD Study was approved by the central Institutional Review Board (IRB) of the University of California, San Diego (IRB# 160091) and by the IRB at each of the 21 participating research sites [59,60]. Written informed consent was obtained from all parents or legal guardians prior to data collection [59,60]. This analysis used the deidentified, publicly available ABCD Study dataset obtained through the NIH Data Hub, and it was deemed exempt from human subject review by the investigators' IRB (Indiana University Bloomington; 2008226356). Participants and families were compensated for the time spent participating in the study, with amounts varying by data collection site.

Measurements

Outcome Variables

Positive Expectancies of Cannabis Use Effects

Positive expectancies of cannabis use effects were assessed using youth self-report on the Marijuana Effect Expectancy Questionnaire-Brief (MEEQ-B) [25]. The items assessed the degree to which adolescents believe that (1) "marijuana helps a person relax and feel less tense," (2) "marijuana helps people get along better with others or feel more romantic," and (3) "marijuana enhances creativity or alters perceptions." The MEEQ-B has been validated among adolescents and young adults, effectively capturing beliefs about the effects of cannabis [61]. Youth responded to 3 positive expectancy questions on a 5-point Likert scale, with higher summed scores (range 3 - 15) reflecting stronger positive expectancies. Internal consistency (Cronbach α) for the positive expectancies of cannabis use effects scale indicated good reliability ($\alpha=.77$ [T1], $.80$ [T2], and $.83$ [T3]).

Predictor Variables

Family Cannabis Use Rules

Aligning with previous studies [62-64], cannabis use rules were measured using parental report on the following question: "What are the family rules about using marijuana for your

son/daughter?” [65-68] Responses were dichotomized as “strict rules” (“not allowed to use marijuana under any circumstances”) versus “lenient/no rules,” which included all other responses (ie, “not allowed to use marijuana in the home but no rules outside the home,” “allowed to use marijuana in the home with permission,” “allowed to use marijuana in the home whenever desired,” “no rules set about marijuana use,” and “have not yet made rules about my child’s marijuana use”). Given our study’s focus on cannabis and the high correlation of family rules regarding cannabis, alcohol, and nicotine use ($r > 0.70$), alcohol- and nicotine-specific rules were excluded from the present analyses to minimize multicollinearity and improve model interpretability.

Parental Monitoring

Parental monitoring was assessed using youth self-report on 4 items measured on a 5-point Likert scale (1=Never, 2=Almost never, 3=Sometimes, 4=Often, and 5=Always or almost always), with higher mean scores (range 1 - 5) indicating greater parental knowledge, involvement, oversight, and communication [69]. The four items were as follows: (1) “How often do your parents/guardians know where you are?” (2) “If you are at home while your parents or guardians are away, how often do you know how to contact them?” (3) “How often do you talk to your parents or guardians about your plans for the following day, such as school activities or other engagements?” and (4) “How many times do you and your parents/guardians eat dinner together?” This measure reflects the widely used conceptualization of parental monitoring in adolescent development research [40,70-72].

Family Conflict

Consistent with previous studies using the ABCD Study dataset for developmental research [47,72-74], family conflict was assessed using youth self-report on 9 items from the Family Conflict Subscale of the ABCD Study Parent Family Environment Scale, adapted from the PhenX toolkit [75]. Items were coded as True=1 and False=0, with reverse coding applied to positively worded items. The following items were included: “We fight a lot in our family” (1=True), “Family members sometimes get so angry they throw things” (1=True), “Family members often criticize each other” (1=True), and “Family members sometimes hit each other” (1=True). Reverse-coded items included statements such as “Family members rarely become openly angry” (1=False), “Family members hardly ever lose their tempers” (1=False), “If there’s a disagreement in our family, we try hard to smooth things over and keep the peace” (1=False), and “In our family, we believe you don’t ever get anywhere by raising your voice” (1=False). The items were averaged together, with higher mean scores indicating greater conflict (range 0 - 9). Internal consistency values (Cronbach α) for this study were .67 (T1), .64 (T2), and .68 (T3).

Covariates

Psychopathology

Consistent with previous studies [76-79], youth psychopathology was assessed with parent-reported standardized total scores from the Child Behavior Checklist (CBCL) [80]. This questionnaire comprises 112 items rated on a 3-point Likert

scale (0=Not at all true, 1=Somewhat true, and 2=Very true). The total t scores were adjusted for age and sex norms derived from population studies, ensuring comparability across participants [79]. Higher t scores reflect more severe psychopathological problems (range 24 - 88). Cronbach α was .95 for each time point.

Demographic Covariates

Demographic covariates included participant age (in years), biological sex assigned at birth (male/female), parent-reported race and ethnicity, and parental highest education and household income [40,55,73,74,81]. Following the ABCD Study—provided race-ethnicity variable and established frameworks developed by sociocultural literature using the ABCD Study [73,82], parent-reported youth race and ethnicity were categorized as Hispanic, non-Hispanic White, non-Hispanic Black, non-Hispanic Asian, and non-Hispanic other/mixed race (including youth whose parents selected multiple racial categories or “Other race”) [83]. Parental education was dichotomized as high school or less versus some college or higher, and household income was dichotomized as less than US \$75,000 versus US \$75,000 or higher [84-86].

State Recreational Cannabis Legalization Status

State recreational cannabis legalization status was coded as legal (Yes) or not legal (No) by the ABCD Study administration based on the participant’s state of residence at baseline in the ABCD Study (approximately 1 year before study T1). Because the dataset does not include time-varying recreational cannabis use policy indicators, this baseline measure served as a proxy for legalization status at T1 (study reference time point).

Statistical Analysis

For the descriptive analysis, unweighted frequencies and weighted proportions were assessed for categorical variables, and weighted means with SDs were calculated for continuous variables at each time point. Differences across time points were evaluated using weighted chi-square tests for categorical variables and weighted ANOVA for continuous variables. Prior to modeling the latent growth models, a bivariate correlation matrix was examined to assess multicollinearity between predictors.

A series of latent growth models was fitted to examine developmental trajectories of positive expectancies of cannabis use effects. Unconditional latent growth curve models (LGCs) were first examined to assess within-person change and determine whether sufficient heterogeneity existed to justify latent class modeling [50,87,88]. Both linear and quadratic LGCs were tested using maximum likelihood estimation with robust SEs.

Subsequently, LCGA models were used to identify distinct subgroups of adolescents with similar trajectories of positive expectancies of cannabis use effects. Consistent with standard practice, all the LCGA models were specified with intercept and slope variances fixed to zero and residual variances constrained to equality across time points [54]. Unconditional LCGA models with 1 to 7 classes were evaluated to assess the optimal number of trajectory classes. Model fit was assessed

using multiple criteria: Akaike information criterion (AIC), Bayesian information criterion (BIC), sample size-adjusted Bayesian information criterion (aBIC), entropy, and Lo-Mendell-Rubin adjusted likelihood ratio test (LMR-aLRT) [89-91]. The optimal model was defined as having the lowest information criterion values, significant LMR-aLRT, entropy ≥ 0.80 , and no class size smaller than 5% of the total sample, which was considered statistically unstable [52].

After determining the best-fitting model, R3STEP (auxiliary procedure that implements the 3-step method for adding predictors of latent class membership specified by Mplus) was applied to examine associations between class membership and time-invariant covariates (ie, age, biological sex, race/ethnicity, parental education, recreational cannabis legal status, and total family income). This procedure accounts for the uncertainty in class assignments by incorporating posterior probabilities into auxiliary multinomial logistic regressions. This approach improves estimation accuracy and protects against biased parameter estimates [92,93]. Race/ethnicity was specified as a nominal variable in Mplus, which dummy-coded the variable using non-Hispanic White as the reference category. Mplus then reported the overall omnibus effect of the race/ethnicity block rather than separate coefficients for each category unless individual dummy-coded contrasts produced statistically separable estimates across class comparisons. The full set of dummy contrasts nevertheless contributed internally to the estimation of the classification error-adjusted multinomial logistic model.

To further explore predictive associations with time-varying variables (ie, family cannabis rules, parental monitoring, family conflict, and psychopathology), 2 complementary models were estimated. A class-specific effects model was used to assess the different effects of time-varying predictors across latent classes without interfering with the predefined trajectory classes. This approach revealed heterogeneity in the associations between time-varying predictors and outcome variables across developmental trajectories. As a sensitivity analysis, a common effects model was used to estimate population-average associations between the time-varying predictors and outcome

variables under the assumption that the effects of the time-varying predictors on the outcome variables are homogeneous across all latent classes. This model provides insights to understand the general exposure effects that are consistent across subpopulations.

All LCGA models were estimated using Mplus 8.11 [94]. To ensure model stability and reduce the risk of convergence on the local maxima, a multistage estimation procedure was used. Each model was initialized with 1000 random sets of starting values, from which the 250 best-fitting solutions were retained for final optimization. To further verify solution stability, log-likelihood values were required to replicate across 20 iterations. Likelihood ratio tests (eg, LMR-aLRT) were conducted with an additional set of 1000 random start replications, with 200 used for preliminary evaluation and 500 selected for final optimization, repeated 100 times, to ensure the reliability of model comparison results. Missing data of predictors were imputed using the nonparametric random forest-based approach, which has been shown to perform well in retaining nonlinear relationships and interactions among variables in mixed-type datasets [95]. Descriptive statistics were conducted with R 4.5.0 (via RStudio, Posit). The reporting of this study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Checklist 1) [96].

Results

Descriptive Statistics

Table 1 presents the descriptive statistics of the study sample across the 3 time points. The positive expectancies of cannabis use effects score measured among the participants demonstrated an increasing trend (T1: mean 6.41, SD 2.85; T2: mean 7.20, SD 2.93; T3: mean 7.96, SD 2.99; $P < .001$). Similarly, the proportion of strict family cannabis use rules increased over time from 97.9% (T1) to 98.9% (T3) ($P < .001$). Moreover, family conflict scores increased from 1.90 (SD 1.88) to 2.09 (SD 1.96) ($P < .001$). Parental monitoring scores showed a slight decrease across waves (T1: mean 4.51, SD 0.45; T3: mean 4.38, SD 0.50; $P < .001$).

Table . Descriptive statistics of participants from time 1 to time 3 in the Adolescent Brain Cognitive Development Study (ABCD Study) (N=7409).

Variable ^a	Time 1 (age 10-11 years) ^b	Time 2 (age 11-12 years) ^b	Time 3 (age 12-13 years) ^b	P value ^c
Positive expectancies of cannabis use effects (range 3-15), mean (SD)	6.41 (2.85)	7.20 (2.93)	7.96 (2.99)	<.001
Biological sex, n (%)				—
Male	4040 (49.0)	— ^d	—	
Female	3369 (51.0)	—	—	
Race/ethnicity, n (%)				—
NH ^e White	4126 (20.7)	—	—	
NH Black	918 (37.6)	—	—	
Hispanic	1421 (28.9)	—	—	
NH Asian	144 (0.4)	—	—	
NH others	800 (12.3)	—	—	
Parental education, n (%)				—
High school or less	1163 (21.5)	—	—	
Some college or higher	6221 (78.5)	—	—	
Recreational cannabis legal status ^f , n (%)				—
No	5114 (72.8)	—	—	
Yes	1973 (27.2)	—	—	
Total family income, n (%)				—
Less than US \$75,000	2647 (74.4)	—	—	
US \$75,000 or higher	4269 (25.6)	—	—	
Age (range 7 - 16 years), mean (SD)	10.55 (0.64)	11.56 (0.71)	12.51 (0.68)	<.001
Standardized psychopathology <i>t</i> score (range 24-88), mean (SD)	45.67 (11.06)	45.11 (11.13)	45.01 (11.25)	<.001
Family conflict score (range 0 - 9), mean (SD)	1.90 (1.88)	1.90 (1.84)	2.09 (1.96)	<.001
Parental monitoring score (range 1 - 5), mean (SD)	4.51 (0.45)	4.50 (0.46)	4.38 (0.50)	<.001
Family cannabis use rules, n (%)				<.001
Lenient/no rules	1685 (2.3)	1331 (1.8)	1010 (1.1)	
Strict rules	5712 (97.9)	6033 (98.2)	6207 (98.9)	

^aExcept for the baseline sociodemographic characteristics (biological sex, race/ethnicity, parental education, and recreational cannabis legal status), all other variables were measured repeatedly from time 1 (T1) to time 3 (T3).

^bValues represent unweighted frequencies and weighted proportions for categorical variables, and weighted means with SDs for continuous variables. Frequencies may not sum to the total sample size due to missing data.

^cP values were generated using weighted ANOVA for continuous variables and weighted chi-square tests for categorical variables to test differences across waves.

^dNot applicable.

^eNH: non-Hispanic.

^fThe cannabis recreational legal status was determined based on the participant's state of residence at the time of their baseline interview in the ABCD Study, which is approximately 1 year prior to T1 in this study.

Unconditional LCGA Model Statistics Regarding Positive Expectancies of Cannabis Use Effects

Table 2 presents the latent class model fit comparisons of the optimal class solutions, ranging from 1 class to 7 classes. Table

3 presents the sizes of the individual classes. While models with a greater number of classes (5-class to 7-class trajectory solutions) were explored, they yielded subgroups with minimal representation (ie, group size <5% of the total sample), raising concerns about model overfitting and limited interpretability.

Table . Latent class model fit comparisons for unconditional latent class growth analysis models regarding positive expectancies of cannabis use effects.

Trajectory (model)	Log likelihood	BIC ^a	aBIC ^b	AIC ^c	LMR-aLRT ^d <i>P</i> value	BLRT ^e <i>P</i> value	Entropy ^f	Minimal class membership ^g (%)
1 class	–55350.179	110744.910	110729.021	110710.358	— ^h	—	—	—
2 classes	–53156.244	106383.722	106358.349	106328.488	<.001	<.001	0.734	38.9
3 classes	–52609.740	105317.495	105282.540	105241.480	<.001	<.001	0.776	16.9
4 classes ⁱ	–52116.646	104358.038	104313.549	104261.292	<.001	<.001	0.827	9.2
5 classes	–51746.873	103645.224	103591.202	103527.746	<.001	<.001	0.841	4.4
6 classes	–51583.031	103344.270	103280.714	103206.061	<.001	<.001	0.838	2.9
7 classes	–51396.675	102998.291	102925.202	102839.351	<.001	<.001	0.866	0.4

^aBIC: Bayesian information criterion.

^baBIC: sample size–adjusted Bayesian information criterion.

^cAIC: Akaike information criterion.

^dLMR-aLRT: Lo-Mendell-Rubin adjusted likelihood ratio test; *P* value for *k*-1 refers to a significant improvement in model fit between the class (*k*) and the preceding class (*k*-1), which compares whether a profile solution with *k* profiles fits significantly better than a profile.

^eBLRT: parametric bootstrapped likelihood ratio test, which is similar to the LMR-aLRT; *P* value refers to a significant improvement in model fit between the class (*k*) and the preceding class (*k*-1).

^fEntropy indicates classification accuracy, with a higher value indicating better classification (range 0-1).

^gMinimal class membership represents the proportion of participants in the latent class with the smallest membership.

^hNot applicable.

ⁱSelected model.

Table . Sizes of the classes (N=7409).

Trajectory (model)	Class ^a						
	Class 1, n (%)	Class 2, n (%)	Class 3, n (%)	Class 4, n (%)	Class 5, n (%)	Class 6, n (%)	Class 7, n (%)
1 class	7409 (100.0)	— ^b	—	—	—	—	—
2 classes	4530 (61.1)	2879 (38.9)	—	—	—	—	—
3 classes	4125 (55.7)	2035 (27.5)	1249 (16.9)	—	—	—	—
4 classes ^c	2111 (28.5)	684 (9.2)	1496 (20.2)	3118 (42.1)	—	—	—
5 classes	1897 (25.6)	328 (4.4)	3054 (41.2)	1470 (19.8)	660 (8.9)	—	—
6 classes	1864 (25.2)	674 (9.1)	502 (6.8)	1375 (18.6)	2774 (37.4)	220 (2.9)	—
7 classes	1247 (16.8)	31 (0.4)	1439 (19.4)	219 (2.9)	1433 (19.3)	2398 (32.4)	642 (8.7)

^aEach cell displays the frequency and corresponding proportion of individuals within each latent class. Frequencies represent the unweighted counts, while proportions are calculated relative to the total number within each class or group.

^bNot applicable.

^cSelected model.

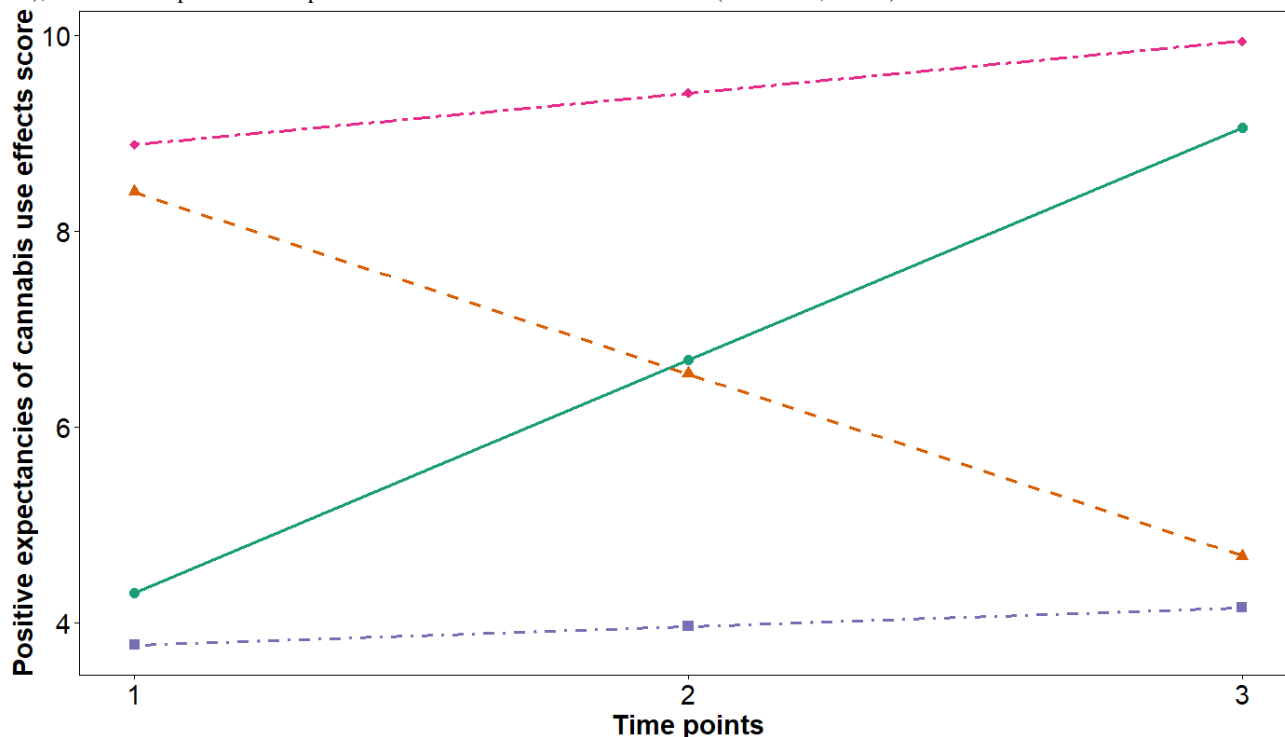
The 4-class model was selected as the optimal solution based on both statistical fitness and conceptual interpretability. This model demonstrated comparatively lower values for the BIC, aBIC, and AIC and higher entropy compared with the 3-class model, indicating improved classification precision. Compared with the 5-class model, it maintained a balanced class distribution, with each subgroup exceeding the recommended

5% minimum threshold (the smallest group being class 2, with 684 cases or 9.2% of the total sample). Therefore, the 4-class solution balanced parsimony with meaningful subgroup differentiation, which avoided interpretive challenges posed by extremely small latent classes observed in higher-order models.

Figure 1 visualizes the 4-class trajectories. The largest subgroup followed a moderate-increasing trajectory that was characterized by a high baseline level but a moderate increasing trend over time (class 4: moderate-increasing class; $n=3118$, 42.1% of the sample). The second most prevalent trajectory followed a high-increasing trajectory that was characterized by a moderate baseline level and a steep increase across the study period (class 1: high-increasing class; $n=2111$, 28.5% of the sample). The

third most prevalent trajectory followed a low-increasing trajectory that was characterized by a low baseline level with a slight increase (class 3: low-increasing class; $n=1496$, 20.2% of the sample). The smallest group followed a high-decreasing trajectory that was characterized by a high baseline level that declined sharply (class 2: high-decreasing class; $n=684$, 9.2% of the sample). Parameter estimates and detailed trajectory features are reported in Table S3 in [Multimedia Appendix 1](#).

Figure 1. The 4-class developmental trajectories of positive expectancies of cannabis use effects at 3 time points. The y-axis represents the mean positive expectancies of cannabis use effects score, and the x-axis represents the 3 examined time points. The 4 trajectories represent latent classes identified through latent class growth modeling: class 1 is plotted with a solid green line and filled circle markers (2111/7409, 28.5%), class 2 is plotted with an orange dashed line and filled triangle markers (684/7409, 9.2%), class 3 is plotted with a purple dot-dash line and filled square markers (1496/7409, 20.2%), and class 4 is plotted with a pink 2-dash line and filled diamond markers (3118/7409, 42.1%).



Associations Between Baseline Time Invariant Variables and Latent Class Membership

Table 4 presents the results of multinomial logistic regression with the low-increasing class (class 3) serving as the reference category. Compared with this group, youth in the high- and moderate-increasing classes were older (adjusted odds ratio

[aOR] 1.13, 95% CI 1.01 - 1.25; $P=.04$ and aOR 1.45, 95% CI 1.31 - 1.60; $P<.001$, respectively). Those in the moderate-increasing class were also more likely to reside in states with legalized recreational cannabis use and be from higher-income families. Multinomial logistic regression findings with other groups as reference categories are reported in Tables S5 - S7 in [Multimedia Appendix 1](#).

Table . Multinomial logistic regression predicting latent class membership (reference class: class 3).

Class ^a and variable ^b	aOR ^{c,d} (95% CI)	P value
Class 1		
Biological sex	0.94 (0.82 - 1.08)	.39
Race/ethnicity	1.03 (0.98 - 1.08)	.27
Parental education	1.06 (0.88 - 1.28)	.53
Recreational cannabis legal status	1.13 (0.96 - 1.32)	.16
Age	1.13 (1.01 - 1.25)	.04 ^e
Total family income	1.00 (0.87 - 1.16)	.97
Class 2		
Biological sex	1.05 (0.88 - 1.27)	.59
Race/ethnicity	0.97 (0.90 - 1.04)	.40
Parental education	0.85 (0.67 - 1.09)	.17
Recreational cannabis legal status	1.06 (0.85 - 1.32)	.60
Age	0.99 (0.85 - 1.14)	.88
Total family income	1.09 (0.90 - 1.32)	.40
Class 4		
Biological sex	1.01 (0.89 - 1.15)	.84
Race/ethnicity	1.02 (0.97 - 1.07)	.38
Parental education	0.99 (0.83 - 1.17)	.88
Recreational cannabis legal status	1.28 (1.11 - 1.49)	.003 ^f
Age	1.45 (1.31 - 1.60)	<.001 ^g
Total family income	1.25 (1.09 - 1.42)	.004 ^f

^aThe reference category for this model is class 3 (low-increasing), which represents 1496 participants (20.2%).

^bFor covariates, the reference groups are as follows: female for biological sex, non-Hispanic White for race/ethnicity, high school education or less for parental education, non-legalized status for recreational cannabis legal status, and total family income below US \$75,000 for family income. Race/ethnicity was specified as a 5-category nominal covariate and was dummy-coded internally by Mplus. Mplus reports a single omnibus effect representing the overall effect of this multicategory covariate.

^caOR: adjusted odds ratio.

^dReported odds ratios represent the relative odds of belonging to each latent class versus the reference class for each covariate category.

^e $P < .05$.

^f $P < .01$.

^g $P < .001$.

Dynamic Associations of Family Environment and Psychopathology With the Trajectories of Positive Expectancies of Cannabis Use Effects Within Each Latent Trajectory Class

Table 5 presents the results from the class-specific effects model estimating the time-varying associations of familial and psychopathological predictors with positive expectancies of cannabis use effects across the 4 identified latent trajectory classes. Each class was modeled independently to capture heterogeneity in relation to the predictors over time. Distinct time-varying familial and psychopathological predictors emerged, underscoring differential developmental processes. In the high-increasing class, lower parental monitoring predicted greater expectancy growth at both T1 ($\beta = -0.152$, $SE = 0.072$; $P = .04$) and T2 ($\beta = -0.477$, $SE = 0.122$; $P < .001$), while increased

family conflict at T3 ($\beta = 0.071$, $SE = 0.019$; $P < .001$) predicted elevated positive expectancies of cannabis use effects. In the high-decreasing class, only family conflict at T2 ($\beta = 0.124$, $SE = 0.063$; $P = .047$) was a significant risk factor, possibly reflecting transient reinforcement of positive expectancies before decline. The low-increasing class exhibited no significant associations across time points, though family conflict at T3 approached significance ($\beta = 0.038$, $SE = 0.021$; $P = .07$). In contrast, the moderate-increasing class (the largest group) showed the most consistent effects: less strict family cannabis use rules were significantly associated with expectancy increases at T1 ($\beta = -0.171$, $SE = 0.063$; $P = .006$) and T2 ($\beta = -0.212$, $SE = 0.091$; $P = .02$), lower parental monitoring was significant at both T2 ($\beta = -0.275$, $SE = 0.088$; $P = .002$) and T3 ($\beta = -0.307$, $SE = 0.066$; $P < .001$), and family conflict was the most robust predictor from T1 to T3 ($P < .005$).

Table . Class-specific estimates of time-varying predictors of positive expectancies of cannabis use effects across 3 time points.

Class, time, and variable ^a	β	SE	z-statistics	P value
Class 1 (high-increasing trajectory)				
Time 1				
Family cannabis use rules	−0.079	0.071	−1.108	.27
Parental monitoring	−0.152	0.072	−2.111	.04 ^b
Psychopathology <i>t</i> score	−0.004	0.003	−1.293	.20
Family conflict	−0.016	0.017	−0.959	.34
Time 2				
Family cannabis use rules	−0.226	0.149	−1.519	.13
Parental monitoring	−0.477	0.122	−3.922	<.001 ^c
Psychopathology <i>t</i> score	−0.008	0.006	−1.312	.19
Family conflict	0.019	0.033	0.587	.56
Time 3				
Family cannabis use rules	0.023	0.099	0.229	.82
Parental monitoring	−0.123	0.077	−1.603	.11
Psychopathology <i>t</i> score	0.005	0.004	1.527	.13
Family conflict	0.071	0.019	3.687	<.001 ^c
Class 2 (high-decreasing trajectory)				
Time 1				
Family cannabis use rules	−0.143	0.141	−1.009	.31
Parental monitoring	0.048	0.139	0.349	.73
Psychopathology <i>t</i> score	−0.004	0.006	−0.765	.44
Family conflict	−0.007	0.037	−0.195	.85
Time 2				
Family cannabis use rules	0.150	0.275	0.544	.59
Parental monitoring	−0.369	0.267	−1.381	.17
Psychopathology <i>t</i> score	−0.006	0.010	−0.620	.54
Family conflict	0.124	0.063	1.982	.047 ^b
Time 3				
Family cannabis use rules	−0.123	0.169	−0.729	.47
Parental monitoring	−0.135	0.129	−1.044	.30
Psychopathology <i>t</i> score	−0.010	0.006	−1.825	.07
Family conflict	0.050	0.033	1.500	.13
Class 3 (low-increasing trajectory)				
Time 1				
Family cannabis use rules	−0.065	0.073	−0.886	.38
Parental monitoring	−0.063	0.064	−0.978	.33
Psychopathology <i>t</i> score	0.004	0.003	1.408	.16
Family conflict	0.013	0.017	0.801	.42
Time 2				
Family cannabis use rules	0.099	0.150	0.661	.51
Parental monitoring	−0.143	0.119	−1.204	.23

Class, time, and variable ^a	β	SE	z-statistics	P value
Psychopathology <i>t</i> score	0.002	0.005	0.410	.68
Family conflict	0.040	0.036	1.111	.27
Time 3				
Family cannabis use rules	0.074	0.107	0.697	.49
Parental monitoring	−0.045	0.069	−0.645	.52
Psychopathology <i>t</i> score	−0.002	0.003	−0.814	.42
Family conflict	0.038	0.021	1.805	.07
Class 4 (moderate-increasing trajectory)				
Time 1				
Family cannabis use rules	−0.171	0.063	−2.733	.006 ^d
Parental monitoring	−0.089	0.068	−1.317	.19
Psychopathology <i>t</i> score	0.004	0.003	1.555	.12
Family conflict	0.046	0.016	2.859	.004 ^d
Time 2				
Family cannabis use rules	−0.212	0.091	−2.317	.02 ^b
Parental monitoring	−0.275	0.088	−3.105	.002 ^d
Psychopathology <i>t</i> score	0.012	0.004	2.908	.004 ^d
Family conflict	0.079	0.022	3.689	<.001 ^c
Time 3				
Family cannabis use rules	0.031	0.078	0.402	.69
Parental monitoring	−0.307	0.066	−4.654	<.001 ^c
Psychopathology <i>t</i> score	0.010	0.003	3.085	.002 ^d
Family conflict	0.074	0.016	4.661	<.001 ^c

^aThe outcome variable is the individual's level of positive expectancies of cannabis use effects at each time point (time 1, time 2, and time 3) within each latent class. All covariates are repeated measures within respondents from time 1 to time 3. This model does not predict the growth trajectory, but instead, it estimates how time-varying predictors are associated with variation in the positive expectancies of cannabis use effects score over time within each trajectory class.

^b $P < .05$.

^c $P < .001$.

^d $P < .01$.

Shared Associations of Family Environment and Psychopathology With Positive Expectancies of Cannabis Use Effects Across Latent Trajectory Classes

Results from the common effects model are presented in Table S8 in [Multimedia Appendix 1](#), where time-varying familial and psychopathological predictors were constrained to have equal influence across all latent trajectory classes. Strict family cannabis use rules were significantly associated with lower positive expectancies of cannabis use effects at T1 only ($\beta = -0.130$, $SE = 0.040$; $P = .001$). However, parental monitoring remained a significant predictor for positive expectancies of cannabis use effects across all 3 time points (T1: $\beta = -0.089$, $SE = 0.040$; $P = .03$; T2: $\beta = -0.315$, $SE = 0.061$; $P < .001$; T3: $\beta = -0.185$, $SE = 0.040$; $P < .001$). Family conflict was a consistent

and robust risk factor, with its influence increasing from T2 to T3 ($P < .001$).

Discussion

Heterogeneous Trajectories of Positive Expectancies of Cannabis Use Effects in Early Adolescence

To the best of our knowledge, this is the first study to use a large-scale longitudinal dataset to examine the developmental trajectories of positive expectancies of cannabis use effects in early adolescents, using a person-centered analytic framework. By modeling the development of positive expectancies of cannabis use effects across early adolescence, this study offers novel insights into the dynamic, heterogeneous nature of the formation of positive expectancies of cannabis use effects during this sensitive developmental phase. It identified the following

4 distinct trajectories of positive expectancies of cannabis use effects: high-increasing, high-decreasing, low-increasing, and moderate-increasing trajectories. These trajectories highlight the substantial variability in both the baseline levels and patterns of change in positive expectancies of cannabis use effects, underscoring early adolescence as an important period for tailoring interventions to prevent cannabis use.

Although weighted descriptive statistics across the sample indicated relatively modest population-level changes over the 3 waves, this pattern is expected given the narrow but critical developmental window of early adolescence (approximately ages 11 - 13 years) represented in our sample from the ABCD Study cohort. During this period, many psychosocial and contextual characteristics exhibit relative stability at the population level [97], yet substantial *within-person* variability persists in cognitive-affective processes such as substance-related expectancies, social-emotional development, and dynamic familial factors [7,98-100]. LCGA, a person-centered approach, is uniquely suited to capturing individual-level heterogeneity because it identifies subgroups of youth who share similar developmental trajectories even when the overall mean trend appears relatively flat. Accordingly, the 4 trajectory classes identified in this study represent distinct and meaningful expectancy development over time rather than simple cross-sectional differences based on average levels [52,101]. In addition, although the trajectory classes are derived from repeated measures of positive expectancies of cannabis use effects, the LCGA analytic framework used in this study helps minimize potential bias arising from factors, such as parental monitoring and family conflict, which may influence both the development of positive expectancies of cannabis use effects and the predictors included in the R3STEP model. LCGA does not stratify individuals on a single observed positive expectancies of cannabis use effects score; instead, it forms subgroups based on model-estimated posterior probabilities that reflect the overall pattern of trajectories. Moreover, R3STEP estimates covariate associations only after class formation and incorporates adjustment for classification uncertainty, reducing the bias that can arise when treating uncertain class assignments as if they are certain [92]. Within this framework, associations between predictors and class membership represent correlational patterns among latent developmental pathways rather than artifacts of the analytic strategy. Thus, the heterogeneity observed across classes reflects meaningful differences in expectancy development over time, highlighting the advantage of mixture modeling for uncovering nuanced developmental processes that would remain obscure in traditional variable-centered analyses.

Using this approach, the largest trajectory class identified in this study was the moderate-increasing trajectory, which was characterized by relatively high initial levels of positive expectancies of cannabis use effects that increased steadily with time, suggesting an active expectancy formation phase. This pattern may reflect normative developmental processes in early adolescence, where adolescents increasingly seek self-identity and autonomy, and become increasingly susceptible to substance use opportunities [102]. Multivariable comparisons revealed that youth in this trajectory were more likely to be older, from

high-income families, and living in states with recreational cannabis legalization. Notably, the consistently elevated and gradually intensifying positive expectancies of cannabis use effects observed in this group are concerning, as the findings point to a sustained expectancy formation process that may heighten the risk for future initiation and persistent use. Youth in this trajectory may be actively shaping their cognitive belief around cannabis use prior to engaging in cannabis use, which may be reinforced by their developmental maturity (older age) and the legal status of recreational cannabis use in their environment. These findings suggest that prevention efforts should extend beyond traditionally high-risk youth to include those on seemingly normative developmental pathways who may nonetheless be building pro-cannabis expectancies that increase long-term vulnerability. The other 3 trajectories provide further insights into heterogeneity in the development of positive expectancies of cannabis use effects, highlighting the substantial variability in both the onset and developmental course of positive expectancies of cannabis use effects and pointing to multiple pathways of risk and resilience in early cannabis-related cognitions.

Familial Protective and Risk Factors

Findings from the common effects model showed that stricter family cannabis use rules and higher levels of parental monitoring were protective against positive expectancies of cannabis use effects during early adolescence. These effects were the strongest at earlier ages, particularly at 10 - 11 years (T1) and 11 - 12 years (T2). Parental monitoring demonstrated a consistent inverse association with positive expectancies of cannabis use effects across all 3 time points, with the strongest effect at ages 11 - 12 years. In contrast, cannabis-specific rules were significant only at T1, with diminished predictive value at later time points. These protective effects align with the findings of a large body of developmental research emphasizing the critical role of structured and engaged parenting in deterring adolescent substance-related cognitions and behaviors [43,103].

The early and pronounced influence of family cannabis use rules underscores their importance in shaping adolescents' cognitive attitudes regarding substance use when they are most embedded within the family context and are more receptive to parental expectations and boundaries [104]. These rules function as clear behavioral norms, potentially counterbalancing early exposure to peer influences and emerging social scripts around cannabis. Although the direct statistical effect weakened by ages 11 - 12 years, such rules may establish enduring internalized norms that persist even when external risks are present. Prior research suggests that early parental rule-setting exerts long-term influence on substance-related decision-making. For example, the authoritative parenting style is characterized by setting limits and is linked to lower substance use and less positive attitudes toward drugs throughout adolescence [105-107].

Parental monitoring demonstrated a more enduring and stable protective effect across the developmental period studied. Unlike rule-setting, monitoring reflects an ongoing dynamic engagement with the daily lives of adolescents, which provides not only behavioral oversight but also emotional attunement

and accountability [108]. This form of proactive parenting has been consistently shown to reduce adolescents' opportunities to engage in risk behaviors and to shape substance-related cognitions in a protective direction [65,108]. The heightened impact observed at ages 11-12 years may indicate a critical developmental "sweet spot," when adolescents begin to seek autonomy but remain highly responsive to external regulation and support. These findings emphasize the importance of initiating family-based prevention efforts during early adolescence, leveraging this window to reinforce cognitive resistance to substance use before peer norms and societal influences exert stronger effects.

Family conflict emerged as a robust risk factor for elevated positive expectancies of cannabis use effects at ages 12-13 years (T3). In addition, class-specific models showed that this effect was the strongest in the moderate- and high-increasing classes, suggesting that sustained family tensions may accelerate the formation of positive expectancies of cannabis use effects, particularly when not offset by protective parenting practices. This finding is consistent with the findings of a substantial body of literature linking family dysfunction to increased vulnerability to substance use [109,110]. Chronic conflict may erode emotional regulation capacities and model maladaptive coping strategies, thereby reinforcing cannabis as a perceived tool for managing stress [111]. These findings highlight the dual importance of reinforcing protective parenting practices and reducing family conflict during this critical developmental period.

Class-Specific Nuances

Unlike the common effects model, which assumes that predictors operate uniformly across all trajectories, the class-specific model allows the effects of parental and familial factors to vary by trajectory and captures heterogeneity in developmental processes. The findings revealed notable differences in the influences of familial and psychopathological factors across the 4 trajectories of positive expectancies of cannabis use effects.

