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Short Communication

An analysis of the level of evidence behind treatments recommended by the Danish Medicines Council

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ABSTRACT

Objectives: We aimed to investigate the quality of evidence and the expected added clinical value of treatments recommended by the Danish Medicines Council (DMC).
Study design: This was an observational study.
Methods: The DMC prepares reports on drugs considered for possible new standard treatments in Danish hospitals. These reports evaluate the available evidence on efficacy and safety. The quality of evidence is systematically rated by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) criteria, and estimates of added clinical value are presented. The recommendations take into account expected economic implications of new treatments. The publicly available reports up until December 29, 2021, were downloaded from the DMC Web page. Reports on drugs marked "recommended" were included. Data on quality of evidence, expected clinical value, and economic implications were imputed in a Microsoft Excel spreadsheet.
Results: Seventy-nine reports were included in the analysis. In 79% of these, the quality of evidence was rated low (24%) or very low (55%), whereas no recommendations were based on evidence rated as high quality. Three (5%) of recommended treatments were expected to add large clinical value.
Conclusions: Most recommendations by the DMC are based on evidence formally rated as low or very low quality by GRADE, and no recommendations were based on evidence rated as high quality. The added clinical value of the treatments was often not documented and rarely large. Continued attention to improve the clinical evidence behind national recommendations is necessary.

Introduction

The Danish Medicines Council (DMC) is an institution created by the Danish Regions in 2017, succeeding two establishments known as KRIS (The Coordinating Council for Implementation of Hospital Medicines) and RADS (The Council for Utilization of Expensive Hospital Medicines). The DMC prepares detailed reports evaluating and recommending drugs as possible new standard treatments in Danish hospitals based on data regarding efficacy, safety, and price from a systematic assessment of the scientific evidence and health-economic evaluations. It is an independent council comprising three units, one of which is composed of specialist committees working on the evaluations of treatments in their respective specialist area.

The council assesses whether or not there is a reasonable relationship between the clinical value and the costs of treatment with the specific drug.[1–3]

Methods applied by the DMC include a framework developed by the German Institute for Quality and Efficiency In Healthcare (IQWiG),[2,4] and these, along with the overall purpose and organization of the council, are comparable to those of the National Institute for Health and Care Excellence of the United Kingdom.

Since its establishment in 2017, all new treatments approved by the Danish Medicines Agency or European Medicines Agency (EMA) may be evaluated by the DMC. Manufacturers can apply for their drug to be evaluated by the DMC, and, in later years, the DMC can commence evaluations of treatments on its own initiative or as enquired by the Danish Regions.

The DMC recommendations for standard treatments are not legally binding, and implementation of recommended treatments is the responsibility of the individual regions, as these are the governing organs of the hospitals in Denmark.[2]

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The aim of this paper was to investigate the formal quality of evidence and the expected added clinical value of the treatments recommended by the DMC.

Methods

All treatments evaluated by the DMC are published as assessment reports on the DMC Web page.[1] We used this Web page to locate treatments evaluated from the establishment of the DMC on January 1, 2017, up until December 29, 2021. We included all treatments marked "Recommended."

The DMC applies the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for assessing the quality of evidence when evaluating drugs for recommendation. This approach operates with four levels of evidence: high, moderate, low, and very low.

The DMC evaluates added clinical value of an evaluated drug by comparison with a relevant comparator, that is, existing treatment options. Added clinical value is graded as negative, not documented, small, moderate, or large.[2,5]

Incremental costs and budget consequences included in the assessment reports are based on calculations from Amgros, a cross-regional institution responsible for negotiations with the pharmaceutical industry on behalf of the Danish health system.[6]

We downloaded assessment reports and supplements and imputed the abovementioned variables in a Microsoft Excel spreadsheet. The results are presented as absolute numbers and percentages, whereas monetary values were expressed as medians and ranges. The latter were converted from DKK to EUR using a conversion factor of 1 EUR = 7.44 DKK.

Results

As of December 29, 2021, the DMC had evaluated 158 treatments, of which 79 were recommended.

Not all variables were available for all approved treatments. Data on quality of evidence were available for 67 (85%) of the treatments, on added clinical value for 66 (84%) treatments, on incremental costs for 55 (70%) treatments, and on budget consequences in the fifth year for 65 (82%) treatments.

The quality of evidence and the added clinical value of evaluated treatments were rated as shown in Table 1.

The median incremental price per patient per year ($n = 55$) was 28,763 (range −893,817 to 2,728,494) EUR. The median budget consequences in the fifth year ($n = 65$) were 725,806 (range −10,793,010 to 40,591,397) EUR.

For treatments with very-low-quality evidence ($n = 37$), the median incremental price per patient was 28,763 (range −893,817 to 702,016) EUR, and the median budget consequences were 509,191 (range 8,736,559 to 14,784,946) EUR.

For treatments that had no documented added clinical value ($n = 12$), the median incremental price per patient was −20 (range −21,927 to 20,565) EUR, and the median budget consequences were 0 (range −5,510,753 to 577,957) EUR. Negative amounts represent a net saving.

Discussion

In this study of the treatments recommended by the DMC and the corresponding evidence ratings, we found that a large proportion (79%) of the ratings of the evidence were very low or low. High-quality evidence is important to ensure high-quality treatments and high levels of patient safety, and from a societal and economic perspective, high-quality evidence is also important to ensure that high expenses are matched by the benefit provided to health care and to patients. Theoretically, and in extreme cases, treatment recommendations based on very-low-quality evidence may impair health care and treatments for individual patients. However, we do not consider this to be likely for treatments recommended by the DMC. The evidence is rated according to GRADE[7] by the DMC in which criteria in five separate domains are applied to assess the quality of evidence. Briefly, these are applied to predefined measures of effect, and the overall rating of the quality of evidence is determined by the measure of effect for which the evidence is rated the lowest.[2] As such, the ratings may be considered excessively conservative. Even then, the generally poor level of evidence does provide the basis for continued attention to improve the clinical evidence for national healthcare recommendations.

We found that only few treatments recommended by the DMC are expected to add a large clinical value, while the added clinical value of many treatments is not documented (18%) or small (18%). The assessment of expected added clinical value is based on the framework developed by the IQWIG, specifying thresholds for relative effects to quantify clinical implications of healthcare initiatives.[4] The framework is applied by the DMC in the shape of a somewhat intricate algorithm, which also involves weighting various outcomes according to importance.[2] These assessments are therefore not easily interpreted or translated into the specific clinical context of each treatment evaluated. At the same time, the use of this framework can be viewed as both rational and comprehensive, as it considers both relative and absolute factors and considers quantitative and qualitative measures. An important reflection in this context is the extent to which a new treatment must add clinical value. In a highly developed welfare society, the public and policy makers may want only the best options available, meaning that even the most minor added clinical value can be important.

We have not been able to locate publications regarding the quality of evidence behind national treatment guidelines or drug recommendations, and few studies have evaluated the quality of evidence behind drug marketing approvals. Mitra-Majumdar et al in 2022 published a study on the evidence behind drug approvals by the Food and Drug Administration. No formal grading of evidence was performed, but they found that new drug approvals were increasingly supported by