Parental monitoring was pronounced among adolescents who followed trajectories marked by moderate- and high-increasing risk, where higher monitoring during early and mid-adolescence (ages 10 - 12 years) was associated with significantly lower positive expectancies of cannabis use effects. Additionally, stricter family cannabis use rules were associated with lower positive expectancies of cannabis use effects in the moderate-increasing group at ages 10-11 and 11-12 years. These effects were most pronounced prior to the age of 13 years, underscoring a sensitive developmental window when parental guidance may shape substance-related cognitions before peer norms and autonomy-seeking dominate [112,113]. It is also possible that elevated parental monitoring reflects a reactive process, wherein parents increase oversight in response to perceiving their child's heightened risk or early signs of problematic behaviors. In this interpretation, monitoring may serve as a preventive and responsive strategy, suggesting that parents who recognize vulnerability may intensify supervision as a preemptive measure against further risk escalation.

However, these protective effects were less evident or absent in the high-decreasing and low-increasing trajectories. In the

high-decreasing group, early high levels of positive expectancies of cannabis use effects declined over time, and neither parental monitoring nor rule-setting was significantly associated with these shifts. This may suggest that reductions in positive expectancies of cannabis use effects were driven by other factors, such as experiential disconfirmation or broader contextual influences, and further research is warranted for this group of youth. In the low-increasing group, neither monitoring nor rule-setting showed significant associations, though family conflict emerged as a marginal risk factor at later ages. The absence of early effects in this group could reflect other protective dispositional factors (eg, low sensation-seeking) or structural buffers (eg, strong school engagement) not captured in our analysis.

Family conflict emerged as the most robust and class-differentiating risk factor across trajectories, particularly for those at elevated or increasing risk. Adolescents in the moderate- and high-increasing groups exhibited significantly elevated positive expectancies of cannabis use effects in association with greater family conflict, especially by ages 12-13 years. This pattern suggests that interpersonal stress within the home may amplify the development of positive expectancies of cannabis use effects during a period of heightened social and emotional reactivity. In line with developmental cascade models [114], chronic exposure to family conflict may erode previously adaptive cognitive trajectories and accelerate the adoption of risk-promoting beliefs. Conflict was also a significant predictor in the high-decreasing group at mid-stage (ages 11-12 years), suggesting a contemporaneous, level-shifting effect of conflict rather than a change in growth rate. In contrast, conflict showed no impact among adolescents in the low-increasing class, potentially reflecting greater resilience or the presence of unmeasured compensatory mechanisms, such as school connectedness and temperamentally based self-regulation.

Psychopathological symptoms played a more nuanced, temporally specific role. Across most trajectories, they were not significant predictors in early adolescence but became increasingly relevant by ages 11-12 and 12-13 years in the moderate-increasing class. This shift may reflect the growing salience of emotional distress in early adolescence, when academic, social, and identity-related demands intensify, and cannabis may be perceived as a coping tool.

Collectively, several effects were close to statistical significance based on the *P* value. It is likely that we detected small effects because of our large sample size. Therefore, the findings warrant replication.

Limitations

Several limitations should be considered when interpreting the findings of this study. First, the analysis was limited to 3 waves of data collected during early adolescence, which restricts the ability to capture the full developmental trajectory of positive expectancies of cannabis use effects into middle and late adolescence. Given that substance-related attitudes and behaviors often intensify during these later periods, future research with a longer follow-up is needed to determine whether the identified trajectories persist, shift, or predict distal actual cannabis use behavior. Second, the measure of recreational

cannabis legalization status was based on state-level policy 1 year prior to this study's baseline (T1) assessment. While useful as a contextual marker, this static measure may not fully reflect the evolving influence of recreational legalization over time, particularly as policy implementation and social norms continue to change. Third, this study used a 3-step LCGA in which covariates and predictors were deliberately excluded from the trajectory formation process and incorporated only in the R3STEP multinomial logistic regression and subsequent class-specific and common effects models. While this approach preserves the integrity of class estimation, unmeasured or imperfectly measured factors may still be associated with both the trajectory of positive expectancies of cannabis use effects and class membership, introducing the possibility of residual confounding. Fourth, the study was unable to account for a range of other social and contextual influences that are becoming increasingly relevant to adolescent development and substance-related behaviors. Given emerging evidence that cannabis-related content on social media can shape adolescents' attitudes, expectancies, and perceived norms, future studies should integrate time-matched assessments of digital media exposure to provide a more comprehensive understanding of expectancy formation.

Public Health Implications

This study fills a critical gap in the literature by identifying 4 distinct developmental trajectories of positive expectancies of cannabis use effects among early adolescents, underscoring the need for prevention strategies that extend beyond universal, one-size-fits-all models. While universal prevention remains important, interventions must be tailored to the heterogeneous developmental pathways identified in this study.

In addition to these practical implications, the observed trajectory patterns and associated family predictors contribute to the development of the current theory. The identification of distinct developmental trajectories of positive expectancies of cannabis use effects suggests that expectancy formation during early adolescence may be heterogeneous rather than uniformly increasing. The findings that stricter household rules and higher parental monitoring were associated with membership in lower or declining classes of positive expectancies of cannabis use effects and that greater family conflict was associated with higher-risk classes of positive expectancies of cannabis use

effects are consistent with the social learning theory that emphasizes the role of family environments in shaping evaluative beliefs and related motivational states. Together, these findings suggest that theoretical models of adolescent cannabis use may benefit from incorporating heterogeneity in the development of positive expectancies of cannabis use effects and accounting for the structuring influence of family dynamics during this critical developmental period.

Parental monitoring and clear cannabis use rules were most protective in early adolescence, particularly between the ages of 10 and 12 years, when parental influence remains salient. Intervening during this sensitive period may delay or suppress the rise in positive expectancies of cannabis use effects before peer norms and autonomy-seeking behaviors exert greater influences. These practices are especially critical for adolescents in moderate- and high-increasing trajectories, where sustained parental engagement may disrupt escalation in expectancies. In contrast, family conflict emerged as a robust risk factor, particularly in the later stages of early adolescence. Chronic conflict may amplify cognitive vulnerability, destabilize otherwise adaptive trajectories, and accelerate the internalization of risk-promoting beliefs. Prevention programs that educate parents about conflict management and communication skills could therefore provide meaningful protection. Psychopathology also became increasingly salient by ages 11 - 13 years, reinforcing the importance of integrated prevention that includes mental health screening and timely intervention. Addressing emotional distress and teaching adaptive coping strategies may reduce the perceived utility of cannabis for managing stress.

Collectively, these findings highlight the value of early, sustained, and nuanced family involvement across developmental stages. Cannabis use prevention programs should also focus on enhancing parental self-efficacy by providing practical tools for effective communication, conflict resolution, and the implementation of developmentally appropriate cannabis use rules [115]. Early adolescence is a critical period during which parental authority still has a dominant influence, particularly for adolescents not yet embedded in high-risk trajectories. For these adolescents, clear and consistent rule-setting within a supportive context may help prevent escalation in expectancies and delay susceptibility.

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Data Availability

Data for this study were derived from the Adolescent Brain Cognitive Development Study (ABCD Study) 5.1 release [118]. Deidentified ABCD Study data are available to qualified investigators through the National Institutes of Health Brain Development Cohorts (NBDC) Data Hub. Information on data access procedures is provided on the ABCD Study data sharing page [119]. The raw data of this study are available on the National Institute of Mental Health Data Archive (NDA) website [120]. Instructions on how to create an NDA study are available on the NDA website [121].

Authors' Contributions

Conceptualization: WAQ, KKE

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Formal analysis: WAQ

Methodology: WAQ, DCS, WJ, SH, KKE

Project administration: WAQ, KKE

Resources: KKE

Software: WAQ, KKE

Supervision: WJ, SH, KKE

Validation: DCS, WJ, SH, KKE

Writing – original draft: WAQ, WJ, KKE

Writing – review & editing: WAQ, DCS, WJ, SH, KKE

Conflicts of Interest

None declared.

Multimedia Appendix 1

Additional data to support the findings of the study.

[DOCX File, 70 KB - [publichealth_v12i1e85652_app1.docx](#)]

Checklist 1

STROBE checklist.

[PDF File, 164 KB - [publichealth_v12i1e85652_app2.pdf](#)]

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Abbreviations

ABCD Study: Adolescent Brain Cognitive Development Study

aBIC: sample size-adjusted Bayesian information criterion

AIC: Akaike information criterion

aOR: adjusted odds ratio

BIC: Bayesian information criterion

IRB: Institutional Review Board

LCGA: latent class growth analysis

LGCM: latent growth curve model

LMR-aLRT: Lo-Mendell-Rubin adjusted likelihood ratio test

MEEQ-B: Marijuana Effect Expectancy Questionnaire-Brief

NIH: National Institutes of Health

PRIME: plans, responses, impulses, motives, and evaluations

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Postpandemic Change in Demographic and Clinical Features of Patients With Omicron Who Were Hospitalized: Territory-Wide Retrospective Repeated Cross-Sectional Study in Hong Kong

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Abstract

Background: The Omicron variant of SARS-CoV-2 underwent several mutations since it was first identified in November 2021, with a large outbreak in Hong Kong in early 2022. Yet, local cases of Omicron infections persist, even though the COVID-19 pandemic ended in May 2023.

Objective: This study aims to describe the changes in demographic and clinical characteristics of patients infected with COVID-19 across different Omicron waves in Hong Kong and determine whether the changes continued into the postpandemic period.

Methods: This retrospective repeated cross-sectional study collected data on patients infected with COVID-19 admitted to public hospitals in Hong Kong between May 1, 2022, and May 31, 2024. These data were later categorized into 3 periods based on the Omicron strain. A subsequent age-stratified descriptive analysis was conducted on each characteristic to identify any significant differences across the periods.

Results: First, the case fatality ratio significantly lowered among those older than 85 years (1.5% proportion decrease, period 1: 11.6%, period 2: 10.1%, effect size: 0.02; $P < .001$). Second, most patients were Chinese ($\geq 68.7\%$ per age group and period), and females were predominantly infected for those aged older than 85 years ($\geq 56.9\%$ per period). Third, the Charlson Comorbidity Index scores in most age groups showed a predominant proportion of infected individuals with 0 scores (more than 70% per period). Fourth, most cases were from slightly disadvantaged populations in Hong Kong ($\geq 30.5\%$ per age group per period). Fifth, clinical management of Omicron hospitalizations showed lowered length of hospital stays among adults and older individuals (≥ 1 d decrease between periods 1 and 3, per age group), as well as increased administration of bronchodilators.

Conclusions: Despite the decreasing incidence of Omicron cases admitted to public hospitals in Hong Kong, the increasing case fatality ratio with age suggests that long-term surveillance of COVID-19 should be maintained to prepare for potential mutations and outbreaks.

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KEYWORDS

emergency department; COVID-19; infectious disease epidemiology; Omicron; SARS-CoV-2

Introduction

The Omicron outbreak in early 2022 resulted in a crude population mortality rate of 37.7 per million, overwhelming the

Hong Kong health system [1,2]. On May 5, 2023, the World Health Organization (WHO) officially declared an end to the pandemic [3]. Nevertheless, reports of COVID-19 outbreaks persisted in Hong Kong and globally [4,5]. By May 2024, the

Communicable Disease Branch of the Center for Health Protection in Hong Kong reported that JN.1, the local dominant SARS-CoV-2 variant, did not cause more severe disease compared to XBB and its descendant lineages, the previous dominant strain [6].

Postpandemic surveillance is crucial for understanding the ongoing impact of COVID-19 and improving future pandemic preparedness. Current literature on the post-COVID-19 era primarily focuses on COVID-19 (long COVID-19) and delayed health care for patients with noncommunicable diseases during the pandemic. Long COVID-19 is a multisystemic condition manifesting as new onset cardiovascular disease, thrombotic disease, cerebrovascular disease, myalgic encephalomyelitis or chronic fatigue syndrome, type 2 diabetes, or postural orthostatic tachycardia syndrome [7]. Delayed health care for patients with noncommunicable diseases has resulted in complications and multimorbidity, contributing to increased health care costs [8,9].

An updated characterization of hospitalized patients with COVID-19 can provide a clearer clinical picture after the COVID-19 pandemic. Previous studies have identified several factors associated with worse prognosis in hospitalized patients with COVID-19, including blood biomarkers [10-13], hypertensive and diabetic medications [14,15], older age [16,17], males [12,13,17], hypertension and diabetes comorbidities [18,19], frailty [20,21], length of hospital stay [22], and lower socioeconomic background [23,24]. A longitudinal investigation into these parameters may enhance our understanding of the ongoing impact of COVID-19.

The aim of this study is to describe the changes in demographic and clinical characteristics of hospitalized patients infected with Omicron across different waves in Hong Kong, and to determine whether these changes continued into the postpandemic period.

By conducting these comparisons, we provide insights into the evolving clinical profile of COVID-19 to inform the development of future public health strategies.

Methods

Participants and Context

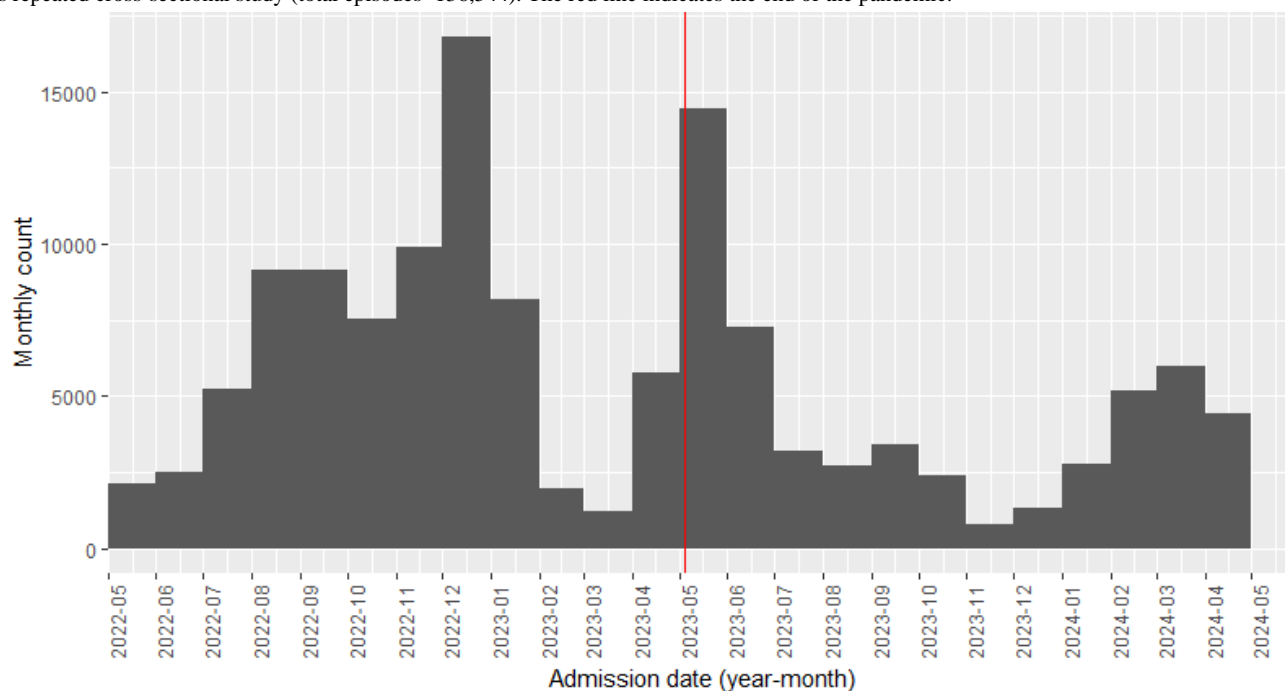
This study used a territory-wide, retrospective, repeated, cross-sectional study design to collect electronic clinical data from May 1, 2022, to May 31, 2024, sourced from the Clinical Data Analysis and Reporting System, managed by the Hong Kong Hospital Authority [25]. The Clinical Data Analysis and Reporting System encompasses data from 18 public hospitals in Hong Kong and has been validated in previous studies for its reliability [26]. Also, the patients included in this study were identified through confirmatory laboratory test results (reverse transcription polymerase chain reaction, multiplex polymerase chain reaction, and polymerase chain reaction) conducted in hospitals or government public health laboratories during the study period.

The study period was divided into 3 groups according to the epidemic waves illustrated in Figure 1:

1. Period 1: between May 1, 2022, and February 28, 2023.
2. Period 2: between March 1, 2023, and November 30, 2023.
3. Period 3: between December 1, 2023, and May 31, 2024.

Based on WHO's declaration of an end to the pandemic on May 5, 2023, [3], changes that continued into the postpandemic period were identified by differences in characteristics between periods 2 and 3. In addition, this study adopted episode count as the primary unit of measurement. An episode was defined as a single hospital admission to discharge occurrence, regardless of readmission of unique patients.

Figure 1. A histogram plot showing the monthly episodes of patients infected with Omicron hospitalized in Hong Kong between 2022 and 2024 in this repeated cross-sectional study (total episodes=136,544). The red line indicates the end of the pandemic.



Defining Demographic Characteristics

This study categorized ages into 5 groups: 0 - 17, 18 - 64, 65 - 74, 75 - 84, and ≥ 85 years. Socioeconomic Deprivation Index (SDI) was defined using the deprivation score in each tertiary planning unit in Hong Kong [27]. The score was calculated based on the 2021 population census, considering factors such as marital status, school attendance, working population, monthly domestic household income, household size, and tenure of accommodation [28]. Charlson Comorbidity Index (CCI) score was calculated using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* codes [29], and categorized into 4 groups: 0, 1, 2 - 3, and ≥ 4 . Specific comorbidities were identified, including unspecified essential hypertension (*ICD-10*: I10), type 2 diabetes mellitus (*ICD-10*: E11.0-E11.9), and unspecified hyperlipidemia (*ICD-10*: E78.5). Frailty-related episodes were identified based on co-occurring *ICD-10* diagnoses related to frailty markers, validated in a previous study [30]. The case fatality ratio (CFR) was defined, according to the WHO definition, as the proportion of COVID-19-related deaths per confirmed case of COVID-19 [31].

Defining Clinical Characteristics

All in-patient drugs administered during each episode were categorized according to Table S2 in [Multimedia Appendix 1](#). For the biomarkers of interest, the earliest laboratory requests made during each episode were obtained to reflect the biomarker value closest to the date of COVID-19 diagnosis. For biomarkers with less than 25% missing data, multiple imputation using k-nearest neighbors with Gower Distance was applied [32]. Also, patients with more than 2 hospital admissions were used to measure readmission.

Descriptive Analysis

Age-stratified descriptive analyses were used to characterize the changes in demographic and clinical characteristics across distinct pandemic periods. Categorical variables (≥ 2 hospital readmissions, sex, comorbidities, race, CCI score, frailty-related episodes, Social Deprivation Index, and drug administration) were presented as frequency (n, %). Continuous variables (length of stay and blood biomarkers) were reported as median (IQR).

To account for varying period durations, the measurements were standardized: categorical variables as episodes per month and continuous variables as mean values per month.

Continuous variables across periods were compared using the Kruskal-Wallis test; categorical variables were compared using the proportions test (Fisher exact test was used if the proportions

test assumptions were violated). Post hoc pairwise comparisons of significant differences were performed (proportions test or Fisher exact test for categorical, Dunn test for continuous variables), with Bonferroni correction for multiple testing.

The effect sizes for significant variables were measured using Cramér V for categorical and Eta squared test for continuous variables. All *P* values were 2-sided; statistical significance was defined as *P* < .05. Analyses were conducted with R (version 4.2.2; R Core Team) [33].

Ethical Considerations

This study received ethical approval from The University of Hong Kong Institutional Review Board (UW 20 - 112). Informed consent was waived by the institutional review board as all the patients' data were collected anonymously. The privacy and confidentiality of human subjects were protected by maintaining anonymity, not collecting personal data, and ensuring that data were securely stored by the principal investigator and deleted after the storage period. This study was conducted in accordance with the Declaration of Helsinki, and no compensation was provided for the human subjects involved.

Results

Hospitalization and Epidemic Trends

Between May 2022 and May 2024, [Figure 1](#) and [Table 1](#) illustrated the 3 distinct epidemic curves corresponding to periods 1-3, each exhibiting progressively lower peaks. This trend was further highlighted in [Tables 2-6](#), which showed depleting total number of hospitalized Omicron cases across the study period among all age groups: 0 - 17 years (75.2% decrease, Period 1: 8399, Period 3: 2081); 18 - 64 years (71.6% decrease, Period 1: 15,274, Period 3: 4340); 65 - 74 years (69.9% decrease, Period 1: 13,549, Period 3: 4072); 75 - 84 years (67.5% decrease, Period 1: 15,622, Period 3: 5076); and older than 85 years (62.8% decrease, Period 1: 19,717, Period 3: 7337). The difference between periods 1 and 3 diminished as the age group got older. Moreover, the rate of hospital readmissions per month decreased across all ages: 0 - 17 years (14.8 episodes per month decrease, Period 1: 41.6 episodes per month, Period 3: 26.8 episodes per month); 18 - 64 years (225.8 episodes per month decrease, Period 1: 296.0 episodes per month, Period 3: 70.2 episodes per month); 65 - 74 years (249.8 episodes per month decrease, Period 1: 346.8 episodes per month, Period 3: 97 episodes per month); 75 - 84 years (332 episodes per month decrease, Period 1: 484.5 episodes per month, Period 3: 152.5 episodes per month); and older than 85 years (480.8 episodes per month decrease, Period 1: 754 episodes per month, Period 3: 273.2 episodes per month).

Table . Frequency of hospitalized patients infected with Omicron in Hong Kong from this repeated cross-sectional study (2022-2024) (total episodes, N=136,544).

Date	Values, n (%)
May 1, 2022	2076 (1.5)
June 1, 2022	2447 (1.8)
July 1, 2022	5202 (3.8)
January 8, 2022	8929 (6.5)
September 1, 2022	9314 (6.8)
October 1, 2022	7483 (5.5)
November 1, 2022	9735 (7.1)
December 1, 2022	16,695 (12.2)
January 1, 2023	8492 (6.2)
February 1, 2023	2098 (1.5)
March 1, 2023	1165 (0.9)
April 1, 2023	5487 (4)
May 1, 2023	14,395 (10.5)
June 1, 2023	7487 (5.5)
July 1, 2023	3276 (2.4)
August 1, 2023	2654 (1.9)
January 9, 2023	3379 (2.5)
October 1, 2023	2484 (1.8)
November 1, 2023	840 (0.6)
December 1, 2023	1246 (0.9)
January 1, 2024	2757 (2)
February 1, 2024	5039 (3.7)
March 1, 2024	6077 (4.5)
April 1, 2024	4407 (3.2)
May 1, 2024	3380 (2.5)

Table . Characteristics of patients infected with Omicron in Hong Kong from this repeated cross-sectional study (2022 - 2024), stratified by ages 0 - 17 years (total episodes, N=14,556).

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
Case fatality ratio	0.1	— ^d	0.1	—	0	—	—	—
≥2 hospital readmissions, n (%)	416 (5)	41.6 (0.5)	250 (6.1)	27.8 (0.68)	161 (7.7)	26.8 (1.28)	<.001 ^e	0.89 ^f
Sex, n (%)								
Male	4689 (55.8)	468.9 (5.58)	2167 (53.2)	240.8 (5.91)	1128 (54.2)	188 (9.03)	.02 ^e	0.02 ^f
Female	3710 (44.2)	371 (4.42)	1909 (46.8)	212.1 (5.2)	953 (45.8)	158.8 (7.63)	.02 ^e	0.02 ^f
Comorbidities, n (%)								
Essential primary hypertension	1 (0)	0.1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	.37 ^g	—
Type 2 diabetes mellitus	3 (0)	0.3 (0)	2 (0)	0.2 (0)	0 (0)	0 (0)	.69 ^g	—
Hyperlipidemia (unspecified)	1 (0)	0.1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	>.99 ^g	—
Race, n (%)								
Chinese	6483 (77.2)	648.3 (7.72)	3035 (74.5)	337.2 (8.28)	1429 (68.7)	238.2 (11.45)	<.001 ^e	0.07 ^f
Non-Chinese	1916 (22.8)	191.6 (2.28)	1041 (25.5)	115.7 (2.83)	652 (31.3)	108.7 (5.21)	<.001 ^e	0.07 ^f
Length of hospital stay (days), median (IQR)	2 (2)	3.19 (0.77)	2 (2)	2.79 (0.83)	2 (2)	2.56 (0.54)	<.001 ^h	0.009 ⁱ
Charlson Comorbidity Index score, n (%)								
0	8236 (98.1)	823.6 (9.81)	3962 (97.2)	440.2 (10.8)	2023 (97.6)	337.2 (16.26)	.003 ^e	0.03 ^f
1	69 (0.8)	6.9 (0.08)	47 (1.2)	5.2 (0.13)	18 (0.9)	3 (0.15)	.18 ^e	—
2 - 3	87 (1)	8.7 (0.1)	63 (1.5)	7 (0.17)	28 (1.4)	4.7 (0.23)	.04 ^e	0.02 ^f
≥4	5 (0.1)	0.5 (0.01)	4 (0.1)	0.4 (0.01)	3 (0.1)	0.5 (0.02)	.36 ^g	—
Frailty-related episodes, n (%)	58 (0.7)	5.8 (0.07)	24 (0.6)	2.7 (0.07)	8 (0.4)	1.3 (0.07)	.26 ^e	—
Social deprivation index, n (%)								
1 (least disadvantaged)	1146 (14)	114.6 (1.4)	620 (15.3)	68.9 (1.7)	309 (14.9)	51.5 (2.48)	.04 ^e	0.02 ^f
2 (slightly disadvantaged)	2935 (35.7)	293.5 (3.57)	1477 (36.4)	164.1 (4.04)	750 (36.1)	125 (6.02)	.31 ^e	—
3 (moderately disadvantaged)	2439 (29.7)	243.9 (2.97)	1070 (26.4)	118.9 (2.93)	544 (26.2)	90.7 (4.37)	<.001 ^e	0.03 ^f
4 (most disadvantaged)	1695 (20.6)	169.5 (2.06)	891 (22)	99 (2.44)	474 (22.8)	79 (3.8)	.01 ^e	0.02 ^f
Drug administration, n (%)								

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
An-giotensin-converting enzyme inhibitors	23 (0.3)	2.3 (0.03)	12 (0.3)	1.3 (0.03)	7 (0.3)	1.2 (0.05)	.89 ^e	—
Antidiabetics	29 (0.3)	2.9 (0.03)	16 (0.4)	1.8 (0.04)	8 (0.4)	1.3 (0.07)	.91 ^e	—
An-tiplatelets and anticoagulants	60 (0.7)	6 (0.07)	48 (1.2)	5.3 (0.13)	25 (1.2)	4.2 (0.2)	.01 ^e	0.02 ^f
Beta blockers	26 (0.3)	2.6 (0.03)	5 (0.1)	0.6 (0.01)	1 (0)	0.2 (0.0)	.02 ^g	0.02 ^f
Bronchodilators	243 (2.9)	24.3 (0.29)	220 (5.4)	24.4 (0.6)	148 (7.1)	24.7 (1.18)	<.001 ^e	0.08 ^f
Calcium channel blocker	14 (0.2)	1.4 (0.02)	17 (0.4)	1.9 (0.04)	2 (0.1)	0.3 (0.02)	.01 ^g	0.02 ^f
Diuretics	49 (0.6)	4.9 (0.06)	42 (1)	4.7 (0.11)	20 (1)	3.3 (0.17)	.01 ^e	0.02 ^f
Inhaled corticosteroids	174 (2.1)	17.4 (0.21)	114 (2.8)	12.7 (0.31)	87 (4.2)	14.5 (0.7)	<.001 ^e	0.04 ^f
Rheumatoid drugs	21 (0.3)	2.1 (0.03)	17 (0.4)	1.9 (0.04)	5 (0.2)	0.8 (0.03)	.24 ^e	—
Statins	1 (0)	0.1 (0)	3 (0.1)	0.3 (0.01)	0 (0)	0 (0)	.17 ^g	—
Systemic corticosteroids	715 (8.5)	71.5 (0.85)	400 (9.8)	44.4 (1.09)	189 (9.1)	31.5 (1.52)	.06 ^e	—
Blood biomarkers, median (IQR)								
Albumin (g/L)	38.82 (3.98)	40.4 (0.3)	38.82 (3.18)	39.8 (0.1)	38.82 (3.58)	39.9 (0.2)	<.001 ^h	0.003 ⁱ
Neutrophil ($\times 10^9/L$)	4.48 (1.27)	4.4 (0.2)	4.48 (1.46)	4.6 (0.1)	4.48 (1.75)	4.8 (0.1)	<.001 ^h	0.0009 ⁱ
Bilirubin ($\mu\text{mol/L}$)	9.30 (14.20)	12.4 (0.6)	9.03 (14.10)	13 (0.6)	8.80 (14.10)	12.6 (0.3)	.67 ^h	—
Lymphocyte ($\times 10^9/L$)	0.86 (0.89)	1.6 (0.2)	1 (1.44)	1.9 (0.2)	1.40 (2.14)	2.3 (0.04)	<.001 ^h	0.02 ⁱ
Platelet ($\times 10^9/L$)	189 (127.50)	216 (7.5)	211 (155.25)	234.6 (7.5)	232 (182)	252.2 (3.2)	<.001 ^h	0.01 ⁱ

^aEpisodes=8399 and head count=8179.

^bEpisodes=4076 and head count=3940.

^cEpisodes=2081 and head count=1995.

^dNot available.

^eProportions test.

^fCramér V test.

^gFisher exact test.

^hKruskal-Wallis test.

ⁱEta squared test.

Table . Characteristics of patients infected with Omicron in Hong Kong from this repeated cross-sectional study (2022 - 2024), stratified by ages 18 - 64 years (total episodes, N=28,183).

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
Case fatality ratio	2.7	— ^d	2.9	—	2.6	—	—	—
≥2 hospital readmissions, n (%)	2960 (19.4)	296 (1.94)	936 (10.9)	104 (1.21)	421 (9.7)	70.2 (1.62)	<.001 ^e	0.72 ^f
Sex, n (%)								
Male	7523 (49.3)	752.3 (4.93)	3984 (46.5)	442.7 (5.17)	2053 (47.3)	342.2 (7.88)	<.001 ^e	0.02 ^f
Female	7751 (50.7)	775.1 (5.07)	4585 (53.5)	509.4 (5.94)	2287 (52.7)	381.2 (8.78)	<.001 ^e	0.02 ^f
Comorbidities, n (%)								
Essential primary hypertension	432 (2.8)	43.2 (0.28)	286 (3.3)	31.8 (0.37)	161 (3.7)	26.8 (0.62)	.005 ^e	0.02 ^f
Type 2 diabetes mellitus	465 (3)	46.5 (0.3)	290 (3.4)	32.2 (0.38)	122 (2.8)	20.3 (0.47)	.16 ^e	—
Hyperlipidemia (unspecified)	173 (1.1)	17.3 (0.11)	110 (1.3)	12.2 (0.14)	47 (1.1)	7.8 (0.18)	.49 ^e	—
Race, n (%)								
Chinese	13,868 (90.8)	1386.8 (9.08)	7801 (91)	866.8 (10.1)	3928 (90.5)	654.7 (15.08)	.60 ^e	—
Non-Chinese	1406 (9.2)	140.6 (0.92)	768 (9)	85.3 (1)	412 (9.5)	68.7 (1.58)	.60 ^e	—
Length of hospital stay (days), median (IQR)	4 (6)	11 (2.7)	3 (5)	10 (3)	3 (4)	6.9 (2.3)	<.001 ^g	0.007 ^h
Charlson Comorbidity Index score, n (%)								
0	11,950 (78.5)	1195 (7.85)	6657 (78)	739.7 (8.67)	3248 (76.5)	541.3 (12.75)	<.001 ^e	0.03 ^f
1	1160 (7.6)	116 (0.76)	744 (8.7)	82.7 (0.97)	405 (9.5)	67.5 (1.58)	<.001 ^e	0.02 ^f
2 - 3	1644 (10.8)	164.4 (1.08)	848 (9.9)	94.2 (1.1)	444 (10.5)	74 (1.75)	.10 ^e	—
≥4	471 (3.1)	47.1 (0.31)	287 (3.4)	31.9 (0.38)	150 (3.5)	25 (0.58)	.34 ^e	—
Frailty-related episodes, n (%)	443 (2.9)	44.3 (0.29)	272 (3.2)	30.2 (0.36)	124 (2.9)	20.7 (0.48)	.43 ^e	—
Social deprivation index, n (%)								
1 (least disadvantaged)	2148 (14.3)	214.8 (1.43)	1118 (13.1)	124.2 (1.46)	573 (13.3)	95.5 (2.22)	.06 ^e	—
2 (slightly disadvantaged)	5241 (34.9)	524.1 (3.49)	3042 (35.7)	338 (3.97)	1541 (35.7)	256.8 (5.95)	.11 ^e	—
3 (moderately disadvantaged)	4343 (28.9)	434.3 (2.89)	2449 (28.7)	272.1 (3.19)	1222 (28.3)	203.7 (4.72)	.88 ^e	—
4 (most disadvantaged)	3283 (21.9)	328.3 (2.19)	1915 (22.5)	212.8 (2.5)	977 (22.7)	162.8 (3.78)	.18 ^e	—
Drug administration, n (%)								

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
An- giotensin-con- verting en- zyme in- hibitors	2496 (16.3)	249.6 (1.63)	1559 (18.2)	173.2 (2.02)	802 (18.5)	133.7 (3.08)	<.001 ^e	0.02 ^f
Antidiabet- ics	2627 (17.2)	262.7 (1.72)	1682 (19.6)	186.9 (2.18)	822 (18.9)	137 (3.15)	<.001 ^e	0.03 ^f
An- tiplatelets and anticoagulants	4311 (28.2)	431.1 (2.82)	2526 (29.5)	280.7 (3.28)	1275 (29.4)	212.5 (4.9)	.08 ^e	—
Beta block- ers	2046 (13.4)	204.6 (1.34)	332 (3.9)	36.9 (0.43)	40 (0.9)	6.7 (0.15)	<.001 ^e	0.52 ^f
Bronchodila- tors	1017 (6.7)	101.7 (0.67)	779 (9.1)	86.6 (1.01)	530 (12.2)	88.3 (2.03)	<.001 ^e	0.07 ^f
Calcium channel block- er	3406 (22.3)	340.6 (2.23)	2060 (24)	228.9 (2.67)	1079 (24.9)	179.8 (4.15)	<.001 ^e	0.02 ^f
Diuretics	1760 (11.5)	176 (1.15)	1074 (12.5)	119.3 (1.39)	613 (14.1)	102.2 (2.35)	<.001 ^e	0.03 ^f
Inhaled cor- ticosteroids	783 (5.1)	78.3 (0.51)	479 (5.6)	53.2 (0.62)	279 (6.4)	46.5 (1.07)	<.001 ^e	0.02 ^f
Rheumatoid drugs	881 (5.8)	88.1 (0.58)	704 (8.2)	78.2 (0.91)	336 (7.7)	56 (1.28)	<.001 ^e	0.04 ^f
Statins	3038 (19.9)	303.8 (1.99)	2026 (23.6)	225.1 (2.62)	1039 (23.9)	173.2 (3.98)	<.001 ^e	0.05 ^f
Systemic corticosteroids	2867 (18.8)	286.7 (1.88)	2330 (27.2)	258.9 (3.02)	1113 (25.6)	185.5 (4.27)	<.001 ^e	0.09 ^f
Blood biomarkers, median (IQR)								
Albumin (g/L)	38.70 (7.10)	37.3 (0.9)	38 (7.50)	36.9 (0.3)	37.90 (8)	36.7 (0.4)	<.001 ^g	0.002 ^h
Neutrophil (×10 ⁹ /L)	4.48 (3.13)	5.6 (0.4)	4.90 (3.58)	5.8 (0.1)	5.12 (3.91)	6.4 (0.2)	<.001 ^g	0.005 ^h
Bilirubin (μmol/L)	8 (7.50)	11.6 (0.7)	7.90 (6.60)	10.8 (0.5)	8 (6.70)	11 (0.7)	<.001 ^g	0.001 ^h
Lympho- cyte (×10 ⁹ /L)	1 (0.89)	1.5 (0.06)	0.96 (0.87)	1.6 (0.1)	1.04 (0.96)	1.7 (0.2)	<.001 ^g	0.002 ^h
Platelet (×10 ⁹ /L)	208 (109)	221.5 (6)	206 (104)	220.5 (4.6)	217 (115)	227.8 (4.7)	<.001 ^g	0.001 ^h

^aEpisodes=15,274 and head count=13,626.

^bEpisodes=8569 and head count=8063.

^cEpisodes=4340 and head count=4107.

^dNot available.

^eProportions test.

^fCramér V test.

^gKruskal-Wallis test.

^hEta squared test.

Table . Characteristics of patients infected with Omicron in Hong Kong from this repeated cross-sectional study (2022 - 2024), stratified by ages 65 - 74 years (total episodes, N=25,045).

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
Case fatality ratio	4.9	— ^d	5.2	—	5.5	—	—	—
≥2 hospital readmissions, n (%)	3468 (25.8)	346.8 (2.58)	1074 (14.5)	119.3 (1.61)	582 (14.3)	97 (2.38)	<.001 ^e	0.64 ^f
Sex, n (%)								
Male	8190 (60.9)	819 (6.09)	4287 (57.7)	476.3 (6.41)	2445 (60)	407.5 (10)	<.001 ^e	0.02 ^f
Female	5269 (39.1)	526.9 (3.91)	3137 (42.3)	348.6 (4.7)	1627 (40)	271.2 (6.67)	<.001 ^e	0.02 ^f
Comorbidities, n (%)								
Essential primary hypertension	662 (4.9)	66.2 (0.49)	445 (6)	49.4 (0.67)	227 (5.6)	37.8 (0.93)	.002 ^e	0.02 ^f
Type 2 diabetes mellitus	677 (5)	67.7 (0.5)	466 (6.3)	51.8 (0.7)	191 (4.7)	31.8 (0.78)	<.001 ^e	0.08 ^f
Hyperlipidemia (unspecified)	294 (2.2)	29.4 (0.22)	215 (2.9)	23.9 (0.32)	106 (2.6)	17.7 (0.43)	.004 ^e	0.02 ^f
Race, n (%)								
Chinese	12,876 (95.7)	1287.6 (9.57)	7124 (96)	791.6 (10.67)	3894 (95.6)	649 (15.93)	.006 ^e	0.02 ^f
Non-Chinese	583 (4.3)	58.3 (0.43)	300 (4)	33.3 (0.44)	178 (4.4)	29.7 (0.73)	.006 ^e	0.02 ^f
Length of hospital stay (days), median (IQR)	6 (7)	10.4 (1.3)	4 (7)	9.1 (1.8)	4 (6)	7.8 (2.3)	<.001 ^g	0.01 ^h
Charlson Comorbidity Index score, n (%)								
0	9740 (72.5)	974 (7.25)	5286 (71.3)	587.3 (7.92)	2845 (71.2)	474.2 (11.87)	.04 ^e	0.01 ^f
1	1706 (12.7)	170.6 (1.27)	1072 (14.5)	119.1 (1.61)	551 (13.8)	91.8 (2.3)	<.001 ^e	0.02 ^f
2 - 3	1516 (11.3)	151.6 (1.13)	769 (10.4)	85.4 (1.16)	432 (10.8)	72 (1.8)	.16 ^e	—
≥4	479 (3.6)	47.9 (0.36)	282 (3.8)	31.3 (0.42)	169 (4.2)	28.2 (0.7)	.17 ^e	—
Frailty-related episodes, n (%)	674 (5)	67.4 (0.5)	490 (6.6)	54.4 (0.73)	218 (5.4)	36.3 (0.9)	<.001 ^e	0.03 ^f
Social deprivation index, n (%)								
1 (least disadvantaged)	1788 (13.3)	178.8 (1.33)	996 (13.5)	110.7 (1.5)	544 (13.4)	90.7 (2.23)	.90 ^e	—
2 (slightly disadvantaged)	4879 (36.4)	487.9 (3.64)	2636 (35.6)	292.9 (3.96)	1465 (36.1)	244.2 (6.02)	.76 ^e	—
3 (moderately disadvantaged)	3901 (29.1)	390.1 (2.91)	2119 (28.6)	235.4 (3.18)	1184 (29.2)	197.3 (4.87)	.83 ^e	—
4 (most disadvantaged)	2826 (21.1)	282.6 (2.11)	1649 (22.3)	183.2 (2.48)	868 (21.4)	144.7 (3.57)	.07 ^e	—
Drug administration, n (%)								

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
An-giotensin-converting enzyme inhibitors	4496 (33.4)	449.6 (3.34)	2545 (34.3)	282.8 (3.81)	1342 (33)	223.7 (5.5)	.20 ^e	—
Antidiabetics	4454 (33.1)	445.4 (3.31)	2631 (35.4)	292.3 (3.93)	1412 (34.7)	235.3 (5.78)	<.001 ^e	0.02 ^f
An-tiplatelets and anticoagulants	6940 (51.6)	694 (5.16)	3873 (52.2)	430.3 (5.8)	2115 (51.9)	352.5 (8.65)	.38 ^e	—
Beta blockers	3311 (24.6)	331.1 (2.46)	569 (7.7)	63.2 (0.86)	52 (1.3)	8.7 (0.22)	<.001 ^e	0.27 ^f
Bronchodilators	1807 (13.4)	180.7 (1.34)	1117 (15)	124.1 (1.67)	813 (20)	135.5 (3.33)	<.001 ^e	0.07 ^f
Calcium channel blocker	5867 (43.6)	586.7 (4.36)	3240 (43.6)	360 (4.84)	1727 (42.4)	287.8 (7.07)	.44 ^e	—
Diuretics	2412 (17.9)	241.2 (1.79)	1326 (17.9)	147.3 (1.99)	912 (22.4)	152 (3.73)	<.001 ^e	0.04 ^f
Inhaled corticosteroids	1013 (7.5)	101.3 (0.75)	540 (7.3)	60 (0.81)	359 (8.8)	59.8 (1.47)	.007 ^e	0.02 ^f
Rheumatoid drugs	1358 (10.1)	135.8 (1.01)	936 (12.6)	104 (1.4)	441 (10.8)	73.5 (1.8)	<.001 ^e	0.04 ^f
Statins	5901 (43.8)	590.1 (4.38)	3701 (49.9)	411.2 (5.54)	1993 (48.9)	332.2 (8.15)	<.001 ^e	0.06 ^f
Systemic corticosteroids	3665 (27.2)	366.5 (2.72)	2622 (35.3)	291.3 (3.92)	1491 (36.6)	248.5 (6.1)	<.001 ^e	0.09 ^f
Blood biomarkers, median (IQR)								
Albumin (g/L)	36.80 (7.90)	35.8 (1.3)	36.30 (7.50)	35.4 (0.3)	35.60 (8.20)	34.6 (0.3)	<.001 ^g	0.004 ^h
Neutrophil ($\times 10^9/L$)	4.62 (3.57)	5.7 (0.5)	5.18 (3.69)	6.1 (0.2)	5.86 (4.47)	6.9 (0.08)	<.001 ^g	0.02 ^h
Bilirubin ($\mu\text{mol/L}$)	8.80 (7.20)	11.7 (0.7)	9 (7)	11.5 (0.6)	9 (7.20)	12.5 (0.5)	.16 ^g	—
Lymphocyte ($\times 10^9/L$)	0.99 (0.74)	1.4 (0.07)	0.90 (0.79)	1.5 (0.2)	1 (0.83)	1.5 (0.09)	<.001 ^g	0.001 ^h
Platelet ($\times 10^9/L$)	201 (104.15)	215.9 (7.9)	195 (103)	209 (4.2)	206 (108)	222.8 (2.8)	<.001 ^g	0.002 ^h

^aEpisodes=13,549 and head count=11,517.

^bEpisodes=7424 and head count=6848.

^cEpisodes=4072 and head count=3760.

^dNot available.

^eProportions test.

^fCramér V test.

^gKruskal-Wallis test.

^hEta squared test.

Table . Characteristics of patients infected with Omicron in Hong Kong from this repeated cross-sectional study (2022 - 2024), stratified by ages 75 - 84 years (total episodes, N=29,743).

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
Case fatality ratio	7.5	— ^d	7.3	—	7.5	—	—	—
≥2 hospital readmissions, n (%)	4845 (31)	484.5 (3.1)	1453 (16.1)	161.4 (1.79)	915 (18)	152.5 (3)	<.001 ^e	0.57 ^e
Sex, n (%)								
Male	9265 (59.3)	926.5 (5.93)	5280 (58.4)	586.7 (6.49)	2890 (58.7)	481.7 (9.78)	.01 ^f	0.02 ^e
Female	6357 (40.7)	635.7 (4.07)	3765 (41.6)	418.3 (4.62)	2096 (41.3)	349.3 (6.88)	.01 ^f	0.02 ^e
Comorbidities, n (%)								
Essential primary hypertension	958 (6.1)	95.8 (0.61)	625 (6.9)	69.4 (0.77)	320 (6.3)	53.3 (1.05)	.05 ^f	—
Type 2 diabetes mellitus	884 (5.7)	88.4 (0.57)	573 (6.3)	63.7 (0.7)	269 (5.3)	44.8 (0.88)	<.001 ^f	0.01 ^e
Hyperlipidemia (unspecified)	372 (2.4)	37.2 (0.24)	293 (3.2)	32.6 (0.36)	156 (3.1)	26 (0.52)	<.001 ^f	0.02 ^e
Race, n (%)								
Chinese	15,178 (97.2)	1517.8 (9.72)	8752 (96.8)	972.4 (10.8)	4902 (96.6)	817 (16.1)	.06 ^f	—
Non-Chinese	444 (2.8)	44.4 (0.28)	293 (3.2)	32.6 (0.36)	174 (3.4)	29 (0.57)	.06 ^f	—
Length of hospital stay (days), median (IQR)	6 (8)	10.5 (0.4)	5 (6)	9.1 (1.1)	4 (6)	7.9 (2.2)	<.001 ^g	0.01 ^h
Charlson Comorbidity Index score, n (%)								
0	11,354 (72.7)	1135.4 (7.27)	6639 (73.5)	737.7 (8.17)	3558 (71.3)	593 (11.88)	<.001 ^f	0.02 ^e
1	2327 (14.9)	232.7 (1.49)	1401 (15.5)	155.7 (1.72)	815 (16.3)	135.8 (2.72)	.11 ^f	—
2 - 3	1560 (10)	156 (1.0)	774 (8.6)	86 (0.96)	482 (9.7)	80.3 (1.62)	.001 ^f	0.02 ^e
≥4	372 (2.4)	37.2 (0.24)	223 (2.5)	24.8 (0.28)	136 (2.7)	22.7 (0.45)	.49 ^f	—
Frailty-related episodes, n (%)	1306 (8.4)	130.6 (0.84)	750 (8.3)	83.3 (0.92)	420 (8.3)	70 (1.38)	.97 ^f	—
Social deprivation index, n (%)								
1 (least disadvantaged)	2187 (14)	218.7 (1.4)	1315 (14.6)	146.1 (1.62)	671 (13.3)	111.8 (2.22)	.09 ^f	—
2 (slightly disadvantaged)	5247 (33.7)	524.7 (3.37)	3039 (33.6)	337.7 (3.73)	1831 (36.2)	305.2 (6.03)	.003 ^f	0.02 ^e
3 (moderately disadvantaged)	4560 (29.3)	456 (2.93)	2503 (27.7)	278.1 (3.08)	1337 (26.4)	222.8 (4.4)	<.001 ^f	0.02 ^e
4 (most disadvantaged)	3589 (23)	358.9 (2.3)	2177 (24.1)	241.9 (2.68)	1219 (24.1)	203.2 (4.02)	.09 ^f	—
Drug administration, n (%)								

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
An- giotensin-con- verting en- zyme in- hibitors	6016 (38.5)	601.6 (3.85)	3593 (39.7)	399.2 (4.41)	2044 (40.3)	340.7 (6.72)	.04 ^f	0.01 ^e
Antidiabet- ics	5439 (34.8)	543.9 (3.48)	3268 (36.1)	363.1 (4.01)	1844 (36.3)	307.3 (6.05)	.04 ^f	0.01 ^e
An- tiplatelets and anticoagulants	9859 (63.1)	985.9 (6.31)	5696 (63)	632.9 (7)	3171 (62.5)	528.5 (10.42)	.71 ^f	—
Beta block- ers	4319 (27.6)	431.9 (2.76)	735 (8.1)	81.7 (0.9)	85 (1.7)	14.2 (0.28)	<.001 ^f	0.29 ^e
Bronchodila- tors	2745 (17.6)	274.5 (1.76)	1891 (20.9)	210.1 (2.32)	1260 (24.8)	210 (4.13)	<.001 ^f	0.07 ^e
Calcium channel block- er	8185 (54.2)	818.5 (5.42)	4613 (51)	512.6 (5.67)	2589 (51)	431.5 (8.5)	.06 ^f	—
Diuretics	3316 (21.2)	331.6 (2.12)	2011 (22.2)	223.4 (2.47)	1315 (25.9)	219.2 (4.32)	<.001 ^f	0.04 ^e
Inhaled cor- ticosteroids	1296 (8.3)	129.6 (0.83)	813 (9)	90.3 (1)	503 (9.9)	83.8 (1.65)	.001 ^f	0.02 ^e
Rheumatoid drugs	1894 (12.1)	189.4 (1.21)	1234 (13.6)	137.1 (1.51)	649 (12.8)	108.2 (2.13)	.003 ^f	0.02 ^e
Statins	7839 (50.2)	783.9 (5.02)	5044 (55.8)	560.4 (6.2)	2876 (56.7)	479.3 (9.45)	<.001 ^f	0.06 ^e
Systemic corticosteroids	4881 (31.2)	488.1 (3.12)	3460 (38.3)	384.4 (4.26)	1907 (37.6)	317.8 (6.27)	<.001 ^f	0.07 ^e
Blood biomarkers, median (IQR)								
Albumin (g/L)	35.20 (8.02)	34.6 (1.1)	35 (7.90)	34.4 (0.4)	34.50 (8.50)	33.8 (0.4)	<.001 ^g	0.002 ^h
Neutrophil (×10 ⁹ /L)	4.83 (3.70)	5.9 (0.5)	5.28 (3.77)	6.2 (0.2)	5.70 (4.24)	6.7 (0.2)	<.001 ^g	0.01 ^h
Bilirubin (μmol/L)	9 (7.10)	11.3 (0.5)	9.20 (7.20)	12.1 (0.4)	9 (6.80)	11.3 (0.3)	.03 ^g	0.002 ^h
Lympho- cyte (×10 ⁹ /L)	0.98 (0.72)	1.4 (0.1)	0.90 (0.77)	1.7 (0.3)	1(0.84)	1.7 (0.2)	<.001 ^g	0.002 ^h
Platelet (×10 ⁹ /L)	194 (102)	210.9 (7.6)	189 (96)	203.7 (3.9)	200 (108)	217.1 (3.2)	<.001 ^g	0.002 ^h

^aEpisodes=15,622 and head count=12,935.^bEpisodes=9045 and head count=8266.^cEpisodes=5076 and head count=4572.^dNot available.^eCramér V test.^fProportions test.^gKruskal-Wallis test.^hEta squared test.

Table . Characteristics of patients infected with Omicron in Hong Kong from this repeated cross-sectional study (2022 - 2024), stratified by ages older than 85 years (total episodes, N=39,107).

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
Case fatality ratio	11.6	— ^d	10.1	—	10.1	—	—	—
≥2 hospital readmissions, n (%)	7540 (38.2)	754 (3.82)	2626 (21.8)	291.8 (2.42)	1639 (22.3)	273.2 (3.72)	<.001 ^e	0.48 ^f
Sex, n (%)								
Male	8444 (42.8)	844.4 (4.28)	5152 (42.7)	572.4 (4.74)	3161 (43.1)	526.8 (7.18)	.89 ^e	—
Female	11,273 (57.2)	1127.3 (5.72)	6901 (57.3)	766.8 (6.37)	4176 (56.9)	696 (9.48)	.89 ^e	—
Comorbidities, n (%)								
Essential primary hypertension	1369 (6.9)	136.9 (0.69)	910 (7.5)	101.1 (0.83)	509 (6.9)	84.8 (1.15)	.10 ^e	—
Type 2 diabetes mellitus	933 (4.7)	93.3 (0.47)	550 (4.6)	61.1 (0.51)	264 (3.6)	44 (0.6)	<.001 ^e	0.02 ^f
Hyperlipidemia (unspecified)	418 (2.1)	41.8 (0.21)	299 (2.5)	33.2 (0.28)	192 (2.6)	32 (0.43)	.02 ^e	0.01 ^f
Race, n (%)								
Chinese	19,356 (98.2)	1935.6 (9.82)	11,832 (98.2)	1314.7 (10.91)	7193 (98)	1198.8 (16.3)	.76 ^e	—
Non-Chinese	361 (1.8)	36.1 (0.18)	221 (1.8)	24.6 (0.2)	144 (2)	24 (0.33)	.76 ^e	—
Length of hospital stay (days), median (IQR)	7 (9)	10.1 (0.8)	5 (6)	8.7 (1.1)	5 (5)	7.6 (1.7)	<.001 ^g	0.02 ^h
Charlson Comorbidity Index score, n (%)								
0	14,820 (75.2)	1482 (7.52)	9364 (77.7)	1040.4 (8.63)	5576 (77.3)	929.3 (12.88)	<.001 ^e	0.02 ^f
1	2952 (15)	295.2 (1.5)	1696 (14.1)	188.4 (1.57)	1014 (14.1)	169 (2.35)	.02 ^e	0.01 ^f
2 - 3	1617 (8.2)	161.7 (0.82)	810 (6.7)	90 (0.74)	529 (7.3)	88.2 (1.22)	<.001 ^e	0.02 ^f
≥4	310 (1.6)	31 (0.16)	178 (1.5)	19.8 (0.17)	98 (1.4)	16.3 (0.23)	.35 ^e	—
Frailty-related episodes, n (%)	1903 (9.7)	190.3 (0.97)	1095 (9.1)	121.7 (1.01)	633 (8.6)	105.5 (1.43)	.02 ^e	0.01 ^f
Social deprivation index								
1 (least disadvantaged)	2715 (13.8)	271.5 (1.38)	1717 (14.3)	190.8 (1.59)	956 (13)	159.3 (2.17)	.06 ^e	—
2 (slightly disadvantaged)	6294 (32)	629.4 (3.2)	3671 (30.5)	407.9 (3.39)	2327 (31.8)	387.8 (5.3)	.02 ^e	0.01 ^f
3 (moderately disadvantaged)	6016 (30.6)	601.6 (3.06)	3656 (30.4)	406.2 (3.38)	2184 (29.8)	364 (4.97)	.50 ^e	—
4 (most disadvantaged)	4666 (23.7)	466.6 (2.37)	3001 (24.9)	333.4 (2.77)	1860 (25.4)	310 (4.23)	.004 ^e	0.02 ^f
Drug administration, n (%)								

Characteristics	Period 1 ^a		Period 2 ^b		Period 3 ^c		P value	Effect size
	Observed	Adjusted	Observed	Adjusted	Observed	Adjusted		
An- giotensin-con- verting en- zyme in- hibitors	6981 (35.4)	698.1 (3.54)	4419 (36.7)	491 (4.08)	2656 (36.2)	442.7 (6.03)	.07 ^e	—
Antidiabet- ics	4840 (24.5)	484 (2.45)	3140 (26.1)	348.9 (2.9)	1932 (26.3)	322 (4.38)	.001 ^e	0.02 ^f
An- tiplatelets and anticoagulants	13,461 (68.3)	1346.1 (6.83)	8039 (66.7)	893.2 (7.41)	4851 (66.1)	808.5 (11.02)	<.001 ^e	0.02 ^f
Beta block- ers	4823 (24.5)	482.3 (2.45)	945 (7.8)	105 (0.87)	104 (1.4)	17.3 (0.23)	<.001 ^e	0.27 ^f
Bronchodila- tors	3790 (19.2)	379 (1.92)	2698 (22.4)	299.8 (2.49)	1934 (26.4)	322.3 (4.4)	<.001 ^e	0.09 ^f
Calcium channel block- er	10,906 (55.3)	1090.6 (5.53)	6713 (55.7)	745.9 (6.19)	4024 (54.8)	670.7 (9.13)	.51 ^e	—
Diuretics	4996 (25.3)	499.6 (2.53)	2968 (24.6)	329.8 (2.73)	2144 (29.2)	357.3 (4.87)	<.001 ^e	0.04 ^f
Inhaled cor- ticosteroids	1442 (7.3)	144.2 (0.73)	918 (7.6)	102 (0.84)	615 (8.4)	102.5 (1.4)	.01 ^e	0.01 ^f
Rheumatoid drugs	2472 (12.5)	247.2 (1.25)	1596 (13.2)	177.3 (1.47)	972 (13.2)	162 (2.2)	.11 ^e	—
Statins	8400 (42.6)	840 (4.26)	5783 (48)	642.6 (5.33)	3565 (48.6)	594.2 (8.1)	<.001 ^e	0.06 ^f
Systemic corticosteroids	6769 (34.3)	676.9 (3.43)	4951 (41.1)	550.1 (4.57)	2882 (39.3)	480.3 (6.55)	<.001 ^e	0.06 ^f
Blood biomarkers, median (IQR)								
Albumin (g/L)	33.30 (8.10)	32.8 (1.1)	33.70 (7.80)	33.1 (0.3)	32.90 (8.20)	32.3 (0.3)	<.001 ^g	0.002 ^h
Neutrophil (×10 ⁹ /L)	5 (3.85)	6.1 (0.6)	5.44 (4)	6.5 (0.2)	5.92 (4.37)	7 (0.2)	<.001 ^g	0.01 ^h
Bilirubin (μmol/L)	9 (7.40)	11.3 (0.4)	9 (7)	11 (0.3)	9 (7.30)	11.1 (0.3)	.01 ^g	0.0002 ^h
Lympho- cyte (×10 ⁹ /L)	1 (0.75)	1.4 (0.05)	0.99 (0.80)	1.6 (0.04)	1.03 (0.87)	1.7 (0.1)	<.001 ^g	0.001 ^h
Platelet (×10 ⁹ /L)	193 (103)	210.1 (9)	187 (99)	204.6 (4.5)	197 (104)	213.6 (2.5)	<.001 ^g	0.001 ^h

^aEpisodes=19,717 and head count=15,529.

^bEpisodes=12,053 and head count=10,639.

^cEpisodes=7337 and head count=6456.

^dNot available.

^eProportions test.

^fCramér V test.

^gKruskal-Wallis test.

^hEta squared test.

Demographic Profile of Hospitalized Patients Across Periods

Tables 2-6 and Table S1 in [Multimedia Appendix 1](#) demonstrated demographic shifts across periods 1 to 3 by age subgroups. First, the CFR increased in each period as the age

groups got older (Figure S1 in [Multimedia Appendix 1](#)) and lowered in patients older than 85 years (1.5% difference, period 1: 11.6%, period 3: 10.1%, $P<.001$, effect size: 0.02). Second, the monthly episodic rate of males and females hospitalized for COVID-19 infection decreased across periods for ages 0 - 84. Females were predominantly accounted for infections in patients

18 - 64, aged older than 85, whereas more males were infected in age groups 0 - 17, 64 - 74, and 75 - 84 (Figure S2 in [Multimedia Appendix 1](#)).

Third, the proportion of individuals of the Chinese race dominated across all age groups, becoming more prominent as age increased (Figure S4 in [Multimedia Appendix 1](#)). Only those aged 0 - 17 reported decreased proportions of Chinese race (8.5% difference, period 1: 77.2%, period 3: 68.7%, $P<.001$, effect size: 0.07). Also reflected in the adjusted measurements (410.1 episodes per month decrease, period 1: 648.3 episodes per month, period 2: 238.2 episodes per month).

Fourth, the Charlson Comorbidity Index scores in most age groups showed a predominant proportion of infected individuals with scores of 0 (more than 70% per period; Figure S5 in [Multimedia Appendix 1](#)), with notable decrease across the study period in age groups 0 - 17 (0.5% difference, period 1: 98.1%, period 3: 97.6%, $P=.003$, effect size: 0.03; 486.4 episodes per month decrease, period 1: 823.6 episodes per month, period 3: 337.2 episodes per month), 18 - 64 (2% difference, period 1: 78.5%, period 3: 76.5%, $P<.001$, effect size: 0.03; 653.7 episodes per month decrease, period 1: 1195 episodes per month, period 3: 541.3 episodes per month), 65 - 74 (1.3% difference, period 1: 72.5%, period 3: 71.2%, $P=.04$, effect size: 0.01; 499.8 episodes per month decrease, period 1: 974 episodes per month, period 3: 474.2 episodes per month), 75 - 84 (1.4% difference, period 1: 72.7%, period 3: 71.3%, $P<.001$, effect size: 0.02; 332 episodes per month decrease, period 1: 484.5 episodes per month, period 3: 152.5 episodes per month). In contrast, infected patients older than 85 showed an increase (2.1% difference, period 1: 75.2%, period 3: 77.3%, $P<.001$, effect size: 0.02), but the adjusted measurements showed otherwise (552.7 episodes per month decrease, period 1: 1482 episodes per month, period 3: 929.3 episodes per month). Although the proportion of infected patients with comorbid essential primary hypertension, type 2 diabetes mellitus, and hyperlipidemia (unspecified) remained below 10% and decreased in rate across periods and age groups (Figure S3 in [Multimedia Appendix 1](#)). Additionally, less than 10% of episodes per period and age group were related to frailty, although this proportion increased with age (Figure S8 in [Multimedia Appendix 1](#)). The rates decreased across periods for each age group.

Fifth, the distribution of the social deprivation index of infected individuals centered around slightly disadvantaged populations in Hong Kong (Figure S6 in [Multimedia Appendix 1](#)). This demographic showed higher proportions across periods among age groups 75 - 84 (2.5% difference, period 1: 33.7%, period 3: 36.2%, $P=.003$, effect size: 0.02) and lower proportions in those older than 85 years (0.2% difference, period 1: 32%, period 3: 31.8%, $P=.02$, effect size: 0.01). Although both age groups decreased in rate across period (age group 75 - 84: 219.5 episodes per month decrease, period 1: 524.7 episodes per month, period 3: 305.2 episodes per month; age group older than 85 years: 241.6 episodes per month decrease, period 1: 629.4 episodes per month, period 3: 387.8 episodes per month).

Clinical Changes in Hospitalized Patients Across Periods

The findings from [Tables 2-6](#) and Table S1 in [Multimedia Appendix 1](#) also showed changes in the clinical management of hospitalized patients infected with Omicron across the study period when stratified by age groups. First, the length of hospital stay decreased across periods for age groups 18 - 64 (1 d decrease, period 1: 4 d, period 3: 3 d, $P<.001$, effect size: 0.007; 4.1 d per month decrease, period 1: 11 d per month, period 3: 6.9 d per month), 65 - 74 (2 d decrease, period 1: 6 d, period 3: 4 d, $P<.001$, effect size: 0.01; 2.6 d per month decrease, period 1: 10.4 d per month, period 3: 7.8 d per month), 75 - 84 (2 d decrease, period 1: 6 d, period 3: 4 d, $P<.001$, effect size: 0.01; 2.6 d per month decrease, period 1: 10.5 d per month, period 3: 7.9 d per month), and older than 85 (2 days decrease, period 1: 7 d, period 3: 5 d, $P<.001$, effect size: 0.02; 2.5 d per month decrease, period 1: 10.1 d per month, period 3: 7.6 d per month). Additionally, a longer length of stay was observed as the demographic aged (Figure S9 in [Multimedia Appendix 1](#)).

Second, calcium channel blockers, statins, antiplatelets, and anticoagulants were the most frequently administered to patients aged 18 and older (Figure S7 in [Multimedia Appendix 1](#)), but the rate of administration reduced over time. Moreover, patients 0 - 17 years received 4.2% more bronchodilators over the course of the study period (period 1: 2.9%, period 3: 7.1%, $P<.001$, effect size: 0.08) and slightly increased rate of administration (0.4 episodes per month, period 1: 24.7 episodes per month decrease, period 3: 24.3 episodes per month); 5.5% more bronchodilators in 18 - 64 years (period 1: 6.7%, period 3: 12.2%, $P<.001$, effect size: 0.07) and decreased rate of administration (13.4 episodes per month decrease, period 1: 101.7 episodes per month, period 3: 88.3 episodes per month); 6.6% more bronchodilators in 65 - 74 years (period 1: 13.4%, period 3: 20%, $P<.001$, effect size: 0.07) and decreasing rate of administration across periods (45.2 episodes per month decrease, period 1: 180.7 episodes per month, period 3: 135.5 episodes per month); 7.2% more bronchodilators in 75 - 84 years (period 1: 17.6%, period 3: 24.8%, $P<.001$, effect size: 0.07) and decreasing rate of administration (64.5 episodes per month decrease, period 1: 274.5 episodes per month, period 3: 210 episodes per month); and 7.2% more bronchodilators in older than 85 (period 1: 19.2%, period 3: 26.4%, $P<.001$, effect size: 0.09) and decreasing rate of administration (56.7 episodes per month decrease, period 1: 379 episodes per month, period 3: 322.3 episodes per month). Meanwhile, systemic corticosteroids were administered the most frequently in the 18 - 64 age group (6.8% difference, period 1: 18.8%, period 3: 25.6%, $P<.001$, effect size: 0.09) with decreasing rate of administration (101.2 episodes per month decrease, period 1: 286.7 episodes per month, period 3: 185.5 episodes per month); and the 65 - 74 age group (9.4% difference, period 1: 27.2%, period 3: 36.6%, $P<.001$, effect size: 0.09) with decreasing rate of administration (118 episodes per month, period 1: 366.5 episodes per month, period 3: 248.5 episodes per month). The highest effect size was observed with the decline in the proportion of patients administered beta blockers over time (effect size in aged 0 - 17: 0.52, 64 - 74: 0.27, 75 - 84: 0.29, older than 85: 0.27).

Third, all the blood biomarkers exhibited minimal changes across periods in each age stratification (Figure S10 in [Multimedia Appendix 1](#)). Median albumin levels lowered, and median neutrophil levels elevated as age groups got older, especially in patients older than 85 years (albumin: 32.9 to 38.82g/L and 37.3 to 36.7g/L per month; neutrophil: 4.48 to 5.92 $\times 10^9$ /L and 5.6 to 6.4 $\times 10^9$ /L per month). Meanwhile, median bilirubin, lymphocyte, and platelet levels fluctuated across age groups.

Discussion

Principal Findings

To our knowledge, this is among the first retrospective, repeated cross-sectional studies to review changes in demographic and clinical characteristics of all patients infected with Omicron admitted to public hospitals in Hong Kong since the Omicron outbreak, including postpandemic periods. Additionally, this study expanded upon existing literature by providing insight into all age groups and incorporating social deprivation index scores.

Trends in Hospitalizations and Case Fatality Rate

Although the epidemic curves demonstrated a decrease in the number of hospitalized Omicron cases, this study observed an increase in the CFR with advancing age, which was consistent with reports from other local and international studies [34,35]. In contrast, the CFR started to decline among patients aged older than 85 years, a trend not observed in previous studies. This finding suggested there were age-related disparities among Omicron infections. Furthermore, the rate of hospital readmission decreased across periods for all ages, which contradicted the findings from a study in the UK [36]. They suggested that recent vaccination reduced the risk of reinfection, and subsequent reinfections demonstrated lower severity [36], but further research is needed to ascertain this in our population group.

Comorbidity Differences

The shift in Omicron infections to patients with more than 1 CCI over time aligned with local and international studies conducted in a postpandemic setting. They further attributed this shift to prolonged viral shedding from SARS-CoV-2 rebound [37-40], but subsequent research is needed to ascertain this hypothesis in our study population. Namely, our findings indicated that the proportion of patients with hypertension and hyperlipidemia comorbidities was low across periods, even though past literature suggested that existing low-grade chronic systemic inflammatory diseases can complicate clinical management of infected patients and increase the risk of poorer outcomes [41].

Gender Differences

Our results also indicated a predominance of male patients in most age groups (0 - 17 y, 64 - 74 y, and 75 - 84 y) throughout the study period, an observation that was well established during the pandemic [42]. Several hypotheses were proposed: one was the lower uptake of the second dose of COVID-19 vaccines

among males [43], while another hypothesized a link to cardiovascular factors [43].

Socioeconomic Demographic Shift

Most infections in our study population occurred among individuals from slightly disadvantaged backgrounds, even though the rate decreased across periods. Few studies explored the impact of the Omicron outbreak on patients from varied socioeconomic statuses. A study conducted during the early phase of COVID-19 in Hong Kong reported an association between socioeconomic disadvantage and a broader spread of infections [44], and was particularly related to essential activities such as living and working. International studies similarly found an association with lower socioeconomic status, hypothesizing that vaccine coverage might be an underlying reason [45,46].

Changes in In-Hospital Drug Administrations

Systemic corticosteroids became an increasingly common and effective treatment for COVID-19, as demonstrated by the rising proportion and reduced rate of administration among patients aged 18 years to 74 years and across periods in our findings, as well as in other studies [47,48]. One study suggested that while such treatments have anti-inflammatory effects, this could induce immunosuppression, potentially delaying viral clearance and increasing the risk of poorer outcomes [49]. This led to differing clinical management recommendations, with the WHO advising against corticosteroid treatments in severe cases [50], while local and Chinese studies recommended low-dose, short-course treatments for severe cases [51,52].

Also, cardiovascular treatments, including calcium channel blockers, statins, antiplatelets, and anticoagulants, were the most frequently administered, with a reduced rate of administration among adults and older individuals in this study. Global studies established a relationship between COVID-19 and cardiovascular complications [53,54]. In particular, studies from China reported a high prevalence of myocardial injury among infected patients with poor prognosis [55]. To mitigate cardiovascular complications, subsequent studies demonstrated improved prognosis in patients with COVID-19 administered with calcium channel blockers [56,57], statins [58], anticoagulants [59], and antiplatelet agents [60]. Therefore, our findings may reflect the common clinical treatment for Omicron cases.

Additionally, we observed an increased use of bronchodilators and a decreasing rate of administration over time. This might have reflected evolving clinical management strategies rather than increased severity, as by 2022, over 90% of the Hong Kong population was vaccinated, and the CFR in our study remained largely static across all age groups [61]. However, further research was required to clarify these observations.

Changes in Biomarker Indicators

Recent studies aligned with our findings and further demonstrated an association with COVID-19-related mortality. For example, one study found that elevated neutrophil levels were associated with increased COVID-19 mortality [62], while another study from China showed that hypoalbuminemia (albumin <35g/L) increased the odds of mortality [63].

Therefore, further research can help better understand the clinical management of infected patients, particularly in those aged over 85 years.

Age Disparities in Omicron Cases

Older age saw a higher case-mortality ratio, likely from the higher CCI scores and frailty also observed in other studies [21,64], making this demographic more susceptible to infection. This was possibly exacerbated by the excess mortality among the older individuals during the Omicron outbreak in Hong Kong [65], the largest local outbreak to date. Such age disparities were reported to persist in the postpandemic setting [65], although differences between age groups appeared to have narrowed. However, the EuCARE-HOSPITALISED international study observed opposite trends [66]. This may be attributed to Hong Kong's low vaccine uptake during the Omicron outbreak, but further research was needed to confirm this hypothesis.

Limitations

Although this study collected a large sample size from all the public hospitals in Hong Kong, several limitations remained. First, our sample is not representative of all cases of COVID-19 infection in Hong Kong as it did not include unreported and

asymptomatic cases, data from private hospitals, or non-Hong Kong residents. Second, our SDI score was based on calculations from 2008. Such definitions may be outdated and differ from the current situation in Hong Kong. The SDI distribution may also be skewed towards more disadvantaged populations with the exclusion of private hospital data. So, the respective findings from Tables 2-6 should be interpreted with caution. Third, the list of frailty-related diagnoses was defined by clinicians from an acute hospital trust in England, which may not be representative of frail patients in Hong Kong. Therefore, our findings should be interpreted with caution. Fourth, the patient's vaccination status was not available, so we cannot understand the impact of vaccination on incidence.

Conclusions

Our study provides an updated descriptive overview of postpandemic Omicron hospitalizations in Hong Kong. The findings highlight the need for age-specific interventions, particularly among older individuals. Further research is essential to understand the effectiveness of the vaccine booster dose in a postpandemic setting. All to improve pandemic preparedness and to develop more effective public health strategies in the ongoing fight against COVID-19.

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Data Availability

The dataset generated or analyzed during this study is available from the corresponding author (AW) on reasonable request.

Authors' Contributions

AKCW and CJYC contributed to the conception and design of the study. CJYC, HHHP, and BKHL contributed to data collection. CJYC, TTLL, and SCLC carried out the data analysis. MSW, TY, CKT, CW, and THR contributed to the revision and read and approved the submitted version of the article.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Drugs and post hoc analysis characterizing patients infected with Omicron.

[DOCX File, 200 KB - [publichealth_v12i1e75635_app1.docx](#)]

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Abbreviations

CCI: Charlson Comorbidity Index

CFR: case fatality ratio

ICD-10: *International Statistical Classification of Diseases and Related Health Problems 10th Revision*

SDI: Social Deprivation Index

WHO: World Health Organization

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Risk Factors Associated With Tuberculosis Diagnostic Delay in the Jiangsu Province, China (2011-2021): Spatiotemporal Database Analysis Study

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Abstract

Background: Tuberculosis (TB) remains a major public health concern. Despite improved diagnostic tools, delays in TB diagnosis persist and hinder control efforts.

Objective: This study aims to investigate the spatiotemporal patterns of TB diagnostic delay and identify individual and spatial risk factors in Jiangsu Province, China, from 2011 to 2021.

Methods: This study included 332,091 patients with TB who reported in Jiangsu Province from 2011 to 2021, using data obtained from the Jiangsu TB Information Management System, and diagnostic delay was defined as an interval of more than 28 days between symptom onset and diagnosis. Logistic regression was used to evaluate individual-level factors associated with delayed status, while a Bayesian spatiotemporal Beta model was used to analyze county-level TB diagnostic delay rates and assess spatial correlation using the global Moran *I*. The panel Granger causality analysis explored the temporal dynamics of delay rate transitions.

Results: Male patients, educators, and those diagnosed at the local Centers for Disease Control and Prevention had lower odds of diagnostic delay, whereas the older adults, agricultural workers, migrants, clinically diagnosed cases, and those diagnosed at community health centers had higher odds of delay. Spatial clustering in TB diagnostic delay rates was significant from 2015 onward (Moran *I*=0.110-0.193; all *P*<.05), excluding 2018 when Moran *I* was 0.054. The Bayesian spatiotemporal Beta model, which accounted for 31.8% of the total variation due to spatial structure, indicated that for each 1-unit increase in the proportion of local patients and for each 100,000-person increase in resident population, the TB diagnostic delay rate decreased by 33.9% (95% CI 0.128-0.498) and 2% (95% CI 0.005-0.033), respectively. The panel Granger causality analysis indicated that TB incidence and health care technicians significantly influenced temporal changes in delay rates.

Conclusions: TB diagnostic delays in Jiangsu were influenced by both individual and spatial factors, with the proportion of local patients and resident population size contributing significantly to spatiotemporal variation. Tailored interventions targeting high-risk groups and health care settings are needed.

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KEYWORDS

tuberculosis; diagnostic delay; Bayesian spatiotemporal model; Moran I index; integrated nested Laplace approximation

Introduction

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* and is primarily transmitted via airborne particles [1]. In 2022, TB was the second leading cause of death from a single infectious agent, surpassed only by

COVID-19 [2]. Globally, an estimated 10.8 million new TB cases occurred in 2023, with an incidence rate of 134 per 100,000 population, posing a grave threat to public health [3]. As the country with the third highest TB burden [4], China has made significant efforts in TB control over recent decades, increasing the case detection rate from 30% in the 1990s to 80% by 2005 and thereby effectively reducing transmission and

incidence [5,6]. In Jiangsu Province, China, TB remains a critical public health challenge, consistently ranking second among reported class A and B infectious diseases [7].

The World Health Organization (WHO) End TB Strategy emphasized the importance of early diagnosis and timely treatment for TB control and prevention, as well as reducing treatment costs [8]. However, most national TB control programs primarily rely on passive case finding, a practice often resulting in treatment delays exceeding 1 month in approximately 42% of patients [9]. The extent of these delays varies globally due to socioeconomic and health care disparities, with particularly severe delays observed in less developed regions. For instance, reported median total delays range significantly from 68 days in France to 104 days in Ghana and up to 366 days in Afghanistan [10]. Therefore, identifying the key factors contributing to delays in specific regions is essential for developing targeted TB interventions and control measures.

Extensive research has examined risk factors contributing to TB diagnostic delays, which arise from complex interactions of individual behaviors, social determinants, and health care system challenges [11]. The declining clinical awareness of TB among health care workers, especially in low-incidence settings, combined with the nonspecific nature of typical TB symptoms, such as persistent cough and sputum production, often leads to early misdiagnosis as common respiratory infections [12]. Meanwhile, misdiagnosis and missed cases are exacerbated by urban-rural disparities in medical resources and surges in diagnostic pressure during peak health care demand periods, such as holidays or influenza seasons [4]. Socioeconomically vulnerable populations, including migrant workers and older adults, often experience delays in seeking medical care due to limited access to health care insurance, language barriers, and varying levels of education [13,14].

Although previous analyses have identified key risk factors, they have generally failed to sufficiently account for the spatial and temporal dependence inherent in TB diagnostic delays [15,16]. Past research using descriptive statistics has highlighted spatial heterogeneity, for instance, by revealing median delays of 30 days in eastern or central China versus 41 days in the west [6] and identifying regional disparities in Portugal [17]; these studies often overlook spatial autocorrelation. To address this limitation, the Bayesian spatiotemporal model provides a rigorous framework that incorporates explanatory variables to capture large-scale trends while also accounting for residual dependencies to reveal robust spatial patterns and potential risk factors [18]. Furthermore, by integrating prior knowledge to quantify uncertainty, this approach enhances both the accuracy and interpretability of findings [19,20]. The integrated nested Laplace approximation (INLA) algorithm offers an efficient approach for implementing Bayesian inference in such complex models [21]. Notably, the spatiotemporal patterns of TB diagnostic delay have been rarely investigated using this Bayesian approach, representing a critical research gap that this study aims to address.

This study used Bayesian spatiotemporal analysis to investigate TB diagnosis delays, capturing spatiotemporal dependencies and examining patterns of temporal and spatial variation. We

have the following three research goals: (1) assess the existence of spatial and temporal autocorrelation in TB diagnostic delays within Jiangsu Province, China; (2) identify individual-level risk factors associated with delayed diagnosis; and (3) determine county-level determinants of diagnostic delay rates, while accounting for potential temporal and spatial random effects.

Methods

Data and Variables

We obtained TB surveillance data from the Jiangsu Tuberculosis Information Management System (TBIMS), spanning January 1, 2011, to December 31, 2021. The original dataset contained 354,274 infection cases reported in Jiangsu Province during this period, including patient information such as names, ages, sex, occupations, sources of patients, types of diagnosis, tracking status, types of hospital, dates of birth, onset dates, diagnostic dates, and so on. A total of 332,091 patients were analyzed in this study following exclusion criteria: (1) patients diagnosed and reported between January 1, 2011, and December 31, 2021, at health care institutions outside Jiangsu Province ($n=8010$); (2) patients with missing critical information ($n=12,889$); and (3) patients whose standardized z value for the total diagnostic delay that exceeded 3 (ie, more than 3 SD from the mean; $n=1266$) [22].

Total diagnostic delay, defined as the interval from the onset of TB symptoms to formal diagnosis, comprises both patient delay and health system delay [13,23]. Patient delay refers to the time between symptom onset and the first medical consultation, while health system delay spans from the time of the first health care visit to diagnosis. This study focused exclusively on total diagnostic delay, as the dataset lacked information regarding the date of the first medical visit. At the individual level, the outcome was defined as the diagnostic delay status, which indicated whether a patient's total diagnostic delay exceeded 28 days, a commonly adopted threshold for total TB diagnostic delay based on previous studies [13]. At the county level, the outcome was the TB diagnostic delay rate, which was calculated by dividing the number of delayed patients (ie, those with more than 28 d of total diagnostic delay) by the total number of patients in each county each year.

In addition to the individual-level TB surveillance data from Jiangsu TBIMS, a total of 9 annual county-level explanatory variables were included, categorized into three distinct domains: (1) demographic factors, comprising the annual proportions of older adult patients (≥ 60 y), male patients, local patients, and agricultural-worker patients among reported cases; (2) socioeconomic and health care indicators, including gross domestic product (GDP) per capita (adjusted to the 2021 Consumer Price Index), resident population size, TB incidence rate (per 1000 population), and the health care technicians (professionals per 1000 population); and (3) pandemic period, a binary variable (1=2020 - 2021; 0=2011 - 2019) introduced to adjust for the potential impact of social isolation policies and health care resource diversion during the COVID-19 pandemic. Data regarding health care technicians, GDP, and resident population were sourced from annual county statistical

yearbooks, while other variables were aggregated directly from the TB surveillance data.

The Bayesian Spatiotemporal Model

To explore the spatial correlation of the TB diagnostic delay rate across 89 districts and counties in Jiangsu Province from 2011 to 2021, we calculated the global Moran I to measure the spatial correlation [24,25]. When the result for Moran I is statistically significant, a positive value for Moran I suggests spatial clustering, while a negative value suggests spatial dispersion. The closer the value of I is to 1 or -1 , the stronger the spatial association, while a value near 0 indicates a random spatial distribution of TB diagnostic delay rates.

Prior to the spatiotemporal modeling, multivariable binary logistic regression was used to identify risk factors associated with individual diagnostic delay status (binary outcome: 1 if total delay >28 d, 0 otherwise). Subsequently, a logit-link Bayesian Beta regression model was then applied, incorporating fixed effects for the proportion of older adult patients, proportion of male patients, proportion of local patients, proportion of agricultural-worker patients, GDP, TB incidence rate, number of health care technicians, and resident population, along with spatial and temporal random effects.

Specifically, let $y(s,t)$ denote the TB diagnostic delay rate in year t over district or county s , with values ranging from 0 to 1. Here, $t=1, 2, \dots, 11$ represents the years 2011 to 2021, and $s=1, 2, \dots, 95$ represents the 95 counties or districts in Jiangsu Province, China. We further assumed that $y(s,t)$ follows a β distribution with mean $\mu(s,t) \in (0,1)$ varying over time across counties or districts, and a constant precision parameter $\phi > 0$. Namely,

$$\text{logit } \mu(s,t) = x(s,t)\beta + \delta t + u_s + (s,t),$$

where the vector $x(s,t)$ represents the regional-level variables in Table 3. The (s,t) term is an unstructured random effect in the model. We employed the first-order Gaussian random walks (RW1) model and the Besag-York-Mollié 2 model to capture the overall temporal random effect δt and spatial random effect u_s [26].

The Besag-York-Mollié 2 model was used to capture spatial random effects by combining structured and unstructured spatial components through a mixing parameter [27]. The spatial effect for area i is expressed as:

$$b_i = 1/\tau_b(1 - \phi v_i^* + \phi u_i^*),$$

where τ_b is the overall precision, u_i^* is a standardized intrinsic conditional auto-regressive component capturing structured spatial dependence, and v_i^* is a standardized Gaussian noise

term representing unstructured spatial variability. The mixing parameter $\phi \in [0,1]$, is a spatial smoothing parameter, measuring the proportion of the marginal variance explained by the structured random effect.

As a latent effect implemented in the R-INLA package, the first-order Gaussian random walk was used to model temporal dependence [26]. For a latent Gaussian field $u=(u_1, \dots, u_n)T$, it is a random walk of order 1 if the increments $\Delta u_i = u_i - u_{i-1}$ are independent and identically distributed Gaussian random variables with zero mean and precision $\tau > 0$ (inverse variance).

Based on the delay rates estimated from the Bayesian spatiotemporal Beta model, we dichotomized at the median and then fitted a Bayesian spatiotemporal binomial model to identify factors associated with a higher likelihood of diagnostic delay. Furthermore, to explore the temporal dynamics and potential drivers of delay rate, we conducted a panel Granger causality analysis [28].

All statistical analyses were conducted using R software (version 4.4.1; R Foundation for Statistical Computing). The *INLA*, *stats*, and *lme4* packages were used to conduct the Bayesian spatiotemporal modeling, logistic regression, and the Granger causality analysis, respectively, with default prior distributions specified for the INLA hyperparameters.

Ethical Considerations

Anonymized data were obtained from the Jiangsu TBIMS, with all personal identifiers (eg, name and ID number) removed prior to analysis. The study protocol was reviewed by the ethical review board of the Jiangsu Provincial Center for Disease Control and Prevention (Jiangsu CDC) and granted an official exemption (acceptance: SL2025-B030-01), as the study was deemed retrospective and the data were deidentified. Data access and usage were strictly governed by a formal Data Usage Agreement between the Jiangsu CDC and the study authors. Informed consent was not required for this retrospective study using anonymized data.

Results

Descriptive Statistics

Table 1 summarizes the demographic and clinical features of patients with TB with delayed (≥ 28 d) and nondelayed (< 28 d) diagnoses, respectively, in Jiangsu Province (2011-2021). Among all patients, the majority were male participants (239,692/332,091, 72.18%), working in agriculture (204,983/332,091, 61.72%), and reported by general hospitals (148,960/332,091, 44.86%), with a high proportion of local residents (239,440/332,091, 72.10%).

Table . Demographic and clinical characteristics of patients with tuberculosis reported in Jiangsu Province, 2011-2021.

Variables	Total delay days (<28), n (%)	Total delay days (≥28), n (%)
Age (y)		
<60	132,502 (39.90)	47,358 (14.26)
≥60	79,287 (23.87)	72,944 (21.97)
Sex		
Female	57,212 (17.23)	35,187 (10.60)
Male	154,577 (46.55)	85,115 (25.63)
Occupation		
Agriculture	128,957 (38.83)	76,026 (22.89)
Education	9219 (2.78)	4523 (1.36)
Health care	913 (0.27)	554 (0.17)
Housekeeping	36,705 (11.05)	20,111 (6.06)
Officials	2264 (0.68)	1415 (0.43)
Service	3660 (1.10)	1778 (0.54)
Worker	20,304 (6.11)	9386 (2.83)
Other	9767 (2.94)	6509 (1.96)
Source of patient		
Local	158,987 (47.87)	80,453 (24.23)
Different county	45,710 (13.76)	35,262 (10.62)
Different city	4471 (1.35)	3482 (1.05)
Different province	2621 (0.79)	1105 (0.33)
Types of diagnosis		
Confirmed	78,554 (23.65)	45,019 (13.56)
Clinically diagnosed	129,551 (39.01)	74,750 (22.51)
Suspected	3684 (1.11)	533 (0.16)
Tracking status		
Recorded	74,344 (22.39)	44,062 (13.27)
Referred	92,716 (27.92)	45,878 (13.81)
Tracked	32,184 (9.69)	23,132 (6.97)
Other	12,545 (3.78)	7230 (2.18)
Types of hospital		
Designated hospital	62,425 (18.80)	37,307 (11.23)
CHC ^a	28,793 (8.67)	15,460 (4.66)
CDC ^b	26,392 (7.95)	11,298 (3.40)
General hospital	93,216 (28.07)	55,744 (16.79)
Other	963 (0.29)	493 (0.15)
COVID-19		
Pre-epidemic	182,934 (55.09)	28,855 (8.69)
Epidemic	103,886 (31.28)	16,416 (4.94)

^aCHC: community health center.^bCDC: Centers for Disease Control and Prevention.

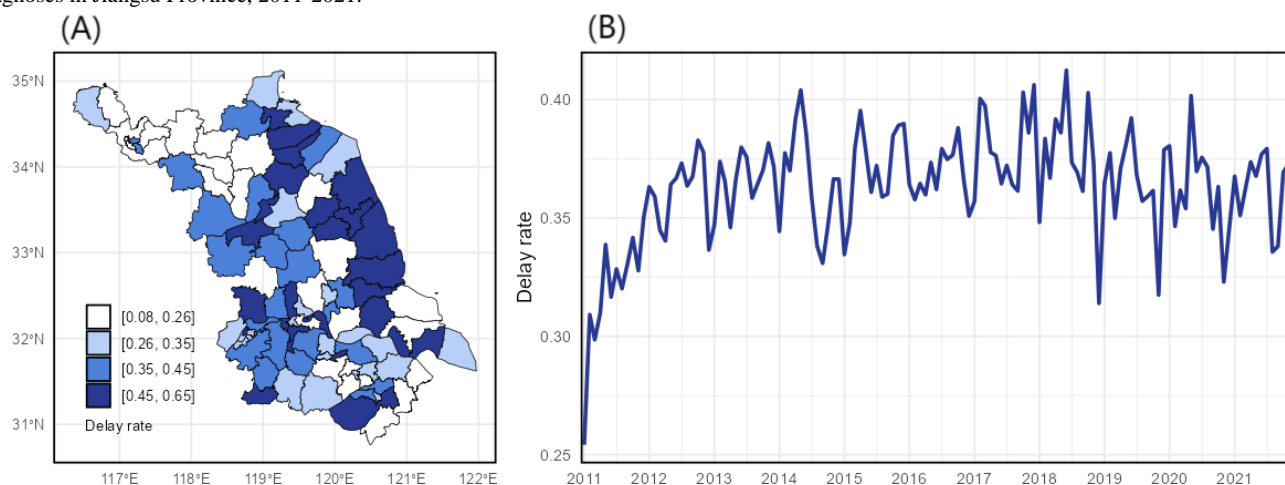
Figure 1A shows the spatial distribution of average TB diagnostic delay rates in Jiangsu Province over the period from

2011 to 2021. The cities of Yancheng and Huaian generally exhibited the highest delay rates, and the Binhai district in

Yancheng recorded a peak delay rate of 93.35% in 2016. Figure 1B illustrates the temporal trend across all 95 counties. An increasing trend was evident from 2011 to 2014, followed by

a plateau. Notable distinct declines in the average delay rate were observed in specific months, including December 2018, November 2019, and November 2020.

Figure 1. Annual average spatial distribution across 95 counties (A) and monthly provincial average temporal trends (B) of tuberculosis delayed diagnoses in Jiangsu Province, 2011-2021.

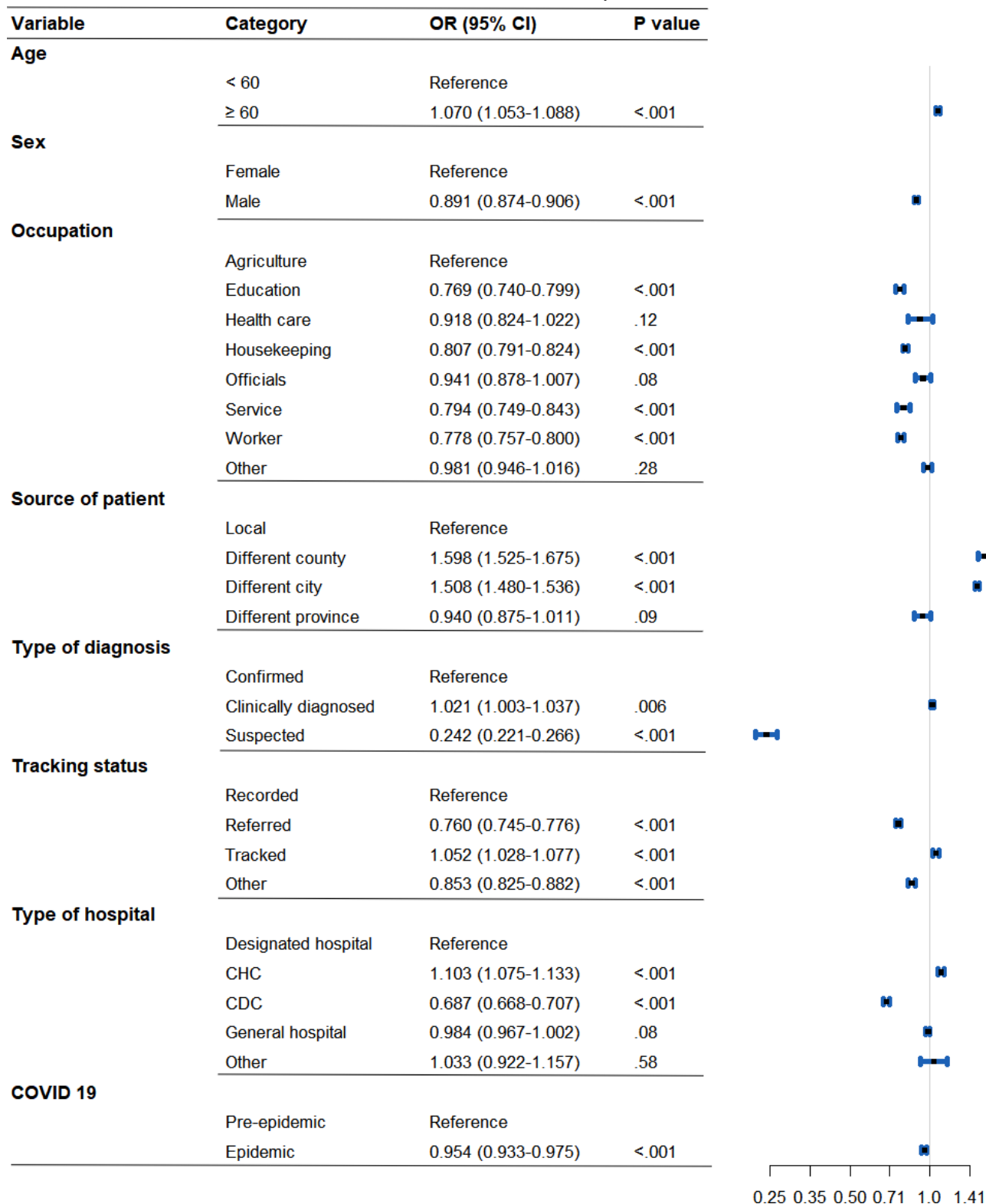


Analysis at the Individual Level

Figure 2 presents the results of a logistic regression analysis used to investigate potential risk factors associated with individual TB diagnosis delay status. Specifically, males had significantly lower odds of experiencing delayed TB diagnosis compared to females (odds ratio [OR] 0.891, 95% CI 0.874-0.906), while patients older than 60 years had slightly higher odds of delayed TB diagnosis compared to those who were younger than 60 years (OR 1.070, 95% CI 1.053-1.088). We also found that patients who worked in agriculture had higher odds of delayed TB diagnosis than patients in other occupations. Particularly, the differences between patients working in agriculture and patients of occupations in education (OR 0.769, 95% CI 0.740-0.799), housekeeping (OR 0.807, 95% CI 0.791-0.824), service (OR 0.794, 95% CI 0.749-0.843), and worker (OR 0.778, 95% CI 0.757-0.800) were statistically significant. Local patients (from the same county/district) had

significantly lower odds of delayed TB diagnosis than patients from different counties (OR 1.598, 95% CI 1.525-1.675) or cities (OR 1.508, 95% CI 1.480-1.536) in Jiangsu. Regarding types of diagnosis, the suspected cases had significantly lower odds of delayed TB diagnosis compared to the confirmed cases (OR 0.242, 95% CI 0.221-0.266), while the clinically diagnosed cases had significantly higher odds of delayed TB diagnosis (OR 1.021, 95% CI 1.003-1.037) compared to the confirmed cases. Patients diagnosed at community health centers (CHCs) had higher odds of delayed diagnosis compared to those diagnosed at designated TB hospitals (OR 1.103, 95% CI 1.075-1.133). However, patients diagnosed at local CDCs had considerably lower odds of delayed diagnosis than those diagnosed at designated TB hospitals (OR 0.687, 95% CI 0.668-0.707). Finally, the COVID-19 period was associated with significantly lower odds of diagnostic delay (OR 0.954, 95% CI 0.933-0.975).

Figure 2. Odds ratios (ORs) from logistic regression model for factors affecting tuberculosis diagnostic delay status at the individual level in Jiangsu Province, 2011-2021. CDC: Centers for Disease Control and Prevention; CHC: community health center.



Analysis at the County Level

Table 2 presents the global Moran I indices for TB diagnostic delay rates from 2011 to 2021. From 2011 to 2014, the Moran I values were close to zero (all $P > .05$), indicating no significant spatial autocorrelation. However, a marked increase in Moran

I was observed from 2015 onwards, suggesting the emergence of substantial spatial clustering. Consequently, the Bayesian spatiotemporal Beta model was used to fully account for the spatial autocorrelation found in TB diagnostic delay rates across the years.

Table . Global Moran I index for tuberculosis diagnostic delay rate in Jiangsu Province, 2011-2021.

Year	Moran I	P value
2011	0.018	.33
2012	0.079	.08
2013	0.047	.19
2014	0.040	.22
2015	0.193	<.001
2016	0.167	.003
2017	0.161	.004
2018	0.054	.16
2019	0.113	.03
2020	0.110	.03
2021	0.085	.07

Table 3 presents the fixed effect estimates for the proportion of older adult patients, proportion of male patients, proportion of local patients, proportion of agricultural-worker patients, GDP, TB incidence rate, number of health care technicians, and resident population from the Bayesian spatiotemporal Beta model. For each 1-unit increase in the proportion of local patients, the TB diagnostic delay rate decreases by 33.9% ($1 - \exp[-0.415]$, 95% CI 0.128-0.498). Additionally, each

100,000-person increase in resident population is associated with a 2% (95% CI 0.005-0.033) decrease in TB diagnostic delay. For random effects, the precision parameter τ_b was estimated as 3.411, indicating a moderate degree of spatial variation in the diagnostic delay rates across counties. In addition, the mixing parameter ϕ was estimated as 0.318, meaning that the structured spatial component accounts for 31.8% of the total spatial variation in TB diagnostic delay rate.

Table . The result of the Bayesian Beta spatiotemporal model of TB^a diagnostic delay rate at the county level in Jiangsu Province, 2011-2021.

Variables	Mean (SD)	0.025 quantile	0.975 quantile
Fixed effect			
Proportion of older adult patients (%)	0.234 (0.261)	-0.281	0.747
Proportion of male patients (%)	-0.002 (0.014)	-0.030	0.026
Proportion of local patients (%)	-0.415 (0.140)	-0.691	-0.138
Proportion of agricultural-worker patients (%)	0.187 (0.184)	-0.176	0.548
GDP ^b (thousand yuan per person)	0.061 (0.037)	-0.014	0.135
TB incidence rate (%)	0.055 (0.062)	-0.068	0.180
Health care technicians (per 1000 residents)	-0.008 (0.008)	-0.024	0.007
Resident population (in 100,000)	-0.020 (0.007)	-0.034	-0.005
COVID-19 (0 - 1)	-0.049 (0.050)	-0.148	0.053
Random effect			
Precision parameter for BYM2 ^c	3.411	2.389	4.828
Mixing parameter for BYM2 (ϕ)	0.318	0.085	0.652

^aTB: tuberculosis.

^bGDP: gross domestic product.

^cBYM2: Besag-York-Mollié 2.

Figure S1 in [Multimedia Appendix 1](#) illustrates the spatiotemporal distribution of the estimated TB diagnostic delay rate obtained from the Bayesian spatiotemporal Beta model. Higher estimated delay rates were concentrated in the northern

coastal cities such as Huaian, Yancheng, and Lianyungang, while lower rates were observed in Xuzhou and Suzhou in the southern region. Among the 95 districts and counties over the 11-year period, Qingjiangpu of Huaian ranked among the top

3 with the highest estimated delay rates, with values of 0.648 in 2021, 0.645 in 2014, and 0.644 in 2018. Meanwhile, from 2011 to 2013, the delay rate exhibited an increasing temporal trend, which was particularly evident in Suqian. In contrast, Figure S2 in [Multimedia Appendix 1](#) presents the observed delay rates, which show much larger fluctuations, reflecting random noise and potential instability due to small-area sample variation. The differences between Figures S1 and S2 in [Multimedia Appendix 1](#) arise because the Bayesian spatiotemporal Beta model smooths random noise and incorporates both spatial and temporal dependencies. By integrating relevant covariates and modeling residual correlation through random effects, it effectively adjusts for unobserved dependence and confounding, producing spatially coherent and statistically reliable estimates.

The median of the estimated TB diagnostic delay rate was 0.352. Based on the obtained median, the results from the Bayesian spatiotemporal binomial model (Table S1 in [Multimedia Appendix 1](#)) show that counties with a higher proportion of agricultural workers and higher GDP were more likely to experience high diagnostic delays. Conversely, counties with larger shares of local patients, larger resident populations, and the COVID-19 period were associated with a lower risk of high delays. Furthermore, Table S2 in [Multimedia Appendix 1](#) indicated that GDP, TB incidence, and health care technicians had significant Granger causal effects on the temporal changes in the delay rate ($P < .05$).

Sensitivity Analysis

The sensitivity analysis confirmed the consistency of our main results. We applied penalized complexity priors to spatial and temporal model parameters to constrain model complexity and prevent overfitting (Tables S3-S6 in [Multimedia Appendix 1](#)) [29]. Across these analyses, the direction and statistical significance of the main variables remained consistent, with a slight change in the magnitude of some coefficients. To examine the impact of risk factors associated with TB diagnostic delays over shorter periods, we divided the study period into 2 subperiods (2011 - 2015 vs 2016 - 2021), representing China's 12th and 13th Five-Year Plans for Tuberculosis Prevention and Control (Table S7 in [Multimedia Appendix 1](#)) [30]. We found that the significant associations between diagnostic delay and residency or occupation observed in the first subperiod disappeared in the second subperiod, likely due to expanded health care access and continuous public health developments in Jiangsu.

Discussion

This research analyzed 332,091 patients with TB in Jiangsu Province from 2011 to 2021, combining individual-level analysis with county-level spatiotemporal modeling to enhance understanding of diagnostic delay risk factors and their spatial and temporal patterns. At the individual level, we found that all 7 risk factors (ie, age, sex, occupation, patient source, type of diagnosis, tracking status, and type of hospital) were significant. At the county level, significant spatial clustering was observed from 2015. Drawing on such spatial dependence, we found that the proportion of local patients and the resident population were

significantly and negatively associated with the TB diagnostic delay rates. Counties with higher proportions of older adults and agricultural-worker patients were more likely to experience high diagnostic delays. Moreover, GDP, TB incidence, and health care technicians exhibited significant effects on temporal changes in the delay rate.

Various individual characteristics were found to be significantly associated with the status of TB diagnostic delay. The odds of experiencing a TB diagnostic delay were significantly lower for males, consistent with the findings of previous studies [31,32]. A study in Portugal suggested that the higher overall TB burden in males (male-to-female ratio 2:1) could increase clinical suspicion and expedite diagnosis when men seek care [33]. The odds of experiencing TB diagnostic delay for education industry workers were also significantly lower, potentially attributed to strict TB screening programs for students and higher health management standards in Jiangsu and elsewhere [34]. We found older adult patients had higher odds of experiencing TB diagnostic delay, mainly due to factors such as lower education levels, poorer health awareness, lack of knowledge on TB prevention and treatment, economic difficulties, and insufficient social support [35,36]. Regarding the type of hospital, patients diagnosed by CHCs had higher odds of experiencing TB diagnostic delay, likely because these CHCs have limited resources and clinical experience [37]. For example, an artificial intelligence-assisted diagnostic platform was launched in Jiangsu Province in 2023, but this system has not been implemented at CHCs [38]. In contrast, patients diagnosed by CDCs had much lower odds of experiencing delay, underscoring the specialized knowledge needed for early TB diagnosis and thus the critical role of CDCs in TB detection. Finally, the significantly lower odds of diagnostic delay during the COVID-19 pandemic likely reflect how rigorous respiratory screening, targeting basically the same symptoms (eg, fever and cough), prompted earlier identification of TB cases that might be otherwise overlooked [2].

The spatial distribution of TB diagnostic delay exhibited clear characteristics of spatial clustering in Jiangsu Province. The global Moran I index showed no significant spatial autocorrelation in TB diagnostic delay rates from 2011 to 2014. Starting in 2015, however, significant spatial clustering emerged (Moran $I=0.110-0.193$; $P < .05$ for 2015-2017 and 2019-2020), indicating that the delay rates formed a stable spatial dependence pattern across counties or districts [25,39]. The mixing parameter of the Bayesian spatiotemporal Beta model was estimated at 0.318, indicating that a substantial portion of the spatial variation was attributable to structured spatial effects, also reflecting interdependency in the delay-risk patterns of neighboring areas. A possible explanation for this is the promotion of rapid drug-resistant TB molecular biological testing equipment in Jiangsu Province, which has improved TB diagnostic efficiency but may be disproportionately allocated across counties/districts due to a limited supply [40].

Our research revealed significant associations between the key factors and the TB diagnostic delay rate. For each unit increase in the proportion of local patients, the TB diagnostic delay rate decreased by 33.9%. This suggested that patients who lived permanently within the county might have had better access to

local health services, greater familiarity with the health care system, or improved continuity of care, all of which could have facilitated earlier diagnosis [41]. Additionally, each increase of 100,000 residents was associated with a 2% decrease in the TB diagnostic delay rate. Larger populations were typically found in more urbanized or economically developed counties, which tended to have better health care infrastructure, higher diagnostic capacity, and more accessible TB services [42]. When counties were classified using the median estimated delay rate, those with larger older adult populations were consistently identified as high-delay areas, which was consistent with the individual-level associations. A higher proportion of agricultural-worker patients was likewise linked to greater diagnostic delays, reflecting structural barriers such as limited health care access, seasonal labor patterns, and insufficient disease awareness [43]. Panel Granger causality tests further indicated that GDP and health care technician density were key drivers of temporal fluctuations in diagnostic delay. Higher GDP likely supported more advanced diagnostic infrastructure and resource allocation, while greater technician density enhanced diagnostic capacity and accelerated case detection [44,45].

The significance of this study lies in three main aspects. First, there had been a lack of large-scale, population-based investigations into diagnostic delay in TB in Jiangsu Province. Based on a comprehensive surveillance system covering 332,091 patients with TB, the study identified several key risk factors associated with TB diagnostic delay in the general population of Jiangsu, providing an essential empirical basis for targeted interventions. Second, the analysis confirmed the existence of spatial correlation and random effects in TB diagnostic delay rates, thereby underscoring the necessity of using a Bayesian spatiotemporal modeling approach to capture the underlying spatial and temporal dependence appropriately. Third, we

conducted statistical analysis at both the individual and county levels, which accounts for geographic disparities while estimating the risk factors associated with TB diagnostic delay rates. This approach leads to more targeted and synergistic public health strategies for reducing regional TB diagnostic delay rates, as well as individual chances of experiencing TB diagnostic delays.

Our study also has several limitations. First, while diagnostic delay may affect the temporal alignment between symptom onset and reporting, the calculation of TB incidence rate was not adjusted for such delays and thereby may be biased [46]. Second, due to data limitations, this study focused on the total diagnostic delay, making it impossible to distinguish between patient delay and health system delay. Future studies with more detailed health care-seeking information are needed to explore these 2 components separately. Third, continuous socioeconomic development over the decade may introduce temporal heterogeneity in the impact of risk factors, limiting the findings to this specific developmental stage.

In conclusion, a multifaceted and targeted approach is essential for effectively reducing diagnostic delays in TB. First, efforts should be made to promote proactive health-seeking behaviors among individuals, particularly among high-risk populations such as agricultural workers, older adults, and female individuals. These groups are more vulnerable to pulmonary diseases and often underrepresented in passive case detection strategies [47]. Second, from a health system perspective, it is necessary to enhance TB screening and testing protocols for migrants by improving access to care and removing systemic barriers that can delay their diagnoses, should they have TB [48]. Third, more resources should be allocated to CHCs to enhance their diagnostic capacity and knowledge of TB, as they are often the first point of contact for patients with TB, especially in underdeveloped areas [49].

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Data Availability

The data analyzed during this study are not publicly available due to restrictions imposed by the Jiangsu Provincial Center for Disease Control and Prevention in eastern China. However, access to the data can be requested from the corresponding author, LZ, upon reasonable request and with appropriate approval.

Authors' Contributions

TL, LZ, and YT developed the methodology and conceptualization. YT prepared the initial draft of the paper and programmed the code. YT and TL analyzed the main results. CC, QL, and LZ conducted the survey and data collection. YL, YT, MC, KW,

and SW processed the original data. CC, QL, LZ, MC, KW, CL, and TL commented on and revised manuscript drafts. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Estimated and observed tuberculosis diagnostic delay rates, sensitivity analyses, Bayesian spatiotemporal binomial model results, and the panel Granger causality analysis results.

[DOCX File, 384 KB - [publichealth_v12i1e80052_app1.docx](#)]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CHC: community health center
GDP: gross domestic product
INLA: integrated nested Laplace approximation
OR: odds ratio
TB: tuberculosis
TBIMS: Tuberculosis Information Management System
WHO: World Health Organization

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Original Paper

The Potential Impact of Federal Funding Cuts on Access to Pre-Exposure Prophylaxis in Atlanta, Georgia: Geographic Modeling Study

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Abstract

Background: Despite major biomedical advances in HIV testing, prevention, and treatment, annual HIV transmissions in the United States remain above 30,000. Geographic access to pre-exposure prophylaxis (PrEP) is critical to HIV prevention efforts, particularly in regions with high HIV burdens, such as metro-Atlanta. Community-based organizations (CBOs) play a central role in delivering culturally competent prevention services, yet many rely on federal funding that is increasingly unstable. Understanding the potential impact of CBO closures on geographic access to PrEP is essential for anticipating inequities and informing policy.

Objective: The aim of this study was to estimate how hypothetical closures of federally funded CBOs providing PrEP affect geographic access to PrEP clinics by car and public transit across metro-Atlanta and to assess whether impacts differ by community racial/ethnic composition.

Methods: We identified 71 PrEP-providing clinics in metro-Atlanta (August 2025), including 12 CBOs. Using 3 simulated closure scenarios in which 25% of CBOs were randomly closed, we calculated one-way travel times from 2466 census block group (CBG) centroids to the nearest PrEP-providing clinic. Travel times were estimated for car and public transit across 3 weekdays and timepoints and then averaged per CBG. Two-sided paired *t* tests were used to compare the change in travel time compared to baseline. Logistic regression assessed associations between racial/ethnic plurality and increased travel times.

Results: Under baseline conditions, 100% of CBGs had car access to a PrEP clinic within 30 minutes compared to only 41.6% (1027/2466) via public transit. Across closure scenarios, 732 CBGs (29.6%; representing over 1 million residents) experienced increased transit times (mean increase 1.2 minutes; range 0.0-11.6; $P<.001$), and 7 CBGs lost transit access entirely. For car travel, 1184 CBGs (48%; representing approximately 1.7 million residents) experienced increased drive times (mean increase 0.5 minutes; range 0.0-6.4; $P=.03$). Black-plurality CBGs had higher odds of increased drive times compared to White-plurality CBGs (odds ratio 1.37, 95% CI 1.15-1.63).

Conclusions: Even limited closure of CBO PrEP providers meaningfully reduces geographic access to HIV prevention services, disproportionately affecting communities already experiencing transportation and HIV-related vulnerabilities. Sustained federal investment in CBOs is essential to preserve equitable PrEP access and prevent avoidable HIV infections.

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KEYWORDS

HIV prevention; pre-exposure prophylaxis; community health centers; health services; geographic access; federal

Introduction

We have arrived at a point in the HIV epidemic in the United States where we arguably have all of the biomedical tools we need to end the epidemic [1]. There are multiple options for HIV screening, including self-testing [2]; multiple formulations and regimens for pre-exposure prophylaxis (PrEP) to prevent HIV infection; and effective treatments that result in full healthy lives for people living with HIV and, for people living with HIV who are virally suppressed, eliminating the risk of onward transmission through sex [3]. Despite these biomedical advances, annual HIV transmissions in the United States remain above 30,000 [4].

The realities of bringing these foundational tools to scale in a coordinated response has proven to be a substantial challenge of implementation and has resulted in increased attention to and funding for implementation science approaches [5-7]. Geographic access to HIV prevention services, including PrEP, is foundational to the “Prevent” pillar of the National HIV/AIDS Strategy [8]. We have previously explored geographic access to HIV prevention and care issues during a time of more certainty and consistency about the funding mechanisms for HIV prevention and care [9-11]. We have found that inequities in geographic access to HIV prevention and care services, and often, commute times disproportionately impact communities of color for whom car ownership may be less [12,13] and for whom public transportation access and route frequency may be more limited [14,15].

As we consider the structural and socioeconomic factors that impact geographic access to HIV prevention services, we are now in an era where federal funding for HIV services is declining or under threats of future reduction or elimination [16-19]. HIV prevention services in the United States are supported through a patchwork of federal funding mechanisms, including direct service delivery grants from the Centers for Disease Control and Prevention, funds administered through the Health Resources and Services Administration like the Ryan White HIV/AIDS Program, the Ending the HIV Epidemic initiative, Title X, Medicaid reimbursement for clinical PrEP services, and time-limited federal demonstration and implementation grants. These funding streams vary in stability, allowable services, and eligibility criteria, creating differential vulnerability to funding reductions across delivery settings. Although most PrEP prescriptions in the United States are provided through traditional health care clinics, community-based organizations (CBOs) contribute disproportionately to PrEP access among marginalized populations through direct provision, partnerships with prescribing clinicians, and intensive navigation services [20]. Given that many CBOs that provide HIV prevention services are supported, at least in part, by federal funding, it is important to consider how reductions in federal funding that lead to the closure of existing prevention providers might impact geographic access to HIV prevention services. Further, given the disparities in new HIV diagnoses related to acquisitions risks (eg, men who have sex with men), racial/ethnic minority groups (eg, Black and Hispanic or Latinx people) and geographic region (eg, the US South), it is important to assess

whether gaps in geographic access to prevention services are differential by these population characteristics. To address these gaps, we used public data about the locations of HIV PrEP providers and previously described methods for estimating commute times to HIV prevention care services [10] to model the potential impact of federal funding cuts on geographic access to PrEP in Atlanta, Georgia.

Methods

We examined how the closing of CBOs that provide HIV prevention services may impact access to PrEP by both car and public transit across the four counties that encompass metro-Atlanta: DeKalb, Cobb, Fulton, and Gwinnett (all of which are “Ending the HIV Epidemic”-prioritized counties for HIV prevention).

Ethical Considerations

This study used publicly available, deidentified census and clinic location data. No human participants were involved, and therefore, no reviews or approvals by an ethics committee or institutional review board were required.

Clinic Data and Closure Scenarios

We identified all PrEP-providing clinics in the metro-Atlanta area as of August 2025 by using the Centers for Disease Control and Prevention’s National Prevention Information Network PrEP Locator directory [21]. Clinics in the database are screened for eligibility if they have at least one health care professional (eg, physician, nurse practitioner, physician assistant) who is qualified to prescribe PrEP and if they have confirmed that they actively prescribe it. In addition to geographic data, each clinic is categorized by its funding type (federally qualified health center, public health department, hospital, CBO, etc). Of the 71 clinics in metro-Atlanta, 12 were designated as a CBO. To simulate potential impacts of federal funding reductions that disproportionately affect CBOs, we created 3 separate closure scenarios. In each scenario, 3 CBOs (approximately 25% of all Atlanta-area CBO PrEP clinics) were randomly selected for closure, and analyses were rerun to estimate the resulting changes in geographic access.

Origin and Destination Specification

Census block groups (CBGs) served as the unit of analysis for travel time estimation. Origin coordinates were defined as the population-weighted centroid of each CBG, representing where residents are most likely to live. CBG-level sociodemographic data were obtained from the American Community Survey 5-year estimates [22]. CBGs were categorized by the racial or ethnic plurality of residents. Destination coordinates were the locations of PrEP-providing clinics identified above. This approach captures area-level variation in accessibility rather than individual travel patterns.

Travel Time Estimation

We estimated one-way travel times between each CBG centroid and the 10 nearest PrEP clinics by using the Google Maps Distance Matrix application programming interface accessed through R [9]. The application programming interface was used to calculate the shortest available route under two transportation

modes: public transit and private vehicle. For both modes, travel times were calculated across 3 weekdays (Tuesday, Friday, and Saturday) and 3 time points (8 AM, noon, and 3:30 PM).

The shortest one-way travel time for each day-time combination was selected and then averaged to provide one estimate per mode for each CBG for each closure scenario. CBGs with no available public transit route to any PrEP clinic, defined as a walking distance of more than 30 minutes to the nearest transit stop, were coded as having no transit access. Transit time estimates included walking time to any transit stops, waiting time, boarding/transfer time, and time in transit.

Statistical Analysis

We used descriptive statistics to describe mean one-way travel times to the nearest PrEP clinic before and after simulated closures, separately for car and public transit. The mean change in travel time (minutes) was averaged across the 3 closure scenarios and compared using a 2-sided paired *t* test. CBGs were dichotomized into those that saw increased travel times compared to no change for both car and public transit. We then used simple logistic regression to model associations between race/ethnicity and increased travel times. All analyses and visualizations were conducted in R software (version 4.3.2; R Foundation for Statistical Computing).

Results

Descriptive Results

A total of 2466 CBGs across metro-Atlanta were included in the analysis. More than half of the CBGs ($n=1361$, 55.2%) had a White plurality. An additional 943 (38.2%) CBGs had a Black plurality, 155 (6.3%) had a Hispanic/Latinx plurality, and only 2 (<1%) CBGs had a plurality of another race or ethnicity. Under baseline conditions, all CBGs had access to at least one PrEP-providing clinic by car within 30 minutes, while only 1027 (41.6%) CBGs had access via public transit within 30 minutes. A total of 567 (22.9%) CBGs did not have access to PrEP via public transit.

Public Transit Changes in Access

Across the 3 simulated CBO closure scenarios ($N=2466$), 732 (29.6%) CBGs experienced longer average public transit times to the nearest PrEP clinic compared with current access. These CBGs represented approximately 1,024,900 residents or about 27.8% of Atlanta's total population. The average change in one-way transit time was 1.2 (range 0.0-11.6) minutes, which was significantly longer than the baseline ($P<.001$). Seven CBGs lost access to a PrEP clinic or CBO via public transit in the modeled closure scenarios. Compared to CBGs with a White plurality, the odds of experiencing increased transit times under the CBO closure scenarios were significantly lower for CBGs with a Hispanic plurality (odds ratio [OR] 0.61, 95% CI 0.40-0.95) but no different for CBGs with a Black plurality (OR 0.99, 95% CI 0.81-1.20).

Drive Time Changes in Access

Across the 3 simulated CBO closure scenarios ($N=2466$), 1184 (48%) CBGs experienced longer average drive times to the nearest PrEP clinic compared with current access. These CBGs

represented approximately 1,698,000 residents or about 46.4% of Atlanta's total population. The average change in one-way drive time was 0.5 (range 0.0-6.4) minutes, which was significantly longer than baseline ($P=.03$). Compared to CBGs with a White plurality, the odds of experiencing increased drive times under the CBO closure scenarios were significantly higher for CBGs with a Black plurality (OR 1.37, 95% CI 1.15-1.63) but no different for CBGs with a Hispanic plurality (OR 0.90, 95% CI 0.64-1.28).

Discussion

Our research explores the potential impact of federal funding cuts on geographic access to PrEP in Atlanta, Georgia. Whereas previous research in this area was proposed to identify geographic areas within cities that would be important locational targets for new services to decrease travel times to care [23-25], we argue that this expansion-oriented framing must be complemented by models of the closing of existing facilities due to cuts in HIV prevention funding to better understand PrEP service availability and the risk of new HIV infections. Our data suggest that increases in travel times related to the closure of community providers were greater for people who used public transit, underscoring the importance of evaluating modal dimensions of transportation time to health care facilities. This is especially relevant given that communities most vulnerable to HIV are also most likely to rely on public transportation [12,26].

Although the differences in travel times might seem modest in some settings, such differences represent meaningful barriers to seeking care among marginalized groups already facing transportation disadvantages. A given level of change in commute time may result in different willingness to travel for people who use different modes of transportation or for people who do not have employment benefits that include paid time for seeking health care [26,27]. It is also important to acknowledge that HIV prevention service providers have both located their facilities in areas with high needs for prevention services, and clinics that provide services in areas with fewer community and economic resources are often set up to meet multiple care and social service needs [28]. Colocation of PrEP services with other health and social services may facilitate engagement in prevention by reducing logistical barriers, normalizing HIV prevention within broader care settings, and leveraging established trust between providers and communities. Such organizations spend decades building trusting relationships with communities, fostering trusting relationships [29,30]. Depending on which facilities close, it is foreseeable that populations with multiple medical and social service needs might lose access to a variety of services that would increase their vulnerability to HIV and other health threats.

Other aspects of our analysis reinforce the stakes in terms of health and equity considerations that would attend closures of existing PrEP-prescribing organizations. Although any licensed medical provider can provide PrEP, CBOs are disproportionately located in high-need areas and serve populations often excluded from traditional health care systems [31]. Thus, the loss of such facilities would create a double impact on PrEP accessibility:

it might create a longer commute time to the nearest PrEP provider, and it might mean that the nearest PrEP provider would be less likely to have culturally competent services [32-34]. Further, it is unclear whether existing clinics that survive the closure would have sufficient clinical capacity to provide PrEP to more patients even if prospective PrEP users are able to commute longer distances to continue to access PrEP [35,36]. Lastly, while our analysis focused on neighborhood level demographics, we know that PrEP-seeking patterns differ across multiple identity groups. For example, White men who have sex with men are more likely to access PrEP through traditional health care systems [37], while Black cisgender women and other groups with high HIV transmission tend to rely more often on community-based and safety-net providers [38]. Therefore, the loss of CBO-based PrEP services may disproportionately impact more marginalized groups.

The eventual impact of closures on the coverage of PrEP and the impacts of limitations on PrEP services are not easy to predict with confidence. However, it is clear that there are limitations to how far people will drive to obtain services for nonemergent health problems (eg, preventive services); several publications suggest that 30 minutes is a common threshold of willingness [39,40]. In any case, distance to receipt of care has an important and converse relationships with receipt of nonurgent health care, including preventive care [41]. A recent analysis suggests that even small decreases in PrEP coverage among people with indications could have substantial impacts on new HIV infections and health care costs. For example, just a 3% reduction in PrEP coverage is forecast to result in over

8000 preventable infections, with lifetime medical costs for HIV care exceeding US \$3.6 billion for those infections [42].

Our findings, while empirically derived and reflective of real-world challenges to transportation to PrEP care services, have several limitations. First, we present one-way estimates of transit times, so the actual additional transportation burden to seeking PrEP care would be double the one-way estimates presented in the analysis. Simulated closures may not reflect actual likelihoods of closure; in the absence of empiric, publicly accessible data about organization-specific funding portfolios, we were unable to weight closures by likelihood and instead selected organizations randomly in the simulation. Future work incorporating such data could identify especially high-risk providers and communities. Conversely, we did not consider the likelihood of other types of organizations that provide PrEP closing; so, our estimates of impact on PrEP service might not reflect the true additional travel burden associated with the closure of facilities. Further, our analysis did not collect new data on, or consider the service capacity of, clinics; so, even if potential PrEP users were willing to travel longer distances, it is possible that existing clinics might not be able to handle an increase in the patient load.

According to our data, the closure of even a small number of current PrEP providers would have important impacts on physical access to HIV prevention services and would be predicted to increase commute times, decrease engagement in PrEP care, and result in avoidable new HIV infections and associated care costs. Therefore, our findings support sustained investment in CBOs as critical access points for HIV prevention services.

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Authors' Contributions

Conceptualization: PSS, NM

Methodology: NM

Formal analysis: NM

Supervision: PSS

Funding acquisition: PSS

Writing - review & editing: NM, PSS

Writing - original draft: NM

Conflicts of Interest

PSS reports a relationship with Gilead Sciences Inc that includes consulting or advisory, funding grants, and speaking and lecture fees; with Merck & Co Inc that includes consulting or advisory and funding grants; with National Institutes of Health that includes consulting or advisory and funding grants; and with Centers for Disease Control and Prevention that includes funding grants and speaking and lecture fees.

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Abbreviations

CBG: census block group
CBO: community-based organization
OR: odds ratio
PrEP: pre-exposure prophylaxis

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Bayesian Models to Generate Small Area Estimates of Population Health: Tutorial for Using Rate Stabilizing Tools and Their Output

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Abstract

The demand for high-quality population health data at the local level calls for expanded tools for those working to enhance the health of communities across the country to easily calculate small area estimates. Statistical models that generate small area estimates often use Bayesian estimation techniques, which are computationally complex and not readily accessible to most public health professionals. We developed 2 tools to facilitate small area estimation. For ArcGIS Pro users, we developed the Rate Stabilizing Toolbox ArcGIS plugin (RSTbx), and for R users, we developed the Rate Stabilizing Tool R package (RSTr). In this tutorial, we demonstrate how to use these tools to calculate small area estimates and evaluate their reliability. We also demonstrate 3 key benefits from using either of these tools: (1) decreased number of geographic units with suppressed estimates, (2) flexibility to set the threshold for statistical reliability, and (3) credible intervals that can be used to identify statistically significant differences between geographic units. Additionally, both tools offer built-in age-standardization capabilities. We created census tract-level maps from North Carolina mortality data and Rhode Island hospitalization data to showcase the benefits of generating small area estimates with these tools. Rate Stabilizing Toolbox and Rate Stabilizing Tool for R are powerful tools that can be used to meet the demand for high-quality local-level data to inform public health programs and tailor health promotion activities to the needs of communities across the country.

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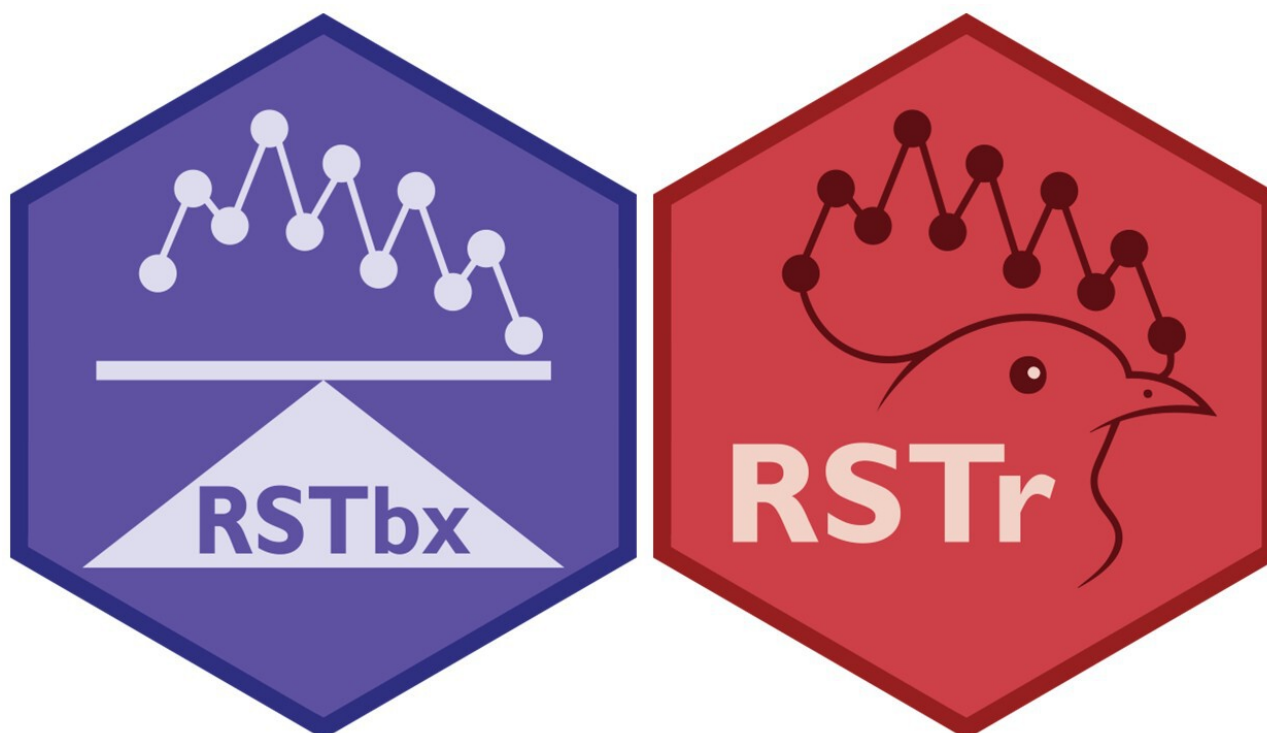
KEYWORDS

small area estimates; spatial analysis; software; geographic information system; GIS; spatiotemporal models; R; Bayesian statistics

Introduction

The demand for high-quality population health data at the local level calls for expanded tools that public health professionals and others can use to easily calculate robust small area estimates [1-3]. A key challenge for calculating robust small area estimates occurs in regions with small population sizes or few numbers of events; these small numbers introduce statistical uncertainty, leading to challenges in the meaningful interpretation of results [4]. Statistical methods that appropriately address these

challenges are often computationally complex and may not be readily accessible to those working to enhance the health of communities across the country. In response to this need, we implemented established statistical models into 2 distinct tools: an ArcGIS toolbox (the Rate Stabilizing Toolbox [RSTbx]) and an R package (the Rate Stabilizing Tool for R [RSTr]) (Figure 1). These tools enable users to input local-level data and calculate robust small area estimates. This tutorial provides step-by-step instructions for how to use each tool along with a demonstration of the benefits derived from using these tools.

Figure 1. Icons for Rate Stabilizing Toolbox (RSTbx; left) and Rate Stabilizing Tool for R (RSTr; right).

Based on Tobler's First Law of Geography [5], which asserts that closer places are more alike than further places, spatial statistical models improve estimate precision by leveraging the data's underlying spatial structure (ie, spatial smoothing). Among these existing models, RSTbx and RSTr are based on the conditional autoregressive (CAR) model developed by Besag, York, and Mollié (BYM) [6], which is used extensively in spatial epidemiology and disease mapping [7]. Outcomes as varied as excess cardiovascular disease death rates in the United States during the COVID-19 pandemic [8], tuberculosis relative risk in Indonesia [9], and under-nutrition among under-five children in Ethiopia [10] have recently been investigated with methodology based on the BYM model. The popularity of the BYM model is further enhanced due to its extensions into spatiotemporal and multivariate settings through the MCAR of Gelfand and Vounatsou [11] and the MSTCAR of Quick et al [12]. Recent developments in BYM models involve strategies to quantify model informativeness and avoid oversmoothing [13,14] and outlining of standards for estimate reliability [15].

The RSTbx and RSTr both offer key benefits for calculating and mapping small area estimates of population health. First, by leveraging spatial and other dependencies in the data, the estimates produced by the RSTbx and RSTr are more precise than those based solely on the observed data. As such, the estimates produced by these tools will be more reliable, resulting in fewer estimates being suppressed, thereby permitting the documentation of geographic patterns with a more comprehensive geographic coverage. Second, both tools allow users to relax the threshold for reliability based on measures of uncertainty (eg, basing thresholds for reliability on the 80% credible intervals [CIs] rather than the standard 95% CIs). Third, these measures of uncertainty can be used to assess statistically significant differences between estimates for geographic units and other domains.

We have divided this tutorial into 3 sections. We begin with an overview of each tool, including how to use the tool, the input and output datasets, and their modeling capabilities. Then, we demonstrate the benefits of using the tools by mapping small area estimates of mortality using RSTbx and hospitalization rates using RSTr. Finally, we review the tools' strengths and limitations and provide a table comparing their major features.

RSTbx: An ArcGIS Toolbox

Overview

RSTbx is a Python-based set of tools designed for Environmental Systems Research Institute's ArcGIS Pro software [16]. Users can input their own local-level data and calculate local-level estimates using Bayesian spatial smoothing methods. RSTbx uses a BYM model framework that smooths across space using data from adjacent geographic units [6]. RSTbx also includes options for data processing, age-standardization, and the generation of CIs. RSTbx, with detailed instructions, is available for download on GitHub [16].

RSTbx is an upgrade to the original Rate Stabilizing Tool (RST) that was created in 2019 [17]. Enhancements include the following:

- A CAR model implementation based on the BYM model to replace the Poisson-gamma empirical Bayes method used in the original RST [7,8].
- The user interface has been revamped for greater ease of use.
- Users can import custom features; they are no longer limited to 2010 US Census geographies.
- Users can import their own population tables, whereas the original RST allowed only population data from the 2010 Census of the Population.

- Age-standardization to 10-year age groups is now possible using either the 2000 US Standard Population or the 2010 US Standard population [18].
- Population tables from the decennial US Census and American Community Survey (ACS; by census tract or county) can now be downloaded directly into an ArcGIS Pro project along with US Census TIGER and cartographic geographic boundaries [19].

RSTbx includes 3 tools: the Census Data Retriever (CDR), the Individual Data Processor (IDP), and the RST. The CDR generates population tables at the county or census tract level using data from the US Census' Decennial Census or the ACS. It can also be used to download TIGER or cartographic boundaries. The IDP aggregates individual-level event data by calculating the number of events within each geographic unit and joining the aggregate counts to the provided population table. The IDP can aggregate individual-level event data by age group to produce aggregate data for each geographic unit. The IDP also performs several data validation checks (eg, the IDP will check for null data, incorrect datatypes, or duplicate geographic units within population data). Finally, the RST runs a BYM model and generates small area estimates.

Installing RSTbx

To install RSTbx, users first download the latest release from the GitHub repository as a zip file [16]. After unzipping this file, users should open an ArcGIS Project, navigate to the Catalog Pane, right-click on Toolboxes, click on Add Toolbox, and find the `rate_stabilizing_toolbox.pyt` file within the unzipped RSTbx folder. After completing these steps, RSTbx is ready to use.

Input Data Requirements

RSTbx requires a minimum of 3 sets of data: event data, population data, and a boundary file. First, users enter event data for the health outcome of interest. RSTbx is designed to accommodate event data at either the individual or group level. For individual-level event data, RSTbx requires a unique identifier for each geographic unit (eg, GEOID). The age of each individual is also required to calculate age-standardized rates. For group-level event data, RSTbx requires a unique

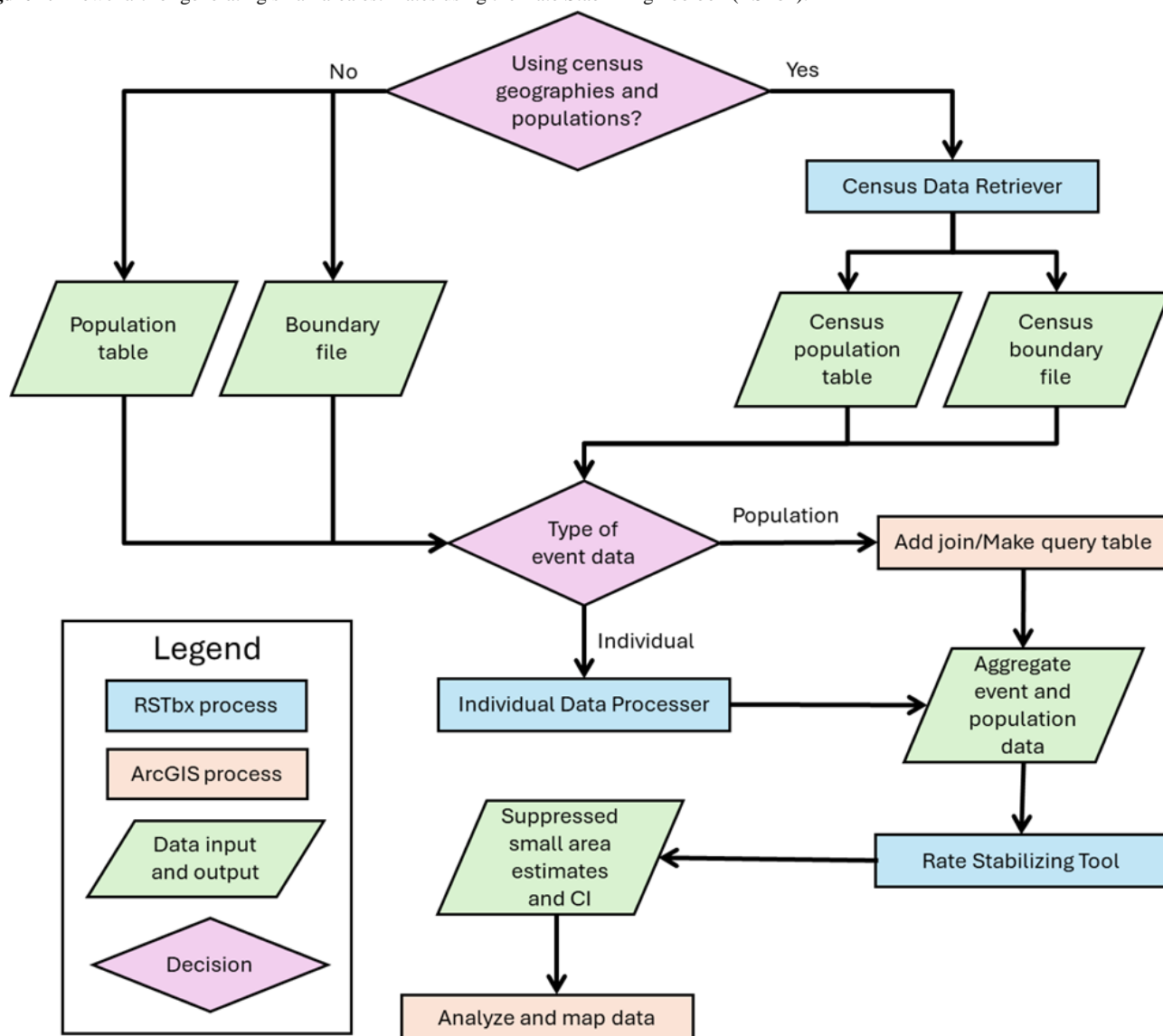
identifier for each geographic unit, the number of events in each geographic unit (ie, the numerator for the health outcome of interest), and the age group. The age group is optional and only required if users want to generate age-standardized rates. If the age group is included, the groups are restricted to: "0-4," "5-14," "15-24," "25-34," "35-44," "45-54," "55-64," "65-74," "75-84," "85up." For both the event and population data, the typical use case is single-year data, but data can be analyzed along any temporal aggregation.

Second, users must provide a table with the population data for each geographic unit or geographic unit-age group combination. Users can either supply their own population-level data or access the CDR within RSTbx to retrieve population data for census geographies. Users with noncensus geographies must provide their own population-level data. Importantly, RSTbx assumes that data for each geographic unit are a census (ie, data represent the entire population).

Finally, users enter a boundary file for the geographic area of interest. RSTbx supports most major file types through ArcGIS Pro, including but not limited to Geodatabase features, GeoPackage features, GeoParquets, and shapefiles. Each geographic unit must have at least 1 neighbor. If users are not using their own geographic boundary files, the CDR can be used to download TIGER or cartographic boundaries from the US Census Bureau.

Generating Small Area Estimates With RSTbx

Figure 2 outlines the steps involved in using RSTbx to calculate local-level measures of population health. The first steps include determining the geographic unit of analysis and obtaining population data and a boundary file for the chosen geographic unit. If the event data (eg, health data) are at the individual level, they must be aggregated to the geographic unit and joined to the population table with the IDP; population-level event data may be directly joined to the population table. The next step entails choosing the desired threshold for reliability. Finally, if conducting age-standardization, it is necessary to choose the age groups and a standard population year to be used in the age-standardization process. Detailed directions are provided within RSTbx and within the GitHub repository [16].

Figure 2. Flowchart for generating small area estimates using the Rate Stabilizing Toolbox (RSTbx).

Output

After running the models, RSTbx generates samples from the posterior distribution for each geographic unit, from which an output table is created. The table includes spatially smoothed estimates (ie, the posterior medians), lower and upper bounds of the user-defined CIs, and the level of reliability (eg, 95%, 90%, 75%) for each geographic unit. If age-standardization is requested, results will be produced for the age-standardized age range and all composite age groups within the data.

RSTr R Package

Overview

RSTr is an R package using Rcpp and RcppArmadillo [20-23] that generates small area estimates of health outcomes using CAR models [24]. Users may choose from one of many BYM-based models to generate small area estimates, including the univariate CAR, multivariate CAR (MCAR), and multivariate spatiotemporal CAR (MSTCAR). RSTr's CAR model smooths across space using data from neighboring geographic units [6,13]. The MCAR expands upon the CAR

model by smoothing across both geographic units and domains (eg, sociodemographic groups) [11]. The MSTCAR further expands the MCAR model by smoothing across geographic units, domains, and time [12]. Statistical and technical details of these models are available in the package documentation [24].

Package Setup

RSTr uses the R statistical software [25] and can be installed from the Comprehensive R Archive Network (CRAN) [24].

Input Data Requirements

RSTr requires 3 pieces of input data: event counts, population data, and the adjacency structure of the geographic units. RSTr uses aggregate, rather than individual-level, data. Requirements for the structure of these inputs are described in detail in the package documentation [24]. Briefly, datasets for the event and population data for each geographic unit should be combined into an R list object. Requirements for the data structure differ based on the selected model. For example, the CAR model uses vectors, the MCAR model uses matrices, and the MSTCAR model uses 3-dimensional arrays. Importantly, RSTr assumes

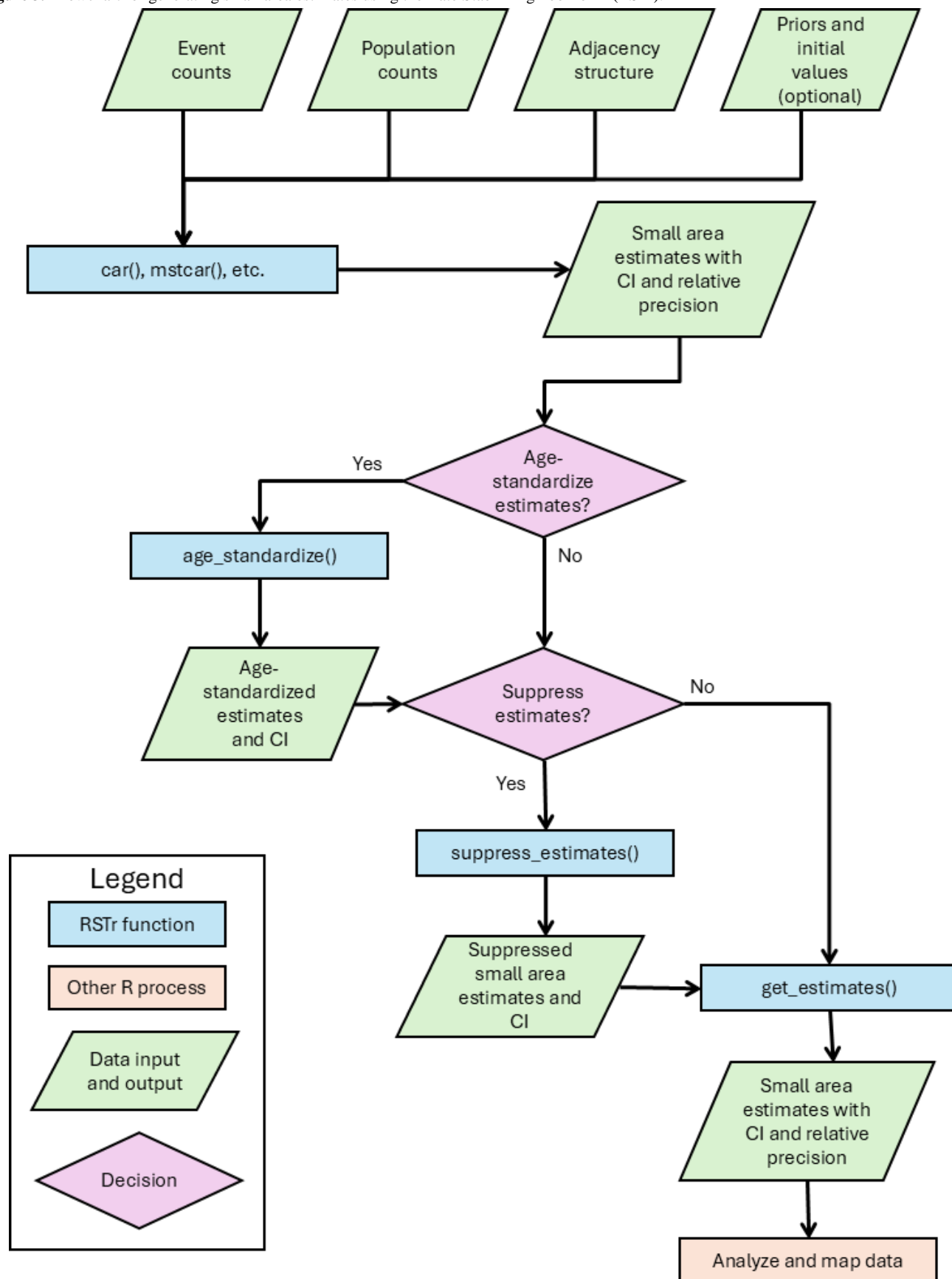
that data for each geographic unit represent a census (ie, data represent the entire population). For both event and population data, the typical use case is single-year data, but data can be analyzed along any temporal aggregation. For the MSTCAR model, any temporal aggregation can be used, but all time periods must be an equal distance apart. Users must supply their own population count data, but can easily acquire data through the use of the `tidycensus` package for downloading 1-year and 5-year ACS estimates, along with 10-year decennial census data [26]. Finally, RSTr's models will impute data for estimates censored due to privacy reasons. For additional information about the data setup process, refer to the vignette titled "01: Understanding and Preparing Your Event Data."

Adjacency information tells RSTr the neighbors of each geographic unit. Each geographic unit must have at least 1 neighbor. These adjacency data should be formatted in a structure the same as that generated by the `poly2nb()` function

from the `spdep` package [27,28]. RSTr supports any filetype supported by GDAL through the use of the `sf` package [29,30], which has drivers for nearly every geospatial format.

Generating Small Area Estimates With RSTr

Figure 3 provides an outline of how to run models with RSTr. When running the model, users specify, at a minimum, the event data, population data, and adjacency structure. However, users may also specify the distribution of the event data (either Poisson or binomial as appropriate), initial values, priors, and other parameters to tune the model. Historically, birth and death data have been assumed to arise from Poisson processes [31], thus prompting the use of Poisson distributions to model birth [14,15] and death data [32,33]. However, because the Poisson distribution can be used to approximate the binomial distribution—and because a binomial might be more appropriate for other types of data—RSTr defaults to using a binomial distribution.

Figure 3. Flowchart for generating small area estimates using the Rate Stabilizing Tool for R (RSTr).

The decision of which model to select depends on the nature of the underlying data. In particular, the UCAR model is appropriate for a single year of data and a single demographic

group, while the MCAR model is appropriate for a single year and multiple demographic groups (ie, multiple age groups to generate age-standardized estimates) and the MSTCAR model

is appropriate for data with both multiple years of data and multiple groups.

Output

Typical of Bayesian models, the RSTr models generate output in the form of samples. These samples are then used to generate small area estimates and CIs. Samples are included as a standalone output; estimates based on those samples, along with their corresponding CIs and relative precisions, are included as part of a larger model object from which these elements can be extracted.

Estimates are defined as the median of these samples and are extracted using the `get_estimates()` function on the RSTr model object. The output of `get_estimates()` is by default a long table containing medians (ie, estimates) for each region, group, and time period included in the model. The `get_estimates()` function also returns the credible interval, event and population counts, and relative precision, defined by Quick et al [13] as the ratio of the posterior median and the width of the user-specified CI, for each estimate. Relative precisions greater than 1 correspond to “reliable” estimates, per the framework of Quick et al [13].

Users may specify thresholds for reliability from 0 to 1 to define the CI used for relative precision calculations. At the default level of 0.95, the CI is defined as the 2.5 and 97.5 percentiles of the samples. This function may be especially beneficial when data are limited and few, if any, estimates would be deemed reliable at the traditional 0.95 level. For example, presenting maps of the estimates that are reliable at the 0.80 level will allow more estimates to be displayed while also acknowledging that a relaxed standard of reliability is being used. This functionality is demonstrated below.

Benefits of Mapping Small Area Estimates Generated by RSTbx and RSTr

Overview

There are many benefits to mapping small area estimates of population health generated by the RSTbx and RSTr. In this section, we demonstrate 3 key benefits: (1) decreased number of geographic units with suppressed estimates, (2) flexibility to set a threshold for reliability, and (3) CIs that can be used to identify statistically significant differences between geographic units.

Datasets Used to Demonstrate the Benefits of RSTbx and RSTr

RSTbx: North Carolina Mortality Data

To demonstrate the benefits of the RSTbx, we used North Carolina mortality data at the census tract level. Specifically,

we examined heart disease deaths among adults aged 35 to 64 years in North Carolina census tracts for the years 2017 to 2019. Heart disease deaths were defined as deaths with International Classification of Disease, 10th revision (*ICD-10*) I00–I09, I11, I13, I20–I51 listed as the underlying cause. Results were age-standardized in 10-year age bands to the 2010 US Standard Population. Underlying data were made available through an agreement with the North Carolina Department of Health and Human Services, Division of Public Health.

RSTr: Rhode Island Hospitalization Data

To demonstrate the RSTr, we use Rhode Island hospitalization data from the Rhode Island Department of Health Hospital Discharge Data Program [34]. Specifically, we examine myocardial infarction and stroke-related inpatient hospitalizations in acute care hospitals among adults aged 20 to 69 years for Rhode Island census tracts in 2021 to 2023. Myocardial infarction and stroke hospitalizations were defined as hospitalizations with *ICD-10* I21-22, I60-63, I65-66 as the primary diagnosis. We ran an MSTCAR model for the years 2021 to 2023 by sex and 10-year age group and used the 2000 US Standard Population in 10-year age bands for age-standardization [18]. We then aggregated across sex and age-standardized across age groups. Underlying data were made available through an agreement with the Rhode Island Department of Health Hospital Discharge Data Program and are not publicly available.

Benefit 1: Decreased Number of Geographic Units With Suppressed Data

Overview

An important advantage of the underlying Bayesian statistical models in RSTbx and RSTr is their ability to increase the precision of estimates, thereby offering the potential to produce reliable estimates even when the event counts and/or population sizes are small. Compared to crude, unmodeled estimates, RSTbx and RSTr generate reliable estimates for a greater number of geographic units and therefore display fewer suppressed geographic units on maps (Figures 4 and 5). In these figures, estimates are deemed reliable based on their 95% CI. Additionally, the models used by these tools attenuate outliers and therefore narrow the range of estimates after spatial smoothing. This change reflects the improved precision and reliability of estimates that are otherwise sporadically high or low.

Figure 4. Rate Stabilizing Toolbox (RSTbx)-generated heart disease death rates by North Carolina census tract, adults aged 35 years and older, 2017 - 2019. The rates displayed in the top map are unsmoothed and suppressed according to United States Cancer Statistics suppression criteria; the rates displayed in the bottom map are spatially smoothed and use suppression criteria based on relative precision using a 95% CI. Comparison of the smoothed and unsmoothed rates shows the decreased percentage of census tracts that have suppressed rates when using RSTbx, demonstrating Benefit 1. Note that cut points on the maps differ, reflecting the attenuation of variance in the spatially smoothed rates.

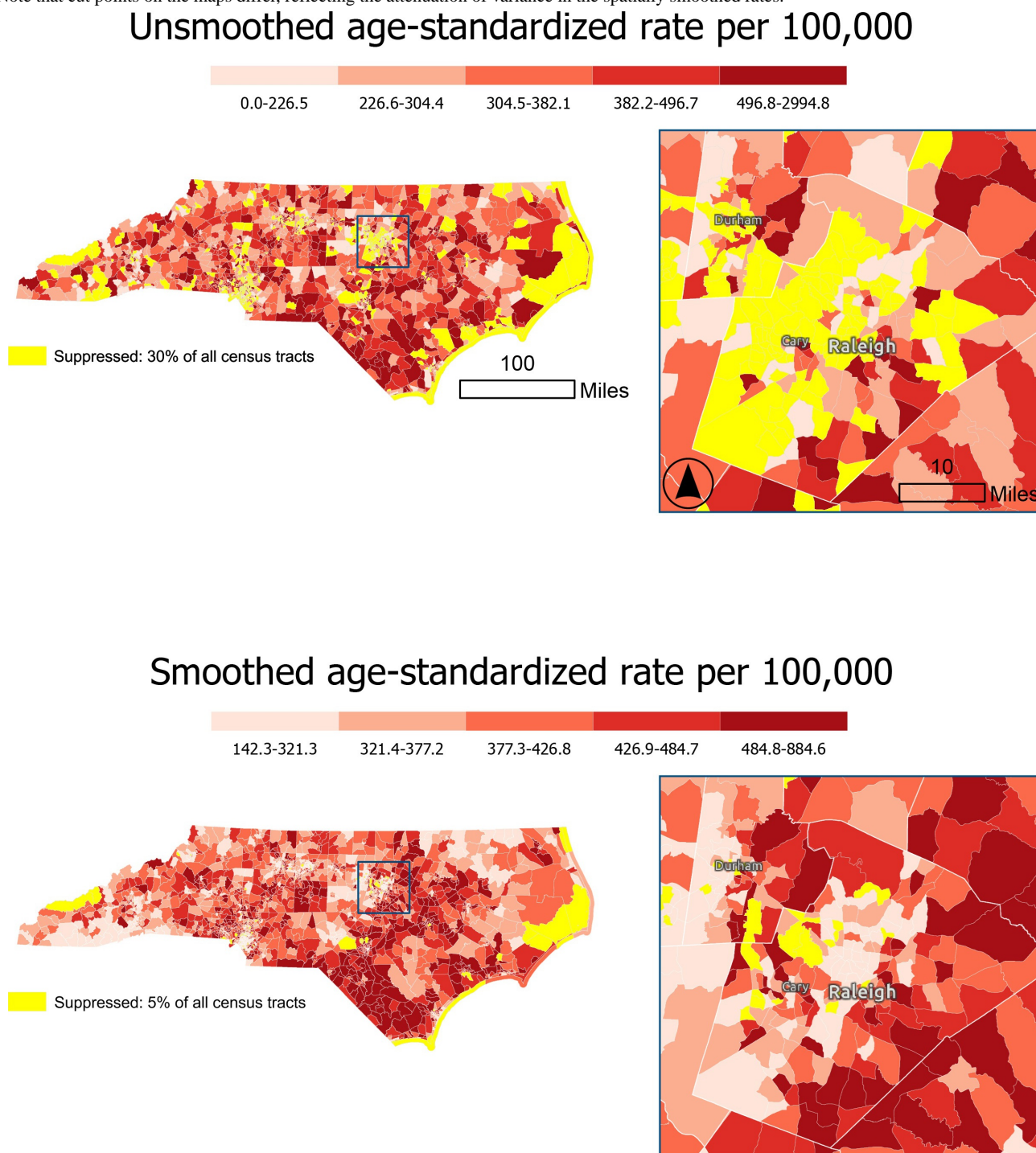


Figure 5. Rate Stabilizing Tool for R (RSTr)-generated myocardial infarction and stroke inpatient hospitalization rates by Rhode Island census tract, adults aged 20 - 69 years, 2021 - 2023. The top map displays unsmoothed hospitalization rates suppressed according to the Rhode Island Department of Health Small Numbers Policy suppression criteria; the bottom map shows spatially smoothed hospitalization rates and use suppression criteria based on relative precision using 95% CIs and an overall census tract population threshold of 100. Comparison of the smoothed and unsmoothed rates shows the decreased percentage of census tracts that have suppressed rates when using RSTr (50% and 7%, respectively), demonstrating Benefit 1. Note that cut points on the maps differ, reflecting the attenuation of variance in the spatially smoothed estimates.

Benefit 1: RSTbx Demonstration

Figure 4 displays age-standardized heart disease death rates for adults aged 35 - 64 years by census tract in North Carolina for the years 2017 - 2019. In the top map of unsmoothed death rates, census tracts with fewer than 16 deaths are suppressed according to United States Cancer Statistics guidelines [35]. Using these guidelines, 30% (n=656) of census tracts were suppressed. The suppressed census tracts were distributed across the state, particularly in coastal regions and urban areas. The bottom map of Figure 4 displays death rates that were spatially smoothed using RSTbx. Here, applying the default threshold for reliability (which is based on the 95% CI) resulted in 5% (n=105) of census tracts being suppressed.

Benefit 1: RSTr Demonstration

Figure 5 displays age-standardized myocardial infarction and stroke inpatient hospitalization rates for adults aged 20 to 69 years by census tract in Rhode Island for the years 2021 to 2023. In the top map, estimates are suppressed according to the Rhode Island Department of Health Small Numbers Reporting Policy [36]; the bottom map is spatially smoothed and suppressed based on precision and population. The Rhode Island Department of Health Small Numbers Policy features data suppression recommendations for a wide variety of data types and data reporting scenarios. In the case of the hospitalization data, several layers of consideration about the data are needed to determine whether or not to suppress rates. In brief, the rates suppressed in the unsmoothed map take into consideration small numerators (number of hospitalizations) paired with large denominators, leading to unreliable or unstable rates. The suppression criteria result in 50% (n=122) of census tracts being suppressed. The suppressed census tracts were primarily located in small Rhode Island towns and villages, especially small coastal towns and villages.

For the spatially smoothed map, relative precision was calculated using a 95% CI and resulted in 7% (n=17) of census tracts being suppressed with an overall census tract population threshold of 100. Additionally, the smoothed map demonstrates an extension

of the spatial patterns in the unsmoothed map. The inner census tracts of Providence have more tracts in the higher categories than in the unsmoothed data, and many less dense areas have low hospitalization rates. In this example, the increase in the number of reliable estimates using the smoothed estimates tells a clearer version of the story presented by the unsmoothed data.

Benefit 2: Flexibility to Set the Threshold for Reliability for Small Area Estimates

Overview

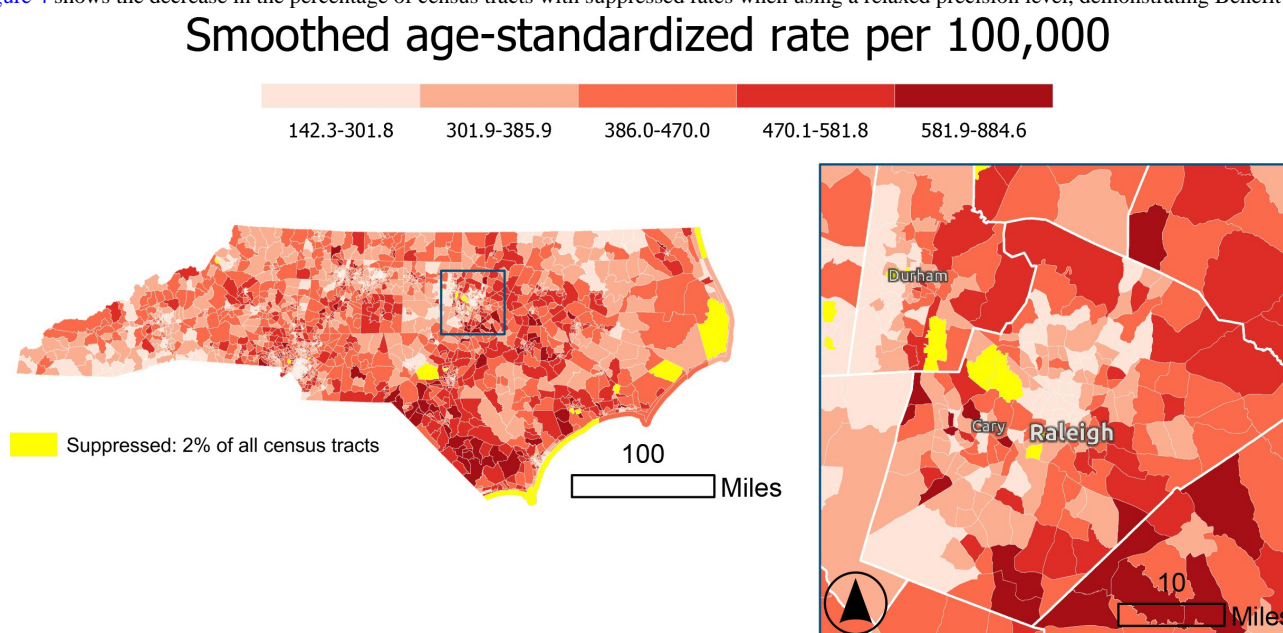
The default threshold for reliability for both RSTbx and RSTr is set at the commonly used 95%. However, RSTbx and RSTr both allow users to relax that threshold to less than 95%. Both tools use the definition in Quick and Song [13] to deem an estimate “reliable” if its relative precision (ie, the ratio of the posterior median and the width of the CI) is greater than 1. RSTbx output includes the maximum CI for which each estimate is deemed reliable, known as its level of reliability. RSTr allows users to relax the threshold for reliability by calculating the relative precision using narrower CIs (eg, 90% or 80%).

This feature allows users to more completely visualize geographic patterns due to less suppression at lower levels of reliability. This advantage, however, comes with a caveat: at some point, with a low enough threshold for reliability (eg, 70%), all geographic units would be considered to have “reliable” estimates. However, estimates with low levels of reliability may be based on very small numbers, leading to potential privacy concerns. Therefore, relaxing the reliability level may need to be accompanied by additional suppression criteria based upon population size.

Benefit 2: RSTbx Demonstration

Figure 6 displays North Carolina heart disease mortality rates for census tracts that meet the threshold for reliability using the 90% CIs. Relaxing the threshold for reliability from 95% in Figure 4 to 90% decreases the percent of census tracts that are suppressed from 5% to 2%.

Figure 6. Rate Stabilizing Toolbox (RSTbx)-generated heart disease death rates by North Carolina census tract, adults aged 35 years and older, 2017 - 2019. The map displays spatially smoothed rates, and reliability is defined by relative precision using 90% CIs. Comparison of this figure with Figure 4 shows the decrease in the percentage of census tracts with suppressed rates when using a relaxed precision level, demonstrating Benefit 2.

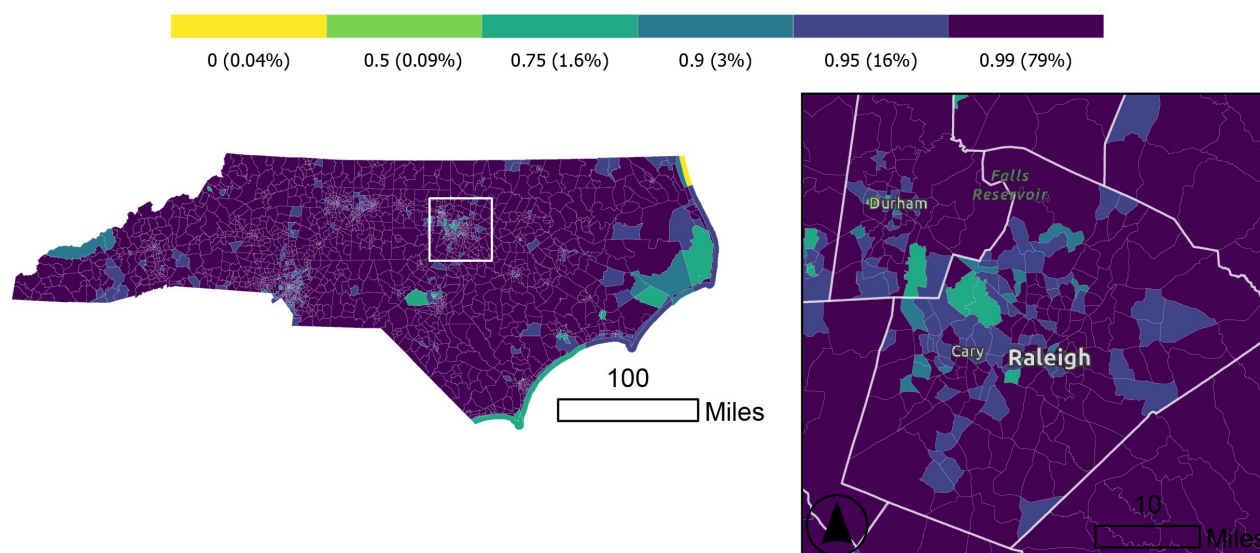


RSTbx also permits users to map geographic units by their level of reliability since those are included in the RSTbx output. Figure 7 displays the level at which the estimate for each census tract is reliable. Estimates for much of the state are reliable at or above 95%. From this map, users can easily see geographic

patterns in the reliability of the estimates and the range of reliability across estimates. As demonstrated in Quick and Song, these maps can be viewed as mapping a measure of uncertainty, as they highlight the geographic variation in the amount of information contributed by each geographic unit [15].

Figure 7. Levels of reliability of Rate Stabilizing Toolbox (RSTbx)-generated age-standardized heart disease death rates by North Carolina census tract, adults aged 35 years and older, 2017 - 2019. This map shows the maximum credible interval level at which stable and reliable smoothed estimates can be produced, illustrating the spatial variation in the quality of RSTbx-derived estimates and demonstrating Benefit 2. Wider credible intervals reflect greater uncertainty, which tends to occur in tracts with smaller total population estimates and lower case counts.

Levels of reliability of tract-level heart disease death rates (% all census tracts)

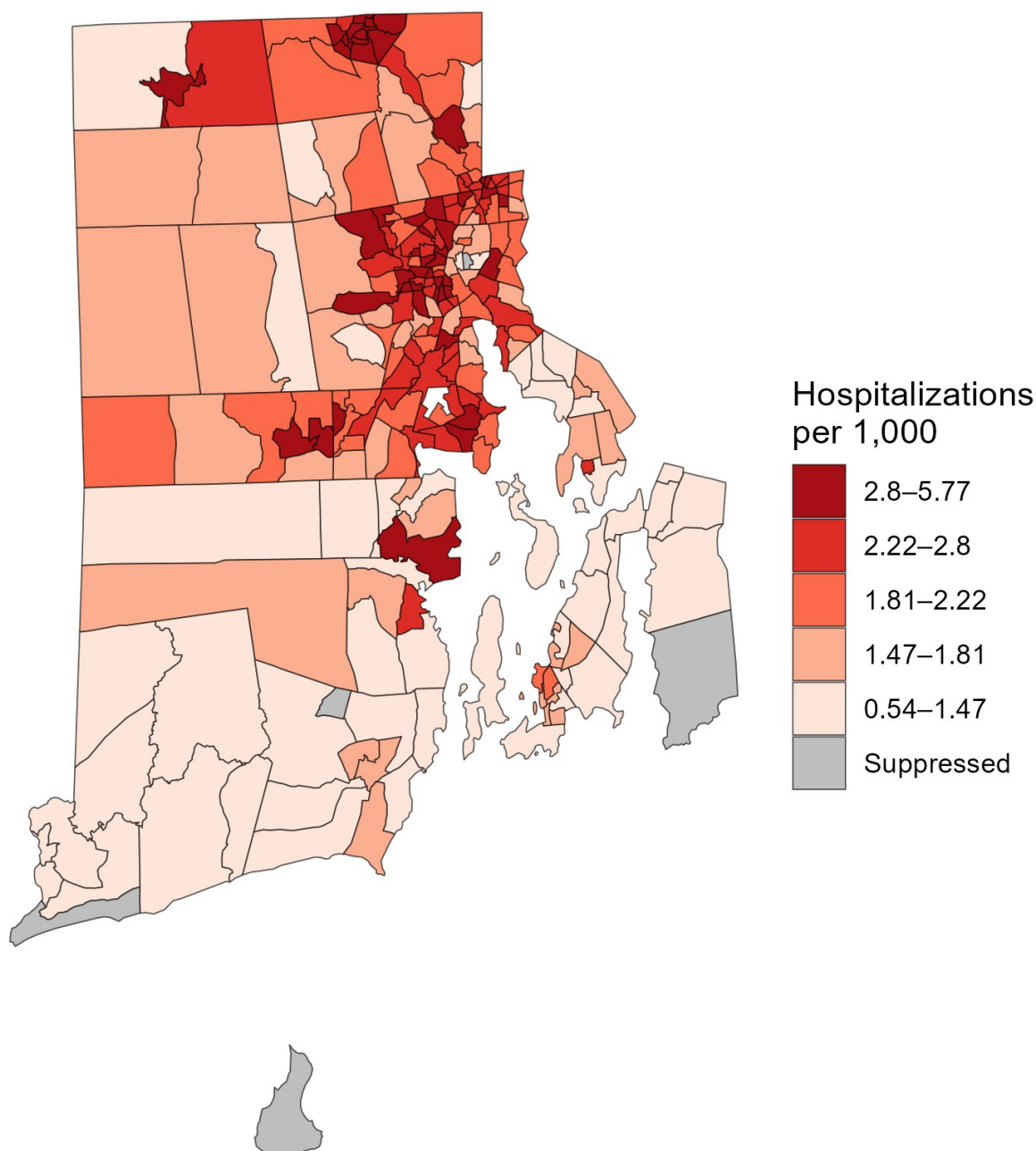


Benefit 2: RSTr Demonstration

Figure 8 displays Rhode Island myocardial infarction and stroke in-patient hospitalization rates for census tracts that meet the

reliability criteria using a 90% CI. Relaxing the CI for the reliability criteria from 95% in Figure 5 to 90% further decreases the percent of census tracts that are suppressed (from 7% to 2%), but includes less precise estimates.

Figure 8. Rate Stabilizing Tool for R (RSTr)-generated myocardial infarction and stroke hospitalization rates by Rhode Island census tract, adults aged 20 - 69 years, 2021 - 2023. The map displays spatially smoothed rates. Reliability is defined by relative precision using a 90% CI. Comparison of this figure with Figure 5 shows the decrease in the number of census tracts with suppressed rates using a relaxed precision level, demonstrating Benefit 2. A total of 5 (2%) of census tracts are suppressed.



Geographic patterns in the levels of reliability (ie, the maximum CI whose width is less than the posterior median) will closely align with the population sizes of the geographic units. However, unlike maps of population sizes—where a given population size may be sufficient to produce reliable estimates for a common outcome and be insufficient to produce reliable estimates for a rare outcome—maps of the reliability levels will be standardized across outcomes. That is, estimates from analyses of different outcomes in different datasets with the same level of reliability can be viewed as being equally precise on a relative basis.

Benefit 3: Using Credible Intervals to Identify Statistically Significant Differences Between Places

Overview

Another benefit of RSTbx and RSTr is the ability to compare estimates for geographic units to another value. This other value may be a single value (eg, a state rate) or another estimate (eg, the census tract with the lowest estimate). This comparison is made by using the CI at a specified level (eg, 95%). Estimates with a CI that excludes a value or that does not overlap with another CI are determined to be statistically different. Importantly, estimates that are unreliable can still be statistically significantly different from a comparison rate. As demonstrated in Figures 9 and 10, this approach can be used to highlight

geographic units (eg, census tracts) that are statistically higher or lower than the state rate.

Figure 9. Comparison of Rate Stabilizing Toolbox (RSTbx)-generated census tract level heart disease death rates to the state rates, ages ≥ 35 years, 2017 - 2019, North Carolina. By using 95% CIs that are generated for each census tract, this map shows census tracts with heart disease death rates that are statistically significantly higher or lower than the North Carolina heart disease death rate, demonstrating Benefit 3.

Significantly different than state average

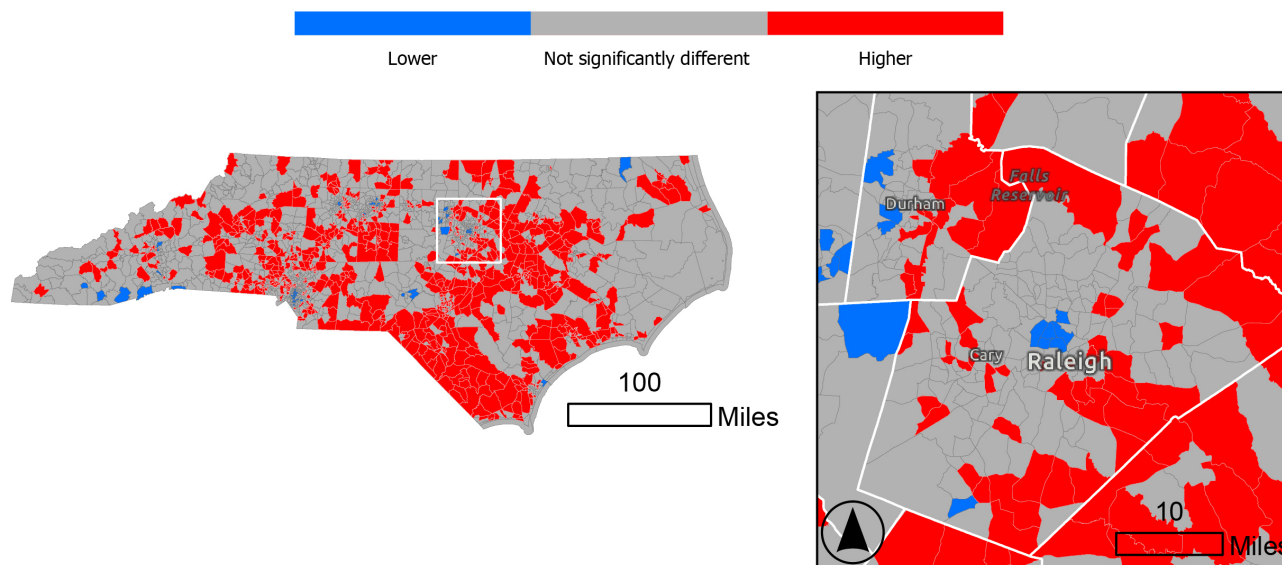
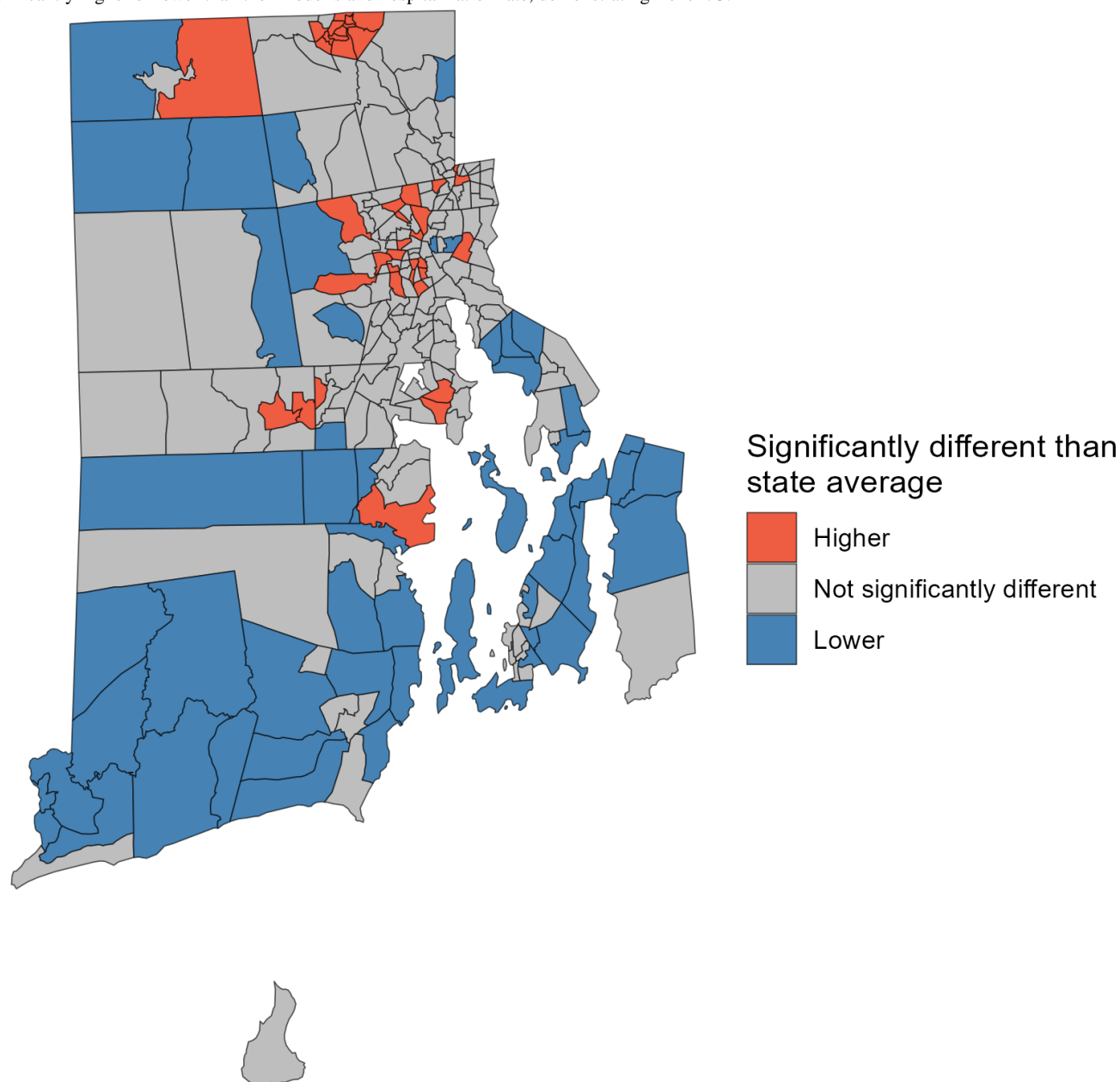


Figure 10. Comparison of Rate Stabilizing Tool for R (RSTr)-generated census tract level myocardial infarction and stroke hospitalization rates to the state rates aged 20 - 69 years, 2021 - 2023, Rhode Island. By using 95% CIs, this map shows census tracts with hospitalization rates that are statistically significantly higher or lower than the Rhode Island hospitalization rate, demonstrating Benefit 3.



Benefit 3: RSTbx Demonstration

Figure 9 displays census tracts in North Carolina for which the age-standardized, spatially smoothed heart disease death rates are statistically higher (red) or lower (blue) than the state level. Statistical significance is determined when the 95% CI for the tract level death rates do not include the state level value. Census tracts with rates that are statistically different from the state rate are found across the state. Notably, statistically higher rates are concentrated in the state's urban areas.

Benefit 3: RSTr Demonstration

Figure 10 displays census tracts in Rhode Island for which the age-standardized, spatially smoothed myocardial infarction and stroke in-patient hospitalization rates are statistically higher (red) or lower (blue) than the state rate. Statistical significance is determined when the 95% CI for the tract level death rates

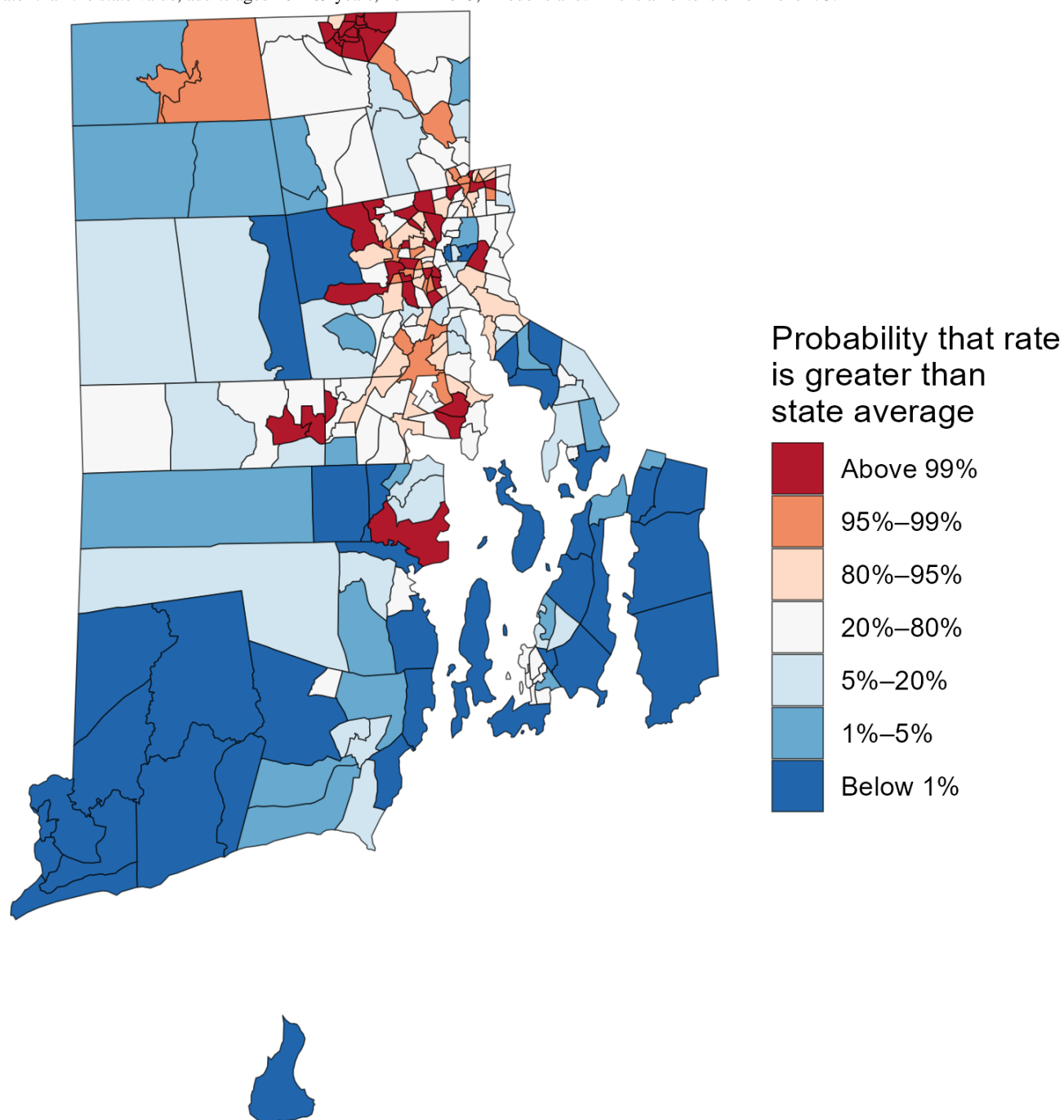
do not include the state rate. Census tracts shown in gray have estimates that are not significantly different from the state hospitalization rate.

Additionally, the output from RSTr allows users to calculate the probability that one value is greater than another, frequently referred to as an exceedance probability. In Figure 11, we demonstrate the probability that the tract level hospitalization rates in Rhode Island exceed that of the state level. Unlike the approach in Figure 10, we are not limited to binary differences in probability, revealing a nuanced look at the statistical strength of the estimates. With RSTr's samples, users can calculate the percent of samples for a given region, group, or time that exceed a given value. In this approach, the percent estimate implies its opposite as well: an 80% chance for an estimate to be greater than the state hospitalization rate implies a 20% chance for the estimate to be less than that rate. In Figure 11, most of the

strongest probabilities of an estimate being greater than the rate for Rhode Island are clustered in urban areas, whereas rural areas tend to have the lowest probabilities of being greater than

the state's hospitalization rate, indicating that their rates may be significantly lower than the state rate.

Figure 11. Probability that Rate Stabilizing Tool for R (RSTr)-generated myocardial infarction and stroke hospitalization rates by census tract are greater than the state value, adults aged 20 - 69 years, 2021 - 2023, Rhode Island. This is an extension of Benefit 3.



Discussion

Strengths and Limitations

RSTbx and RSTr have many strengths. First, as we have demonstrated, the outputs of both RSTbx and RSTr can be used to map small area estimates or statistical comparisons, with varying thresholds for reliability. Second, these tools allow users to quickly run complex Bayesian models. Third, users can easily generate age-standardized rates. RSTbx includes integrated standardization to either the 2000 US Standard

Population or the 2010 US Standard Population in 10-year age groups. RSTr users may age-standardize to any population and are able to aggregate by domains other than age, such as race, sex, year, or region.

Though software such as JAGS, Stan, and BUGS [37-39] have addressed many of the same issues as RSTr and RSTbx and provide many of the statistical models used by our tools in a more generic framework, our tools come with distinct advantages. First, RSTr features a wider family of CAR models to choose from with more complex specifications available;

Stan and JAGS, for example, provide at best an MCAR model for estimation, and BUGS only provides a BYM CAR model. Additionally, since RSTbx and RSTr are designed specifically to run CAR models, their parameters and initial values are pre-specified based on existing work in the literature. More general software like Stan and BUGS requires a more hands-on approach and can lead to nonideal CAR model specification. Finally, RSTbx and RSTr utilize recent advances in CAR model methodology not seen in other statistical packages. The UCAR model implemented in both tools features enhancements that restrict the strength of the spatial smoothing using models which aim to establish a minimum on the amount of data required to yield a reliable estimate [13,15].

Both RSTbx and RSTr have limitations. First, the input data are assumed to be a census or representative sample of the population being studied. Neither tool is designed to accommodate survey weights or potential disparities in reporting quality (eg, undercounts). Any data quality issues that would cause the crude values (ie, the event counts divided by the population sizes) to be biased would also affect the quality of the estimates. Spatial data in general are prone to many limitations; nuances such as the modifiable areal unit problem, the ecological fallacy, and edge effects should all be considered when interpreting results generated by RSTbx and RSTr. Additionally, RSTbx includes only the UCAR model, meaning that smoothing occurs only over space and not over time or other domains.

Finally, our statistical models have some limitations. In contrast to the UCAR models used in both tools, RSTr's MCAR and MSTCAR models do not feature enhancements to restrict the strength of the spatial smoothing and thus have the potential to yield estimates with relative precisions greater than one when zero events have been observed. As a result, these models may produce estimates that are overly smooth (ie, reduced geographic disparities between adjacent geographic units) and overly precise

(ie, inflated levels of reliability). To address this limitation, users can flag estimates generated by RSTr as unreliable when population sizes are not sufficiently large in addition to the use of relative precision. While Quick and Song do not provide guidance regarding requirements for population sizes, others have suggested requiring population sizes be at least 30 or 100 in order to display estimates [12]. Development of restricted MCAR and MSTCAR models is an active area of research, and future updates to RSTr and RSTbx aim to include such models. Additionally, there are future plans to expand RSTbx to use open-source GIS software, such as QGIS. Future versions of RSTbx will also include imputation of censored data and further streamline the data setup process.

Conclusion

RSTbx and RSTr facilitate the calculation of small area estimates of population health for ArcGIS and R users, respectively. Table 1 summarizes the main features for RSTbx and RSTr. Overall, both tools simplify the implementation of complicated Bayesian spatial and spatiotemporal models. Both tools also take advantage of recent methodological developments for the CAR model and easily age-standardize estimates. Using census tract-level data from North Carolina and Rhode Island, we demonstrated the benefits of using RSTbx and RSTr to generate and map small area estimates, especially when there are small numbers of events or population sizes. We focused on three key benefits of using these tools: (1) decreased number of geographic units with estimates being suppressed based on reliability criteria, (2) flexibility to set the threshold for reliability, and (3) using credible intervals to identify statistically significant differences between geographic units. In summary, RSTbx and RSTr are powerful tools that can be used to meet the demand for high-quality, local-level data to inform public health programs and tailor health promotion activities to the needs of communities across the country.

Table . Comparison of Rate Stabilizing Toolbox and Rate Stabilizing Tool for R functionality.

	RSTbx ^a	RSTr ^b
Platform	Esri ^j ArcGIS Geoprocessing Tool(s)	R package
Geographic units	Any user-specified geographic unit ^d	Any user-specified geographic unit ^d
Census interface	The CDR ^e is a component of RSTbx that can be used to generate age-stratified or unstratified tables using US Census decennial or American Community Survey data at the county or census tract level	No census interface; users gather any census data of interest on their own. There are R packages to assist with this, eg, tidycensus, censusapi, etc
Age-standardization	Yes	Yes
CAR ^f models ^g	CAR	CAR, MCAR ^h , MSTCAR ⁱ
Input data format	Event/population data: <ul style="list-style-type: none"> • Geodatabase table • dBASE (.dbf) • Delimited files <ul style="list-style-type: none"> • Comma-delimited files (.csv, .txt, .asc) • Tab-delimited files (.tsv and .tab) • Pipe-delimited files (.psv) Boundary file: <ul style="list-style-type: none"> • Geodatabase feature • GeoPackage feature • GeoParquet • Shapefile 	Event/population data: A list of arrays whose dimensions depend on the input data, including vector (UCAR), matrix (MCAR), and three-dimensional array (MSTCAR) Adjacency data: A list of vectors which represent the index of their neighboring regions
Additional tools/software needed	ArcGIS Pro	R
Output data format	The following table formats are supported as outputs: <ul style="list-style-type: none"> • Geodatabase table • dBASE (.dbf) • Delimited files <ul style="list-style-type: none"> • Comma-delimited files (.csv, .txt, and .asc) • Tab-delimited files (.tsv and .tab) • Pipe-delimited files (.psv) By default, tables are written to the current ArcGIS project default geodatabase	Outputs an RSTr model object from which a long table containing estimates, events, populations, CIs, and relative precisions can be extracted. The model object requires additional processing for age-standardization and suppressed estimates
Group aggregation	None	Geographic units, race/ethnicity, sex, year
Reliability calculations	Generated automatically in the output data	Generated automatically in the output data
Probability calculations	Not calculable with the output data	Not directly available, but can be generated by user

^aRSTbx: Rate Stabilizing Toolbox.^bRSTr: Rate Stabilizing Tool for R.^cEsri: Environmental Systems Research Institute.^dAssumes that the user has numerator and denominator data for the same geographic unit (eg, census tract, county)^eCDR: Census Data Retriever.^fCAR: conditional autoregressive.^gFor a description of the CAR models used in RSTbx and RSTr, please refer to the overview section for that specific software.^hMCAR: multivariate CAR.ⁱMSTCAR: multivariate spatiotemporal CAR.

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The authors attest that there was no use of generative artificial intelligence (AI) technology in the generation of text, figures, or other informational content of this manuscript. The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services

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Conflicts of Interest

None declared.

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Abbreviations

ACS: American Community Survey
BYM: Besag, York, and Mollié
CAR: conditional autoregressive
CDR: Census Data Retriever
ICD-10: International Classification of Disease, 10th revision
IDP: Individual Data Processor
MCAR: multivariate CAR
MSTCAR: multivariate spatiotemporal CAR
RST: Rate Stabilizing Tool
RSTbx: Rate Stabilizing Toolbox
RSTr: Rate Stabilizing Tool for R
UCAR: univariate CAR

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Comparison of In Vitro Metrics With Real-World Risk of Drug-Induced Parkinsonism Due to Antipsychotic Drugs: Retrospective Cohort Study

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Abstract

Background: Drug-induced parkinsonism (DIP) predominantly occurs due to antipsychotic drugs (APDs) blocking dopamine D2 receptors (D₂Rs). However, in vitro assays often fail to fully reflect real-world variability in clinical outcomes.

Objective: This study aimed to evaluate whether in vitro pharmacological metrics correspond to real-world risk of DIP associated with APD use.

Methods: For 8 commonly used APDs, key in vitro parameters—including inhibition constants (K_i) of D₂Rs and the serotonin 2A receptor, reversal rate (K_r) of D₂Rs, and blood-brain barrier (BBB) penetration rate—were compiled to construct 6 composite DIP risk metrics. The real-world DIP risk was assessed using the Seoul National University Hospital common data model (2002 - 2021). APD users were matched 1:1 to selective serotonin reuptake inhibitor users using propensity score matching, and Cox proportional hazard regression was performed to estimate the hazard ratios (HRs) for DIP risk. Correlation between each in vitro metric and real-world DIP risk was evaluated using logarithmic regression models.

Results: Among 44,664 patients from 8 matched cohorts, haloperidol showed the highest DIP risk (HR=4.56, 95% CI 2.29 - 9.07), whereas aripiprazole exhibited the lowest risk (HR=2.11, 95% CI 1.56 - 2.86). Metric 4 (pK_r × BBB penetration rate) exhibited the strongest correlation with real-world DIP risk (R²=0.95). The correlation decreased when aripiprazole, a partial D₂R agonist, was included in the analysis (R²=0.58).

Conclusions: Integrating receptor-binding kinetics with BBB penetration may provide an in vitro framework that reflects real-world variation in DIP risk among D₂R-antagonizing APDs. These findings support the relevance of combining kinetic and central nervous system exposure parameters for early safety evaluation.

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KEYWORDS

drug-induced parkinsonism; antipsychotic drug; binding affinity; dopamine D2 receptor; blood-brain barrier

Introduction

The pharmacological action of drugs generally occurs through receptor binding, and side effects are often the consequences of these interactions [1]. To understand how drugs function and anticipate their potential side effects, extensive in vitro

experiments on drug-receptor interactions are conducted from the early stages of drug development. However, relying on in vitro analysis, often referred to as “test tube experiments,” makes it difficult to predict how often side effects will occur in real-world patients [2,3]. This translational gap has highlighted the need for mechanistically informed models that integrate

binding kinetics and pharmacokinetic factors to better approximate real-world safety outcomes [3].

Drug-induced parkinsonism (DIP), predominantly caused by antipsychotic drugs (APDs), is one of the most common forms of secondary parkinsonism and remains a clinically significant dose-limiting adverse effect [4]. DIP arises primarily from dopamine D₂ receptor (D₂R) blockade within the nigrostriatal pathway, leading to symptoms of movement disorders such as muscle stiffness, slow movements, and tremors [5-10]. Because these symptoms can impair quality of life and daily functioning, understanding the pharmacologic determinants that underlie variability in DIP risk across APDs has become an important clinical and research priority [11,12].

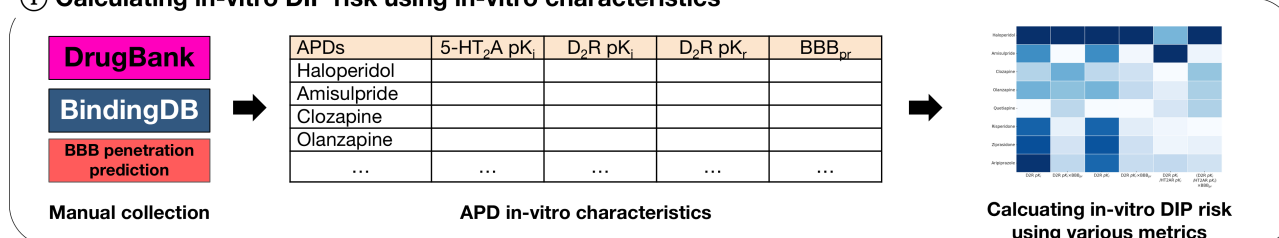
In efforts to explain interdrug differences, the inhibition constant (K_i) and dissociation constant (K_d) have been widely used as a key measure for D₂R blockade; lower values indicate stronger binding to D₂Rs at equivalent drug concentrations [13]. Sykes et al [14] further expanded this framework by demonstrating that receptor-rebinding kinetics—reflecting the probability that a ligand re-engages adjacent receptors after dissociation—can also account for differences in extrapyramidal symptom liability. Other studies have implicated the serotonin 2A receptor (5-HT_{2A}R) in DIP modulation, with newer APDs often exhibiting a higher 5-HT_{2A}R-to-D₂R affinity ratio associated with lower DIP risk [15-17]. While binding kinetics contributes

to understanding variation in APD-related neurological syndromes, additional pharmacological factors also appear to play important roles. A recent meta-analysis demonstrated that the dose of APDs and D₂R occupancy correlate with extrapyramidal symptom onset, indicating that in vivo exposure should be considered alongside in vitro parameters [18,19]. Furthermore, blood-brain barrier (BBB) permeability, which regulates central nervous system (CNS) drug exposure and can change with certain clinical conditions, may also influence the clinical expression of D₂R blockade [20].

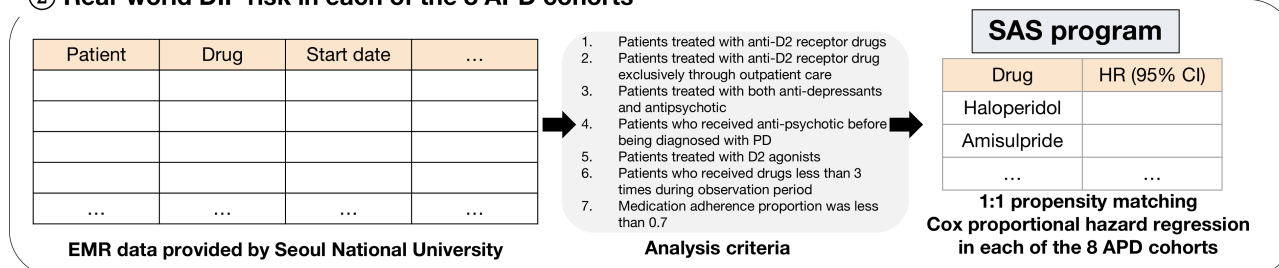
These prior observations collectively suggest that DIP risk reflects an interplay among receptor-binding kinetics, CNS pharmacokinetics, and dose-response. However, despite extensive research on DIP, its precise mechanism and the quantitative translation between in vitro pharmacological parameters and real-world DIP risk remain unclear [6,7,21]. Therefore, this study aimed to evaluate whether specific in vitro pharmacological metrics correspond to variation in real-world DIP risk, with a particular focus on D₂R-antagonizing APDs. First, we derived multiple candidate in vitro DIP risk metrics based on receptor-binding and pharmacokinetic parameters of APDs (Figure 1). Second, using longitudinal real-world data (RWD), we estimated the DIP risk associated with commonly used APDs. Finally, we assessed the extent to which each in vitro metric correlated with the observed real-world DIP risk.

Figure 1. Study overview. 5-HT_{2A}R: serotonin 2A receptor; APD: antipsychotic drug; BBB_{pr}: blood-brain barrier penetration rate; D₂R: dopamine D₂ receptor; DIP: drug-induced parkinsonism; EMR: electronic medical record; HR: hazard ratio; PD: Parkinson disease.

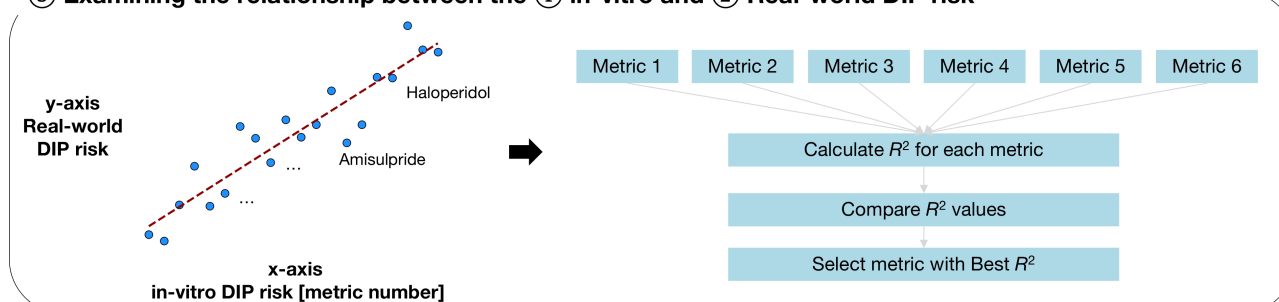
① Calculating in-vitro DIP risk using in-vitro characteristics



② Real-world DIP risk in each of the 8 APD cohorts



③ Examining the relationship between the ① in-vitro and ② Real-world DIP risk



Methods

Study Design and Overview

This study consisted of two components: (1) an assessment of in vitro pharmacological parameters of APDs related to DIP and (2) a retrospective cohort study evaluating the effect of APDs on the risk of DIP using the common data model (CDM) of Seoul National University Hospital. We subsequently examined the relationship between in vitro metrics and the real-world DIP risk. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [22].

In Vitro DIP Risk Metrics

The key parameters of the APDs used to calculate the in vitro DIP risk were the pK_r values for D_2R s and $5-HT_{2A}R$ collected from DrugBank and BindingDB [23–25]. The receptor reversal rate (K_r) values for D_2R s as suggested by Sykes et al [14] were also obtained. Considering that the primary site of action for APDs is within the CNS, the BBB penetration rate of each APD was considered an adjustment factor [26]. The 6 main metrics for the in vitro DIP risk were as follows:

- Metric 1: pK_i for D_2R s
- Metric 2: (pK_i for D_2R s) \times BBB penetration rate
- Metric 3: pK_r for D_2R s
- Metric 4: (pK_r for D_2R s) \times BBB penetration rate
- Metric 5: (pK_i for D_2R s) / (pK_i for $5-HT_{2A}R$)
- Metric 6: (pK_i for D_2R s) / (pK_i for $5-HT_{2A}R$) \times BBB penetration rate

All the data were collected through a manual search conducted by the research team. When multiple values were reported, the geometric mean was used as an integrated value.

RWD Source

The CDM of Seoul National University Hospital included longitudinal data on patient demographics, diagnostic information (such as Parkinson disease and other comorbidities), and prescription details (including prescribed drugs, prescription dates, dosages, and duration of use) from 2002 to 2021. The CDM includes standardized fields for these domains, so conventional item-level missingness is minimal; however, care and prescriptions received outside the hospital are not captured and may result in incomplete ascertainment of medication exposure and clinical events, which was considered when interpreting the results.

Study Population

Patients were recruited into the study cohort based on prescription records. The experimental group consisted of patients prescribed APDs, including haloperidol, olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, clozapine, and ziprasidone. The active comparator group, which served as the control, consisted of patients treated with selective serotonin reuptake inhibitors (SSRIs), including citalopram and escitalopram, fluoxetine, paroxetine, and sertraline, which are known to have minimal D_2R binding affinity (K_i of approximately 10,000 nM) [23–25].

The index date was defined as the date of the first outpatient prescription of an APD or an SSRI during the study period. To maintain methodological consistency, only outpatient prescriptions of the oral formulations of the study drugs were included in the analysis. Patients were excluded based on the following criteria: (1) concurrent prescriptions of APDs and SSRIs; (2) diagnosis of Parkinson disease prior to the index date as the study focused on identifying new-onset DIP attributable to drug exposure; (3) use of D_2R agonists within 1 year prior to the index date; (4) fewer than 3 prescriptions of the study drugs after the index date because such limited exposure is unlikely to represent sustained treatment and may not meaningfully influence DIP onset (in our setting, outpatient prescriptions of APDs and SSRIs are usually written for short durations [approximately 2–4 weeks], so at least 3 prescriptions typically correspond to 2 to 3 months of continuous therapy and help avoid misclassifying sporadic or trial use as ongoing treatment, consistent with previous register-based studies evaluating psychotropic and antipsychotic medication exposure [27,28]); and (5) poor medication adherence, defined as a proportion of days covered of less than 0.7 as inconsistent medication use could confound assessments of DIP risk [29].

Outcome Assessment

The onset of DIP was defined by the presence of diagnostic codes for DIP (G21.1, G21.2, G21.8, and G21.9) based on the *International Classification of Diseases, 10th Revision* [30]. To enhance diagnostic specificity, patients were considered to have developed DIP only if they received prescriptions for D_2R agonists or anticholinergic agents (standard treatments for DIP) within 60 days of initial diagnosis.

Covariates

A total of 28 covariates were selected based on the presence of comorbidities or concurrent medication history within 1 year of the start date of medication use. The 11 comorbidities included chronic obstructive pulmonary disease, dementia, diabetes mellitus, dyslipidemia, end-stage renal disease, gout, hypertension, liver disease, osteoarthritis, osteoporosis, and stroke. The list of *International Classification of Diseases, 10th Revision* codes for comorbidities is shown in Table S1 in [Multimedia Appendix 1](#). The 17 concurrent medications included renin-angiotensin-aldosterone system inhibitors, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; alpha-glucosidase inhibitors; anticonvulsants; anxiolytics; beta-blockers; calcium channel blockers; dipeptidyl peptidase-4 inhibitors; erythropoiesis-stimulating agents; glucagonlike peptide-1 receptor agonists; insulin; iron; loop diuretics; meglitinides; metformin; sodium-glucose cotransporter 2 inhibitors; statins; and sulfonylureas. A detailed list of concurrent medications is provided in Table S2 in [Multimedia Appendix 1](#).

Statistical Analysis

Statistical analyses were performed for the treated population. Patients were followed up on until the earliest events of DIP onset, the last day the patient took their prescribed medication + 30 days, or the end of the 1-year study period. Each APD user was matched 1:1 to an SSRI user, and the distribution of the

propensity score was inspected [31]. The matching variables included age, sex, comorbidities, and concurrent medications. A standardized difference of >0.1 was regarded as a sign of imbalance [32]. The baseline characteristics were summarized using descriptive statistics. Cox proportional hazard regression was used to estimate the hazard ratio (HR) and 95% CI for the risk of DIP associated with APD use. A dose-response analysis was performed by stratifying patients according to their average daily exposure based on the defined daily dose (DDD) [33]. Patients were categorized into 3 groups (<0.5 the DDD, $0.5 - 1.5$ the DDD, and ≥ 1.5 the DDD) to contextualize the in vitro correlation within a clinical dose-response pattern.

Correlation Analysis

To explore the relationship between the in vitro and real-world DIP risks, we correlated the 6 in vitro metrics with the HR estimated from the real-world cohort. Coefficients of determination (R^2) were calculated to quantify the explanatory strength of each association, and an R^2 value of 0.7 was used as a descriptive threshold for a strong relationship [34]. The primary analysis focused on APDs with D_2R antagonist properties, whereas aripiprazole—a partial agonist—was examined separately in an exploratory analysis to reflect its distinct pharmacologic profile [35].

For each drug i , the association between the clinical outcome—expressed as an HR—and the corresponding in vitro pharmacological metric (metric 1 - 6) was modeled using a logarithmic regression:

$$HR_i = \beta_0 + \beta_1 \ln(X_i) + \epsilon_i$$

In this expression, X_i represents the in vitro metric for the i th drug. As each HR estimate was accompanied by a 95% CI, weighted least squares was used to incorporate the varying uncertainty across drugs, allowing the regression to account for the differing precision of each HR estimate. A 95% confidence band for the fitted regression line was constructed based on the SE of the mean predicted HR values:

$$CI_{95\%}(x) = HR^{\wedge}(x) \pm t_{0.975, df} \cdot SE_{HR^{\wedge}(x)}$$

In this equation, $HR^{\wedge}(x)$ is the predicted HR at a given in vitro metric value x ; $t_{0.975, df}$ is the 2-tailed critical value from the Student t distribution at a 95% confidence level, with df representing the df ; and $SE_{HR^{\wedge}(x)}$ is the SE of the estimated mean HR at x , derived from the variance-covariance matrix of the weighted least squares model. The upper and lower confidence limits were visualized as a shaded band around the fitted trend line for each metric. All analyses were performed using SAS (version 9.4; SAS Institute) and Python (version 3.12.12; Python Software Foundation).

Sensitivity Analysis

A sensitivity analysis was conducted in which the outcome definition was modified by removing the requirement for anticholinergic prescriptions within 60 days of initial DIP diagnosis, allowing for the assessment of potential misclassification. In a second analysis, we recalculated the in vitro metrics using pK_i values extracted exclusively from the single-source dataset reported by Sykes et al [14]. Because this recalculation affected only the pK_i -dependent metrics, the additional evaluation was performed to determine whether the observed in vitro–clinical relationships were robust to variability in pK_i data sources.

Ethical Considerations

This study was approved by the institutional review boards of Gachon University Gil Hospital (1044396-202312-HR-230-01) and Seoul National University Hospital (E-2409-042-1569). The requirement for informed consent was waived by both review boards because the study involved a retrospective analysis of fully anonymized data, and no identifiable personal information was accessed. All procedures adhered to applicable local and national regulations regarding the protection of personal information, privacy, and confidentiality. As this study involved only secondary analysis of existing anonymized data, no compensation was provided to participants. All personal information was encrypted to ensure that the individuals could not be identified, and access to the dataset was restricted to authorized investigators in accordance with institutional data governance policies.

Results

In Vitro DIP Risks

The in vitro pharmacological characteristics of APDs used to derive the 6 in vitro DIP risk metrics are summarized in Table S3 in [Multimedia Appendix 1](#), and corresponding metric values are visualized in [Figure 2](#). Haloperidol showed consistently high values across metrics, ranking first in 4 of the 6 metrics. In contrast, quetiapine exhibited the lowest overall metric values. Amisulpride ranked lower on most measures but held first place in metric 5 (D_2R $pK_i/5-HT_{2A}R$ $pK_i = 1.70$), reflecting its particularly low affinity for $5-HT_{2A}R$. Clozapine showed a mixed pattern: although it had relatively low D_2R pK_i , its BBB penetration rate—adjusted values were higher, placing it second in both metric 2 (D_2R $pK_i \times$ BBB penetration rate = 19.08) and metric 6 (D_2R $pK_i/5-HT_{2A}R$ $pK_i \times$ BBB penetration rate = 2.34). Olanzapine, risperidone, and ziprasidone generally exhibited low to intermediate levels across metrics. Aripiprazole showed high values for several metrics, ranking first in metric 3 (D_2R $pK_i=8.87$) despite its distinct partial agonist mechanism.

Figure 2. Calculated in vitro risk metrics for drug-induced parkinsonism. The intensity of the blue color represents the relative magnitude of the antipsychotic drug's metric within the same in vitro measurement. 5-HT_{2A}R: serotonin 2A receptor; BBB_{pr}: blood-brain barrier penetration rate; D₂R: dopamine D2 receptor.

	Metric 1	Metric 2	Metric 3	Metric 4	Metric 5	Metric 6
Haloperidol	8.81	33.71	2.88	11.02	1.26	4.82
Amisulpride	8.64	4.74	1.99	1.09	1.70	0.93
Clozapine	7.11	19.08	1.08	2.89	0.87	2.34
Olanzapine	8.08	17.77	1.58	3.47	0.96	2.10
Quetiapine	6.80	13.71	0.40	0.80	1.01	2.04
Risperidone	8.61	6.93	2.38	1.91	0.90	0.72
Ziprasidone	8.46	9.71	2.54	2.92	0.91	1.04
Aripiprazole	8.87	12.46	2.35	3.30	1.09	1.53

Metric 1: D₂R pK_i
 Metric 2: D₂R pK_i × BBB_{pr}
 Metric 3: D₂R pK_r
 Metric 4: D₂R pK_r × BBB_{pr}
 Metric 5: D₂R pK_i / 5-HT_{2A}R pK_i
 Metric 6: (D₂R pK_i / 5-HT_{2A}R pK_i) × BBB_{pr}

Patient Characteristics

A total of 324,449 patients who were exclusively prescribed APDs or SSRIs during outpatient visits were included in the cohort (Figure 3). After eligibility assessment, the final eligible cohort included 109,436 SSRI users and 28,945 APD users. Table 1 presents the baseline characteristics of the haloperidol cohort as a representative example, and those of the remaining cohorts are shown in Tables S4-S10 in Multimedia Appendix 1. Before matching, SSRI users were generally older, whereas APD users showed higher anticonvulsant use. After 1:1 propensity score matching, the final matched cohort included the following numbers for each drug: 575 for haloperidol, 657

for amisulpride, 1013 for clozapine, 3328 for olanzapine, 6693 for quetiapine, 5454 for risperidone, 657 for ziprasidone, and 3955 for aripiprazole. Differences in age and anticonvulsant use, along with other minor discrepancies, were substantially reduced, resulting in well-balanced matched cohorts. Standardized differences for all covariates were below 0.1 across all study cohorts. The median follow-up period was 287 (IQR 142 - 366) days across all participants, with a median of 298 (IQR 159 - 366) days in the SSRI group and 272 (IQR 131 - 364) days in the APD group. The median time to DIP was 71 (IQR 28 - 171) days for the entire dataset, 90 (IQR 39 - 194) days for the SSRI group, and 63 (IQR 23 - 157) days for the APD group.

Figure 3. Flowchart of real-world data analysis. PD: Parkinson disease.

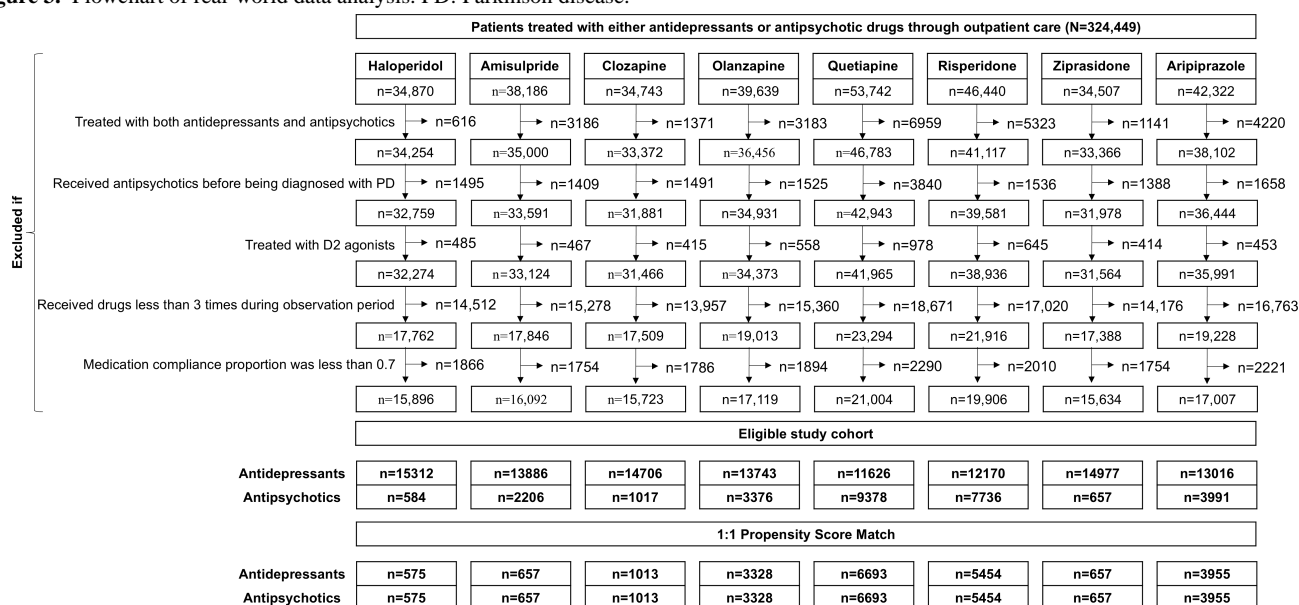


Table . Baseline characteristics of the haloperidol cohort.

Variable	Before matching			After matching		
	SSRI ^a (n=15,312)	Haloperidol (n=584)	Standardized difference	SSRI (n=575)	Haloperidol (n=575)	Standardized difference
Sex (male), n (%)	6789 (44.3)	362 (62.0)	0.3	361 (62.8)	356 (61.9)	−0.01
Age (y), mean (SD)	44.0 (20.7)	39.0 (22.7)	−0.2	41.4 (22.4)	38.6 (22.6)	−0.1
Comorbidities, n (%)						
COPD ^b	76 (0.5)	6 (1.0)	0.06	5 (0.9)	5 (0.9)	0
Dementia	1074 (7.0)	21 (3.6)	−0.1	18 (3.1)	21 (3.7)	0.02
DM ^c	695 (4.5)	38 (6.5)	0.08	33 (5.7)	33 (5.7)	0
Dyslipidemia	725 (4.7)	17 (2.9)	−0.09	21 (3.7)	17 (3.0)	−0.03
ESRD ^d	53 (0.3)	9 (1.5)	0.1	5 (0.9)	8 (1.4)	0.04
Gout	25 (0.2)	2 (0.3)	0.03	1 (0.2)	2 (0.3)	0.03
Hypertension	978 (6.4)	27 (4.6)	−0.07	27 (4.7)	26 (4.5)	−0.008
Liver disease	7 (0.0)	12 (2.1)	0.2	4 (0.7)	3 (0.5)	−0.02
Osteoarthritis	329 (2.1)	6 (1.0)	−0.09	4 (0.7)	6 (1.0)	0.03
Osteoporosis	197 (1.3)	10 (1.7)	0.03	8 (1.4)	9 (1.6)	0.01
Stroke	1412 (9.2)	47 (8.0)	−0.04	50 (8.7)	45 (7.8)	−0.03
Concurrent medications, n (%)						
ACEIs ^e and ARBs ^f	1223 (8.0)	52 (8.9)	0.03	53 (9.2)	50 (8.7)	−0.01
BBs ^g	2545 (16.6)	136 (23.3)	0.1	135 (23.5)	129 (22.4)	−0.02
CCBs ^h	1269 (8.3)	74 (12.7)	0.1	68 (11.8)	67 (11.7)	−0.005
Anticonvulsants	2084 (13.6)	138 (23.6)	0.2	153 (26.6)	138 (24.0)	−0.06
Anxiolytics	8643 (56.4)	286 (49.0)	−0.1	231 (40.2)	279 (48.5)	0.1
ESAs ⁱ	74 (0.5)	13 (2.2)	0.1	8 (1.4)	12 (2.1)	0.05
Iron	14 (0.1)	2 (0.3)	0.05	0 (0.0)	2 (0.3)	0.08
Loop diuretics	302 (2.0)	58 (9.9)	0.3	41 (7.1)	50 (8.7)	0.05
Other diuretics	743 (4.9)	72 (12.3)	0.2	57 (9.9)	63 (11.0)	0.03
Statins	1403 (9.2)	54 (9.2)	0.003	52 (9.0)	49 (8.5)	−0.01
AGIs ^j	55 (0.4)	2 (0.3)	−0.003	0 (0.0)	2 (0.3)	0.08
DPP4 ^k inhibitors	179 (1.2)	26 (4.5)	0.2	20 (3.5)	21 (3.7)	0.009
GLP-1 ^l agonists	2 (0.0)	0 (0.0)	−0.01	0 (0.0)	0 (0.0)	0
Insulin	247 (1.6)	41 (7.0)	0.2	31 (5.4)	34 (5.9)	0.02
Meglitinides	28 (0.2)	2 (0.3)	0.03	2 (0.3)	2 (0.3)	0
Metformin	441 (2.9)	34 (5.8)	0.1	29 (5.0)	30 (5.2)	0.007
SGLT2 ^m inhibitors	29 (0.2)	3 (0.5)	0.05	2 (0.3)	3 (0.5)	0.02
Sulfonylurea	291 (1.9)	19 (3.3)	0.08	15 (2.6)	16 (2.8)	0.01

^aSSRI: selective serotonin reuptake inhibitor.^bCOPD: chronic obstructive pulmonary disease.^cDM: diabetes mellitus.^dESRD: end-stage renal disease.^eACEI: angiotensin-converting enzyme inhibitor.^fARB: angiotensin II receptor blocker.

^gBB: beta-blocker.

^hCCB: calcium channel blocker.

ⁱESA: erythropoiesis-stimulating agent.

^jAGI: alpha-glucosidase inhibitor.

^kDPP4: dipeptidyl peptidase-4.

^lGLP-1: glucagonlike peptide-1.

^mSGLT2: sodium-glucose cotransporter-2.

Real-World DIP Risks

The HRs and 95% CIs for DIP across various medications are summarized in Table 2. The typical APD, haloperidol, had the highest DIP risk (HR=4.56, 95% CI 2.29 - 9.07). Among the atypical APDs, clozapine (HR=3.59, 95% CI 2.33 - 5.52), olanzapine (HR=3.53, 95% CI 2.68 - 4.66), risperidone (HR=3.16, 95% CI 2.45 - 4.06), and ziprasidone (HR=3.04,

95% CI 1.68 - 5.50) showed relatively higher risks. Lower HRs were observed with amisulpride (HR=2.36, 95% CI 1.67 - 3.34), quetiapine (HR=2.21, 95% CI 1.76 - 2.78), and aripiprazole (HR=2.11, 95% CI 1.56 - 2.86). Overall, among the medications analyzed, haloperidol exhibited the highest DIP risk, whereas aripiprazole and quetiapine were associated with the lowest risks.

Table . Hazard ratios of drug-induced parkinsonism associated with antipsychotic drugs vs selective serotonin reuptake inhibitors.

Antipsychotic drug	Hazard ratio (95% CI)
Haloperidol	4.56 (2.29 - 9.07)
Amisulpride	2.36 (1.67 - 3.34)
Clozapine	3.59 (2.33 - 5.52)
Olanzapine	3.53 (2.68 - 4.66)
Quetiapine	2.21 (1.76 - 2.78)
Risperidone	3.16 (2.45 - 4.06)
Ziprasidone	3.04 (1.68 - 5.50)
Aripiprazole	2.11 (1.56 - 2.86)

Correlation Between In Vitro and Real-World DIP Risks

Among the 6 in vitro metrics evaluated, metric 4 (D_2R $pK_r \times$ BBB penetration rate) demonstrated the strongest correlation with real-world DIP risk ($R^2=0.95$), whereas metric 5 (D_2R $pK_i/5-HT_{2A}R$ pK_i) showed the weakest correlation ($R^2=0.03$; Figure 4). Incorporating BBB penetration markedly improved the explanatory strength across all metric pairs (metric 1 vs metric 2, metric 3 vs metric 4, and metric 5 vs metric 6).

Aripiprazole, a partial D_2R agonist, deviated from the pattern observed among D_2R antagonists. When aripiprazole was included in the analysis for metric 4, the correlation coefficient decreased substantially from 0.95 to 0.58, reflecting its fundamentally different pharmacological mechanism. Across all 6 metrics, stratification by DDD suggested a trend toward higher DIP risk with increasing exposure (Figure 5). For metric 4, the stratified curves showed the clearest parallel pattern across exposure groups, although the explanatory strength declined within strata.

Figure 4. Correlation analysis of in vitro metrics with clinical risk of drug-induced parkinsonism: (A) dopamine D2 receptor (D₂R) pK_i (metric 1); (B) D₂R pK_i × blood-brain barrier penetration rate (BBB_{pr}; metric 2); (C) D₂R pK_r (metric 3); (D) D₂R pK_r × BBB_{pr} (metric 4); (E) D₂R pK_i/serotonin 2A receptor (5-HT_{2A}R) pK_i (metric 5); and (F) D₂R pK_i/5-HT_{2A}R pK_i × BBB_{pr} (metric 6). The vertical error bars represent the 95% CIs of the hazard ratios. The blue dashed line and yellow-shaded region indicate the logarithmic regression and 95% confidence band, respectively. The coefficient of determination (R^2) is shown for models calculated with and without aripiprazole (Ari). Ami: amisulpride; Clo: clozapine; Hal: haloperidol; Ola: olanzapine; Ris: risperidone; Zip: ziprasidone.

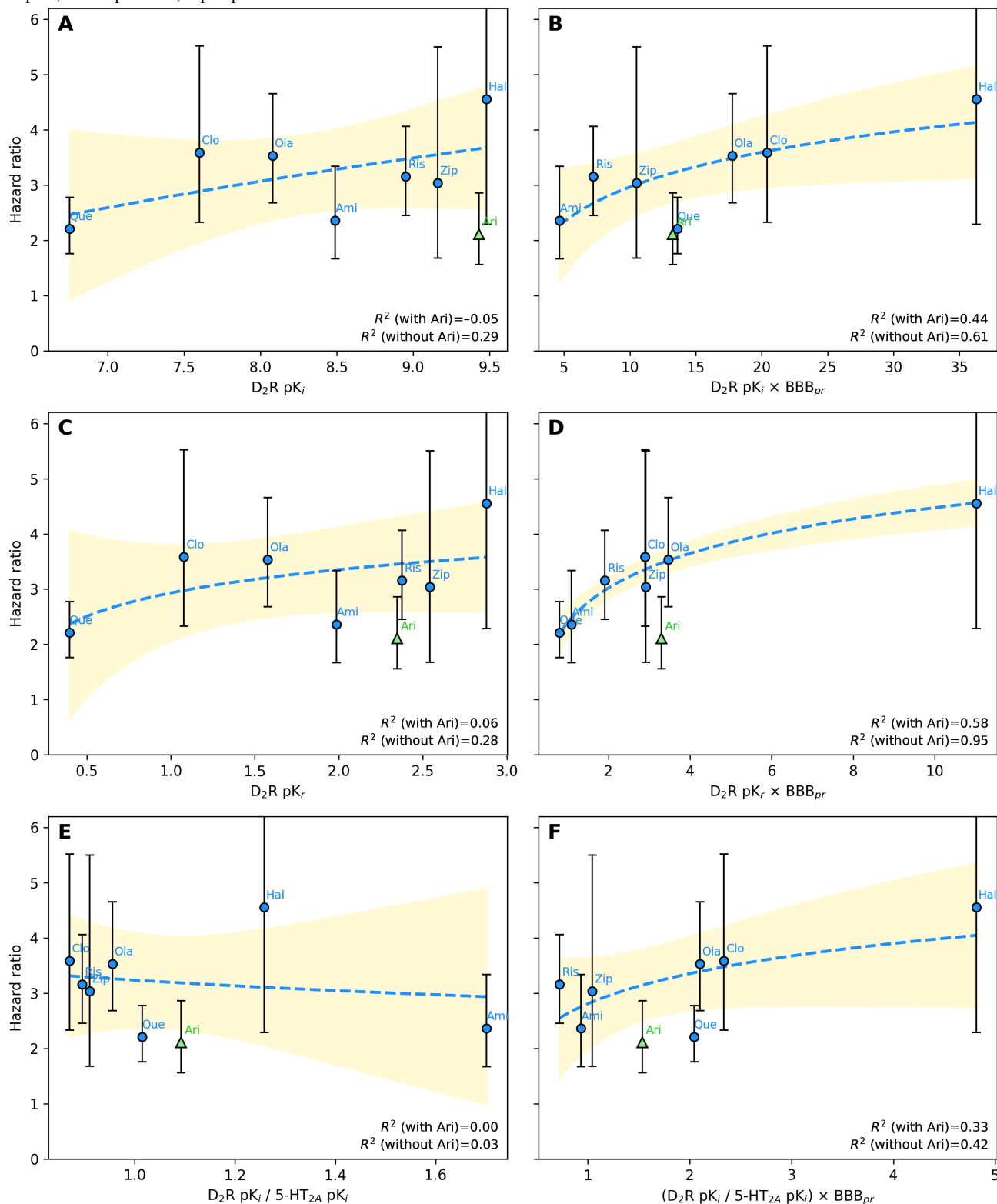
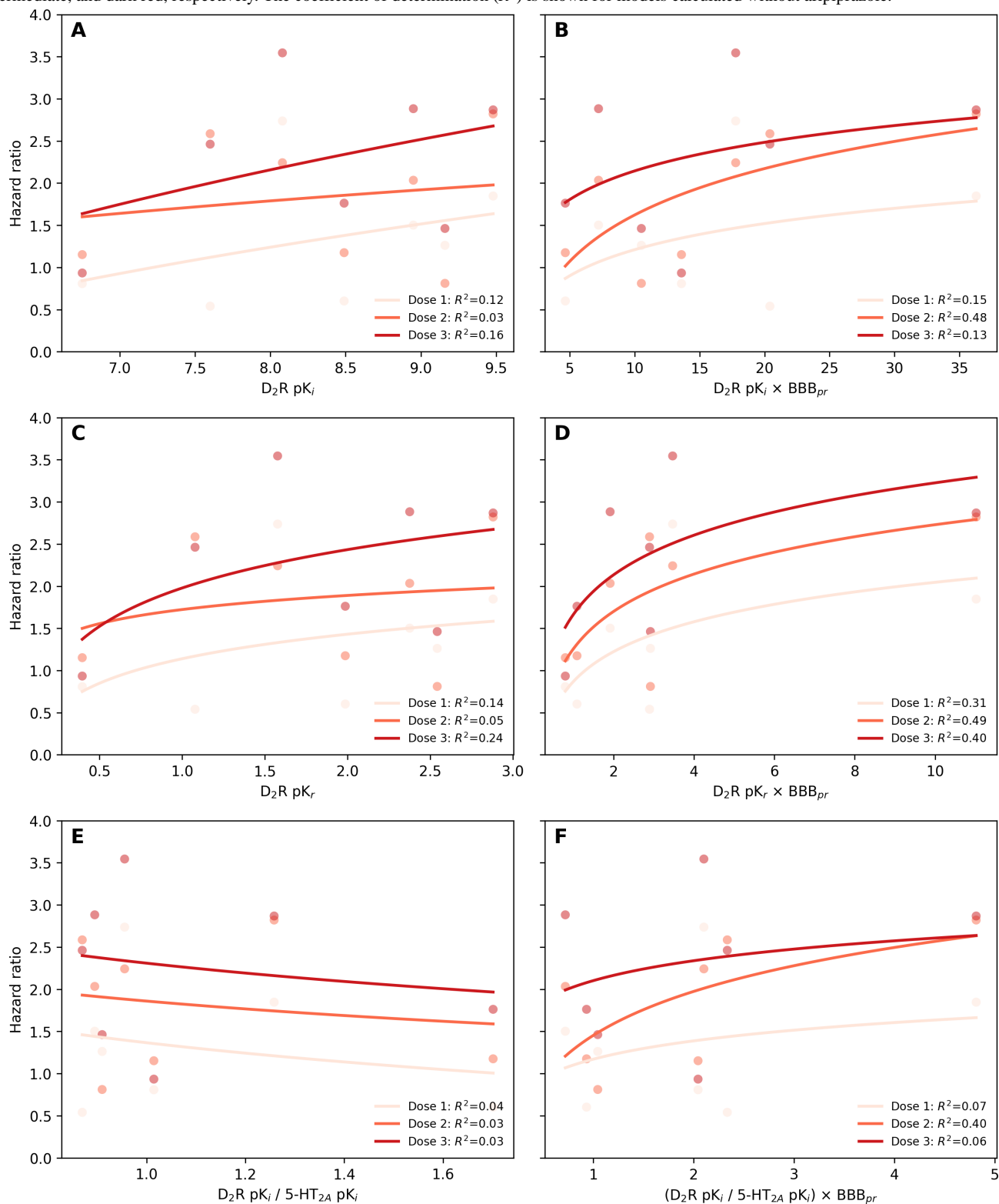


Figure 5. Dose-response analysis of in vitro metrics with clinical risk of drug-induced parkinsonism: (A) dopamine D2 receptor (D₂R) pK_i (metric 1); (B) D₂R pK_i × blood-brain barrier penetration rate (BBB_{pr}; metric 2); (C) D₂R pK_i (metric 3); (D) D₂R pK_i × BBB_{pr} (metric 4); (E) D₂R pK_i/serotonin 2A receptor (5-HT_{2A}R) pK_i (metric 5); and (F) D₂R pK_i/5-HT_{2A}R pK_i × BBB_{pr} (metric 6). Each curve represents the fitted logarithmic regression within a dose stratum. Dose 1 (<0.5 the defined daily dose [DDD]), dose 2 (0.5 - 1.5 the DDD), and dose 3 (≥1.5 the DDD) are shown in light, intermediate, and dark red, respectively. The coefficient of determination (R^2) is shown for models calculated without aripiprazole.



Sensitivity Analysis

In the sensitivity analysis using an outcome definition without anticholinergic confirmation, all overall correlation patterns were preserved, and metric 4 continued to show the strongest

correlation, with $R^2=0.83$ (Figure S1 in [Multimedia Appendix 1](#)). When the in vitro metrics were recalculated using pK_i values derived from a single-study source, the overall correlation

pattern remained similar (Table S11 in [Multimedia Appendix 1](#)).

Discussion

Principal Findings

In this study, we demonstrated that in vitro–derived DIP risk was closely related to the risk of DIP due to the use of APDs observed in real-world clinical settings. Previous studies have evaluated the inhibitory effects of APDs on D₂Rs or 5-HT_{2A}R through in vitro experiments [14,36–38]. However, such in vitro receptor affinity measures alone often fail to reliably predict the frequency of clinical adverse events such as DIP [24,25]. Conversely, RWD studies have assessed the impact of APDs on the incidence of DIP. However, most of these studies have often been limited by the evaluation of only a small subset of medications or lack of appropriate active comparator groups [30,39–43]. Consequently, numerous randomized controlled trials comparing the risk of DIP among patients taking APDs have been conducted over time, resulting in significant expenditure of time and resources [44–51]. A notable strength of this study is that it provides a comprehensive comparison of DIP risks associated with 8 commonly used APDs within a single institutional cohort using robust matching techniques to minimize confounding and demonstrating the relationship between in vitro pharmacological metrics and observed clinical outcomes. These findings suggest that integrating in vitro pharmacological data with clinical evidence may help generate hypotheses for future safety evaluation frameworks, particularly in early exploratory stages of drug development.

Consistent with previous literature, APDs significantly increased the risk of DIP compared to SSRIs, which served as active comparators [14,40,52]. Haloperidol, a typical APD, exhibited the highest DIP risks in both the in vitro metrics and the real-world analysis, aligning with its strong D₂R antagonist properties. In contrast, atypical APDs showed lower HRs, with aripiprazole exhibiting the lowest DIP risk despite its relatively high receptor affinity and kinetic parameters (pK_i , pK_r , and $pK_r \times \text{BBB penetration rate}$). Sensitivity analyses supported the robustness of the overall associations: using an outcome definition without anticholinergic confirmation yielded correlation patterns that were directionally similar, and recalculating the in vitro metrics with pK_i values derived from a single-study source produced a correlation structure comparable to that of the main analysis. Although the DDD-based stratification was exploratory, the generally increasing DIP risk across exposure levels offers qualitative support for a dose-response pattern consistent with prior pharmacological understanding of D₂R blockade [18,40]. This pattern was most apparent for metric 4, which showed a broadly similar ranking across dose strata. However, the reduced explanatory strength within strata suggests that dose-based subgrouping introduces analytic instability, likely reflecting loss of covariate balance and reduced variability after stratification. These observations indicate that, while dose may influence the in vitro–clinical relationship, larger datasets with broader dosing distributions and more detailed exposure metrics,

such as treatment duration and receptor occupancy, will be required to more robustly characterize dose-dependent effects.

Aripiprazole deviated from the general correlation pattern, presenting a lower HR than that expected from metric 4 ($D_2R \text{ } pK_r \times \text{BBB penetration rate}$), with similar discrepancies across other metrics. This divergence is most likely attributable to the unique pharmacodynamic profile of aripiprazole as a partial D₂R agonist [35]. Unlike full antagonists, aripiprazole displays intrinsic activity at the D₂Rs, enabling it to maintain a degree of dopaminergic signaling even at high receptor occupancy. A number of positron emission tomography studies have demonstrated that therapeutic doses of aripiprazole achieve high D₂R occupancy without producing corresponding extrapyramidal adverse effects, indicating that occupancy does not translate directly into functional blockade for partial agonists [53–55]. Additionally, aripiprazole exhibits functional selectivity and stabilizes D₂R signaling rather than fully suppressing it, which reduces the likelihood of inducing movement disorders despite strong binding [35]. Such pharmacological nuances highlight that future extensions of this framework may require incorporating measures of functional efficacy, such as intrinsic activity, partial agonist efficacy, or occupancy-response weighting, to more accurately model APDs whose clinical effects diverge from antagonist-based predictions.

Another key finding of this study was that K_r better reflects the DIP risks observed in clinical settings than K_i . This observation aligns with that made in a previous study by Sykes et al [14], which highlighted the importance of rebinding kinetics in DIP. Our study extends these findings by integrating BBB penetration rate, which improved the strength of the correlation across all metrics. Among the models tested, the combination of D₂R pK_r and BBB penetration rate (metric 4) showed the strongest correlation with clinical DIP risk. Notably, the correlation coefficient increased from 0.28 (pK_r alone) to 0.95 ($pK_r \times \text{BBB penetration rate}$), indicating that accounting for CNS exposure meaningfully shifted the strength of the association. Conversely, the metrics that incorporated D₂R K_i did not sufficiently reflect the variations in real-world DIP risk. Taken together, these findings suggest that CNS accessibility and rebinding kinetics capture important mechanistic features underlying observed differences among APDs.

Several studies have illustrated the relevance of incorporating BBB penetration rate into risk models. Amisulpride and risperidone, both of which have BBB penetration rate values below 1 (0.55 and 0.81, respectively), appeared below the trend line in unadjusted models, indicating a lower-than-expected DIP risk despite high in vitro receptor affinity (Figures 4A and 4C). This discrepancy is likely due to the limited BBB penetration. When BBB penetration rate–adjusted metrics were applied (Figures 4B and 4D), both drugs aligned closer to the trend line. A similar trend was observed for olanzapine and clozapine, which showed comparable HRs in the clinical data. Although olanzapine exhibited a 46% higher pK_r value than clozapine, this difference was reduced to 20% after adjusting for BBB penetration rate, suggesting that the superior BBB penetration of clozapine may compensate for its lower binding

affinity, highlighting the importance of accounting for BBB permeability in DIP risk prediction.

Limitations

Our study had several limitations. First, the in vitro indicators presented herein are aggregate estimates that are not intended for individual patient prediction. Future research could develop individualized risk prediction models that incorporate these indicators. Second, because most patients in the cohort were treated with relatively low APD doses (≤ 1.0 the DDD), dose-response characterization was inherently limited, and the relationship between the in vitro metrics and clinical risk across the full dosing spectrum remains unvalidated. Future studies encompassing a wider dosing distribution will be needed to more fully delineate dose-dependent patterns. Third, while the metrics demonstrated correlation with real-world DIP risk among D₂R antagonists, the analysis could not cover all APDs owing to insufficient prescribing frequency, and the current framework does not incorporate intrinsic efficacy, limiting its applicability to partial agonists such as aripiprazole. Therefore, expansion to additional APDs and methodological extensions that account for intrinsic efficacy will be essential for assessing generalizability. Finally, this study used a single-institution

CDM database; prescribing patterns and clinical characteristics outside this setting were not captured, and residual confounding inherent to the observational nature may remain despite rigorous propensity score matching. In addition, the identification of DIP onset, even with an enhanced operational definition, may still allow for potential misclassification. Multicenter studies will be valuable to further evaluate the generalizability of the proposed framework. Given these constraints, the findings should be interpreted as exploratory associations rather than definitive causal inferences.

Conclusions

In conclusion, this study demonstrated that combining receptor-binding kinetics with BBB penetration provides robust in vitro metrics that strongly correlate with the real-world clinical risk of DIP. These findings underscore the importance of integrating receptor kinetics and neuropharmacokinetics with real-world evidence, offering a conceptual foundation that may support more mechanistically informed approaches to future pharmacovigilance and adverse event predictions. Ultimately, such integrative methodologies may help refine early safety assessment and improve decision-making across the drug development continuum, potentially reducing the cost and duration of clinical trials.

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Data Availability

The data generated or analyzed during this study are not publicly available due to institutional restrictions but are available from the corresponding author upon reasonable request and with permission from Seoul National University Hospital.

Authors' Contributions

HYJ and YMY conceptualized, supervised the study, and served as corresponding authors. HYJ, YMY, HWL, and WTL contributed to data acquisition, analysis, and interpretation. All authors participated in drafting and critically revising the manuscript. All authors have approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Tables S1-S11 and Figure S1.

[DOC File, 671 KB - [publichealth_v12i1e81876_app1.DOC](#)]

Checklist 1

STROBE checklist.

[PDF File, 217 KB - [publichealth_v12i1e81876_app2.pdf](#)]

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Abbreviations

5-HT_{2A}R: serotonin 2A receptor

APD: antipsychotic drug

BBB: blood-brain barrier

CDM: common data model

CNS: central nervous system

D₂R: dopamine D2 receptor

DDD: defined daily dose

DIP: drug-induced parkinsonism

HR: hazard ratio

RWD: real-world data

SSRI: selective serotonin reuptake inhibitor

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Cross-Sectional Study on Oral Nicotine Product Sales Trends in Scandinavia From 2018 to 2025

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Abstract

This cross-sectional analysis of more than 19 million e-commerce orders from Sweden and Norway indicates that nicotine pouches have overtaken traditional snus in market share in both countries, reinforcing the potential of nicotine pouches as a harm reduction tool.

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KEYWORDS

Norway; Sweden; market research; sales; nicotine pouch; snus; harm reduction

Introduction

Nicotine pouches (NPs) are rapidly gaining market traction, particularly in countries with established smokeless tobacco use. They differ from snus, a widely used smokeless tobacco product in Scandinavia, in that they do not contain any tobacco leaf. Chemical analyses confirmed that NPs contain substantially fewer and lower levels of toxicants compared with snus, with toxicant profiles similar to pharmaceutical nicotine replacement therapies [1]. Nicotine is dependence forming and should not be used by vulnerable populations such as youth, pregnant women, and individuals with certain health conditions; however, for adults who choose to use nicotine, NPs are increasingly popular. The United States is the largest NP market, and emerging evidence suggests that daily NP use is most common among adults who recently quit another product and rare among people who never used nicotine [2]. This encouraging trend suggests that NPs—originally designed as a harm reduction tool [3]—are indeed displacing more harmful products. This study examines whether a similar pattern is emerging in two Nordic countries where snus has traditionally been the dominant tobacco product.

Methods

Study Design

This cross-sectional study analyzed HAYPP Group AB (Stockholm, Sweden) sales data from January 1, 2018, to September 17, 2025, on 19,528,087 purchases of snus and NPs by 1,721,752 customers from seven e-commerce websites in two countries (Sweden: snusbolaget.se, haypp.se, nettobak.se, and snusnetto.se; Norway: snuslageret.no, snushjem.no, and

snus.com). In both countries, purchases are age-verified with government-issued identification numbers that encode each customer's birth date and gender. This information is authenticated by payment service providers. After anonymization (permanently removing all identifiers), aggregated data were used to calculate volume shares by product and by gender. The number of cans of NPs or snus sold in each year was divided by the total number of cans of both products sold in each country.

Ethical Considerations

Under Swedish law (Ethical Review Act, SFS 2003:460 [4]), ethical approval is required for research involving physical intervention on humans, biological material traceable to individuals, or processing of sensitive personal data. This study analyzed fully anonymized, aggregated sales data without any personal identifiers or direct human participation. Therefore, it falls outside the scope of the Act and was not submitted for ethical review. Under the European Union (EU) General Data Protection Regulation (GDPR 2016/679 [5]), ethical approval was not required for this market research study because it used fully anonymized sales data, and no personal data or direct human participation was involved. The study complies with the International Chamber of Commerce/European Society for Opinion and Market Research (ICC/ESOMAR) International Code on Market, Opinion and Social Research, and Data Analytics [6].

All customers consented to use of their anonymized, aggregated data when reviewing and accepting the privacy policy [7]. No compensation was provided for the use of these sales data.

Results

The sales data cover 13,995,343 and 5,532,744 individual orders from 1,253,066 and 468,686 unique customers in Sweden and Norway, respectively. NPs surpassed snus in market share in 2025 in both countries (Figure 1). The Swedish NP volume share rose from 5% in 2018 to 55% in 2025, while snus declined

from 95% to 45%. In Norway, the NP share rose from 22% to 56% over the same period, with snus declining from 78% to 44%.

Women first purchased more NPs than snus in 2022 (Figure 2) due to their lower 2018 market shares of snus (~25%). Men still purchase more snus than NPs in both countries, but this could change in 2026 if trends persist.

Figure 1. Cross-sectional volume shares of the oral nicotine product markets (2018 - 2025) for nicotine pouches (NP, solid lines) and snus (dotted lines) in Sweden (left) and Norway (right).

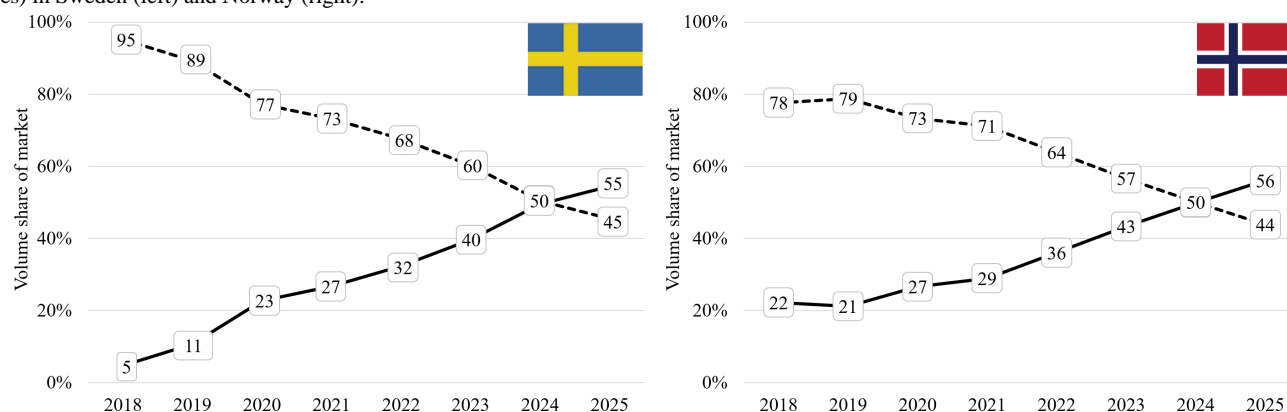
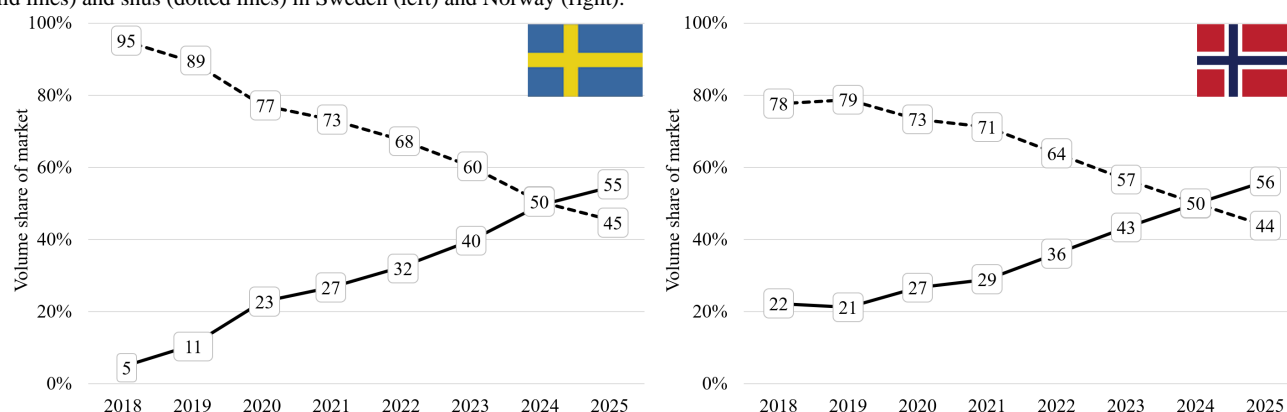


Figure 2. Cross-sectional volume shares of the oral nicotine product markets (2018 - 2025) for men (blue) and women (red) for nicotine pouches (NP, solid lines) and snus (dotted lines) in Sweden (left) and Norway (right).



Discussion

This descriptive analysis is the first cross-country comparison of NP and snus sales trends in Scandinavia. Data from more than 19 million e-commerce orders show that NPs overtook snus in the market share in Sweden and Norway in 2025, offering early evidence of market displacement in both countries. Taken together with US findings [2], these results suggest that NPs could be reshaping nicotine consumption in ways aligned with tobacco harm reduction, although ongoing monitoring and regulation will be critical to maximize benefits and minimize risks.

Although these observations do not reflect individual-level use, they highlight important shifts in consumer behavior that mirror the original “Swedish experience” where 50 years ago, men shifted from cigarettes to snus [8], and daily smoking decreased from 40% to 15% between 1976 and 2002 [9]. Over the same time frame, daily smoking rates for Swedish women dropped from 34% to 20% [9]. A similar trend materialized in Norway after low-nitrosamine snus was introduced in the 1990s, with

men moving away from cigarettes before women [10,11]. The EU banned snus in 1992, but Sweden obtained an exemption. Norway is not part of the EU. Long-term epidemiological data indicate that this shift offers a substantial harm reduction benefit, as evidenced by low incidences of tobacco-related disease in Sweden compared to the rest of the EU [12].

The US Food & Drug Administration recognizes snus as a lower-risk alternative to cigarettes, authorizing eight products with the claim: “Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis” [13]. NPs contain even fewer toxicants [1], placing them at the lowest risk end of the non-medicinal tobacco and nicotine product continuum. Maximizing public health would require encouraging switching from higher-risk products to lower-risk products such as NPs, clear regulation, youth access prevention, and efforts to support cessation among current users who would like to stop using nicotine.

A limitation of this study is its reliance on sales data from a single e-commerce company. However, these platforms account

for considerable snus and NP market shares in both countries. National surveys currently lack comparable precision. Statistisk Sentralbyrå (Norway) does not distinguish between snus and NPs, and Folkhälsomyndigheten (Sweden) only began differentiating between snus and NPs in 2022. While future surveys will provide more nuanced nationally representative

information, these market data likely offer a more accurate and timelier picture of an evolving Nordic nicotine landscape. Future research should explore user transitions across cigarettes, snus, NPs, and cessation, alongside long-term health and policy effects.

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HAYPP Group AB is an online e-commerce company that sells non-combustible nicotine products and is the sponsor of this research. The Group operates independently and is not under the ownership or control of any tobacco or nicotine manufacturers.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: MAM, LR

Data curation: DH

Formal analysis: DH

Investigation: DH, MAM

Supervision: MAM

Validation: LR

Visualization: LR

Writing – original draft: LR

Writing – review & editing: LR, DH, MAM

Conflicts of Interest

MAM declares employment from HAYPP Limited, a subsidiary of HAYPP Group AB; non-financial support from UK Vaping Industry Association, for which she serves as a Director; and owns stock in HAYPP and British American Tobacco. DH and LR declare employment from Snusbolaget AB, a subsidiary of HAYPP Group AB.

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Abbreviations

EU: European Union

NP: nicotine pouch

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Research Letter

Intersecting Sex Work and Substance Use Risk Among Sexual and Gender Minoritized Individuals Recruited Online in San Francisco, California: Survey Results

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Abstract

This research letter examines sex work and substance use associations in a sample of sexual and gender minoritized individuals recruited online in San Francisco, California. This study found that a history of sex work was prevalent and that people with a history of sex work were more likely to recently report using controlled substances and experience domestic violence.

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KEYWORDS

sex work; substance use; domestic violence; intimate partner violence; online recruitment; sexual and gender minoritized community health; social media

Introduction

Sexual and gender minoritized (SGM) communities experience victimization because of structural oppression [1]. The confluence of social exclusion, economic hardship, and the internet supports the formation of a sex work economy [2,3]. People in sex work experience health inequities due to their unique occupational health exposures [4]. Yet there is little research on online help-seeking SGM populations [5]. We address this gap and characterize the prevalence of sex work history among SGM individuals seeking help online and their sexual and substance use-related prevention and treatment needs.

Methods

Ethical Considerations

The study was approved by the University of California, San Francisco institutional review board (20-33169). Participants provided informed consent, could opt out anytime, and received

US \$30. Data were deidentified to protect participants' privacy and confidentiality.

Study Design and Recruitment

This is a cross-sectional analysis of 409 people recruited online in San Francisco by using social medial advertisements on Facebook, Instagram, and Grindr in 2022-2024. Advertisements sought out potential participants seeking help for substance use, mental health, and HIV. Once they clicked on the advertisement and were directed to a study interest website, they were contacted by staff to screen for eligibility, informed consent was obtained electronically, and they completed a baseline assessment. Eligibility criteria included aged 18 years or older, seeking help for substance use prevention/treatment or related health topics (eg, HIV, mental health), live in San Francisco, identify as a man who had sex with men or a trans woman, and had smartphone access.

Measures and Analysis

We analyzed the following demographics: age, race/ethnicity, gender identity, sexual orientation, HIV status, housing stability,

and socioeconomic status. Recent substance use was measured by asking how many days in the last 30 days, if any, did they use each of the following substances: tobacco, vaping products, binge drinking (having 5 or more alcoholic beverages at the same time or within a couple of hours of each other for people assigned male sex at birth), marijuana, prescription opioids, nonprescription opioids, other prescription drugs, illicit drugs (crack/cocaine, amphetamine/methamphetamine, hallucinogens, inhalants), and injection drug use [6]. Responses were recoded dichotomously for any recent use (yes/no). We measured participants' history of sex work if they had ever had sex with someone in exchange for money, drugs, or shelter (yes/no) [6]. We assessed participants' risk perception of harm when engaging in condomless sex and sex while using drugs or alcohol. Responses were dichotomized into low risk (no risk, slight risk, unknown risk) and high risk (moderate risk, great risk). Self-efficacy to refuse condomless sex was assessed by participants' agreement with the statement, "I could refuse if someone wanted to have sex without a condom or dental dam" [6]. Responses were dichotomized into agree (strongly agree, agree) and disagree (disagree, strongly disagree). Domestic

violence was measured by asking participants if anyone with whom they had an intimate relationship had emotionally, physically, or sexually abused them in the last 3 months (yes/no) [6]. STATA version 17 was used to create logistic regression models to test associations between history of sex work and recent substance use and sexual risk outcomes, adjusted for age, gender identity, race/ethnicity, socioeconomic status, and housing stability.

Results

Many participants (168/409, 41.08%) reported a history of sex work. The most frequently reported in the last 30 days was illicit drugs (227/409, 55.50%) followed by marijuana (220/409, 53.79%), binge drinking (160/409, 39.12%), and tobacco (155/409, 37.90%). A majority of participants perceived condomless sex (287/409, 70.17%) and sex while using drugs or alcohol (349/409, 85.33%) as high risk and could refuse condomless sex (361/409, 88.26%). Almost 22.98% (94/409) had experienced domestic violence in the last 3 months (Table 1).

Table 1. Sample characteristics, recent substance use, sexual risk perception, and self-efficacy to refuse condomless sex and behaviors among sexual and gender minoritized people recruited online in San Francisco, California, 2022-2024 (N=409).

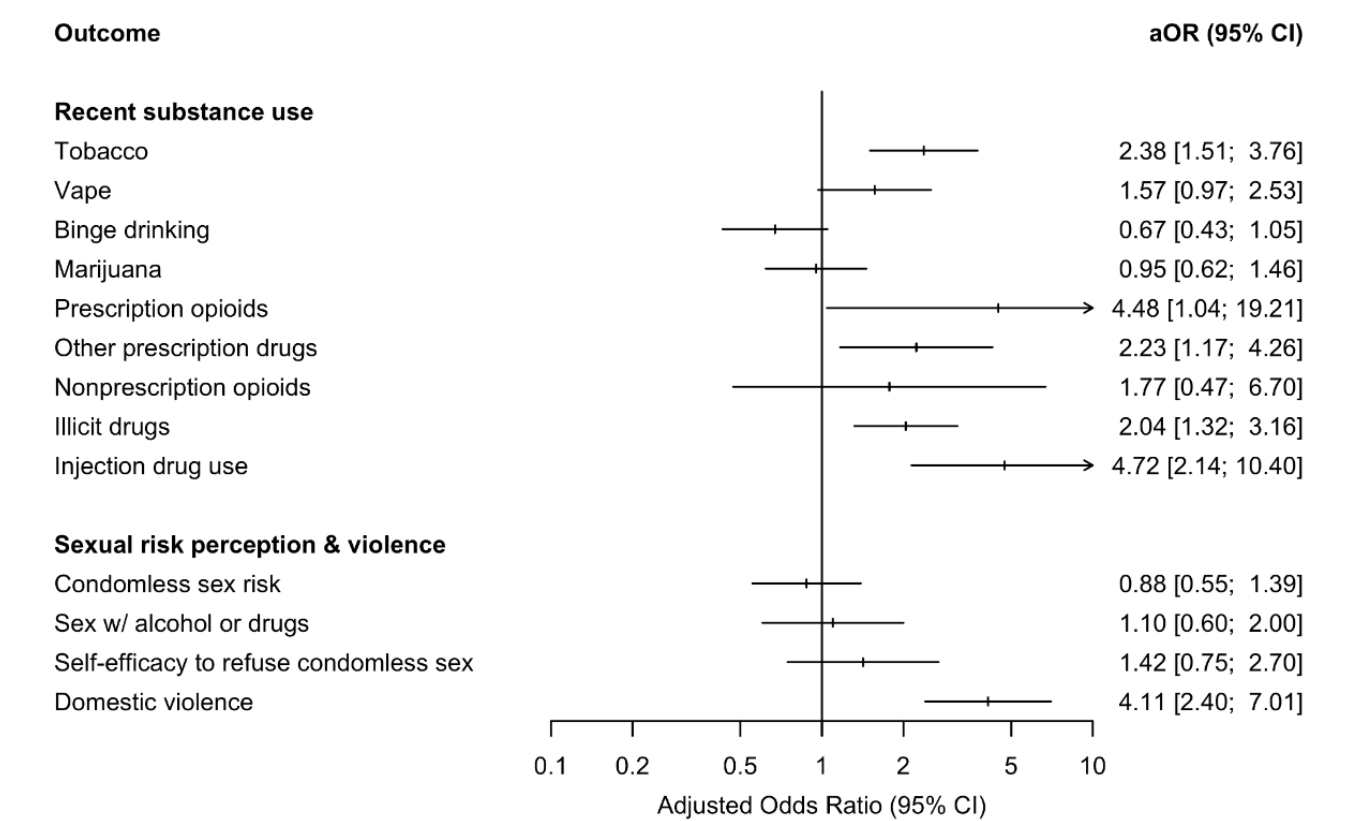
	Overall (N=409), n (%)	Sex work status	
		Yes (n=168), n (%)	No (n=241), n (%)
Demographics			
Age (y)			
18-29	103 (25.18)	31 (18.45)	72 (29.88)
30-39	112 (27.38)	54 (32.14)	58 (24.07)
40-49	77 (18.83)	34 (20.24)	43 (17.84)
50+	117 (28.61)	49 (29.17)	68 (28.22)
Race/ethnicity			
White	169 (41.32)	71 (42.26)	98 (40.66)
Latino/a/x/e	113 (27.63)	51 (30.36)	62 (25.73)
Asian, Pacific Islander, and Native Hawaiian	50 (12.22)	13 (7.74)	37 (15.35)
Black	38 (9.29)	16 (9.52)	22 (9.13)
More than one or other	39 (9.54)	17 (10.12)	22 (9.13)
Gender identity			
Cisgender man	327 (79.95)	123 (73.21)	204 (84.65)
Transgender woman or gender expansive	82 (20.05)	45 (26.79)	37 (15.35)
Sexual orientation			
Bisexual	47 (11.49)	22 (13.10)	25 (10.37)
Gay/lesbian	282 (68.95)	105 (62.50)	177 (73.44)
Other	48 (11.74)	22 (13.10)	26 (10.79)
Straight/heterosexual	32 (7.82)	19 (11.31)	13 (5.39)
HIV status			
Not a person with HIV	278 (67.97)	96 (57.14)	182 (75.52)
Person with HIV	131 (32.03)	72 (42.86)	59 (24.48)
Housing stability			
Stable	337 (82.40)	123 (73.21)	214 (88.80)
Unstable	72 (17.60)	45 (26.79)	27 (11.20)
Socioeconomic status			
Above federal poverty line	338 (82.64)	124 (73.81)	214 (88.80)
Below federal poverty line	71 (17.36)	44 (26.19)	27 (11.20)
Recent substance use (last 30 days)			
Used tobacco			
No	254 (62.10)	81 (48.21)	173 (71.78)
Yes	155 (37.90)	87 (51.79)	68 (28.22)
Used vaping products			
No	288 (70.42)	109 (64.88)	179 (74.27)
Yes	121 (29.58)	59 (35.12)	62 (25.73)
Binge drinking			
No	249 (60.88)	116 (69.05)	133 (55.19)
Yes	160 (39.12)	52 (30.95)	108 (44.81)
Used marijuana			

	Overall (N=409), n (%)	Sex work status	
		Yes (n=168), n (%)	No (n=241), n (%)
No	189 (46.21)	77 (45.83)	112 (46.47)
Yes	220 (53.79)	91 (54.17)	129 (53.53)
Used prescription opioid drugs			
No	398 (97.31)	160 (95.24)	238 (98.76)
Yes	11 (2.69)	8 (4.76)	3 (1.24)
Used nonprescription opioid drugs			
No	396 (96.82)	159 (94.64)	237 (98.34)
Yes	13 (3.18)	9 (5.36)	4 (1.66)
Used other prescription drugs			
No	361 (88.26)	141 (83.93)	220 (91.29)
Yes	48 (11.74)	27 (16.07)	21 (8.71)
Used illicit drugs			
No	182 (44.50)	56 (33.33)	126 (52.28)
Yes	227 (55.50)	112 (66.67)	115 (47.72)
Injected drugs			
No	366 (89.49)	135 (80.36)	231 (95.85)
Yes	43 (10.51)	33 (19.64)	10 (4.15)
Sexual risk perception, efficacy and behaviors			
Condomless sex			
High risk	287 (70.17)	122 (72.62)	165 (68.46)
Low risk	122 (29.83)	46 (27.38)	76 (31.54)
Sex while using drugs or alcohol			
High risk	349 (85.33)	142 (84.52)	207 (85.89)
Low risk	60 (14.67)	26 (15.48)	34 (14.11)
Self-efficacy to refuse condomless sex			
Disagree	48 (11.74)	25 (14.88)	23 (9.54)
Agree	361 (88.26)	143 (85.12)	218 (90.46)
Domestic violence (past 3 months)			
No	315 (77.02)	102 (60.71)	213 (88.38)
Yes	94 (22.98)	66 (39.29)	28 (11.62)

Adjusting for potential confounders, people with a history of sex work (Figure 1) were more likely to report using tobacco (adjusted odds ratio [aOR] 2.38, 95% CI 1.51-3.76), prescription opioid drugs (aOR 4.48, 95% CI 1.04-19.21), other prescription drugs (aOR 2.23, 95% CI 1.17-4.26), illicit drugs (aOR 2.04, 95% CI 1.32-3.16), and have injected drugs (aOR 4.72, 95%

CI 2.14-10.40) compared to people with no sex work history. People with a history of sex work had 4.11 times the odds of experiencing domestic violence recently compared to counterparts with no sex work history (95% CI 2.40-7.01). No statistically significant association was observed between history of sex work and self-efficacy to refuse condomless sex.

Figure 1. Associations between history of sex work and recent substance use and between sexual risk perception and violence among sexual and gender minoritized people recruited online in San Francisco, California, 2022-2024 (N=409). aOR: adjusted odds ratio.



Discussion

We found that SGM participants with a history of sex work were more likely to report recent use of controlled substances. Although no statistically significant associations exist between history of sex work and sexual risk perception level and self-efficacy to refuse condom use, our findings indicate that domestic violence may be heightened for SGM people with a history of sex work. SGM populations report similar or greater rates of domestic or intimate partner violence compared to their non-SGM counterparts [7], and intimate partner violence is a common experience among people who engage in sex work [8]. Relationship dynamics among SGM partnerships can vary in composition with relationship to sexual and gender roles, power, and how violence is enacted and experienced. A recent systematic literature review found that bidirectional violence

was the most common among SGM intimate partners compared to non-SGM partners [9]. The interplay between substance use, violence, and trauma are complex and must be explored in future [10]. This study has limited generalizability because of its design and possible sampling bias toward people seeking help online who may be experiencing heightened risk. Despite this, these findings reinforce the need for substance use prevention efforts to serve people with a history of sex work and address domestic violence as a unique violence exposure. Although stigma remains a significant barrier for people engaged in sex work and those using substances, addressing domestic violence may offer a whole-person alternative to intervene on the material impacts of violence and substance use behaviors that may be both enabling and coping mechanisms of violence. Public health interventions that cross-train substance use providers about domestic violence and sex work literacy, and conversely, are needed to better facilitate screening, referral, and treatment.

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Data Availability

The datasets generated or analyzed during this study are not publicly available as they contain details that could be used to identify participants but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

aOR: adjusted odds ratio

SGM: sexual and gender minoritized

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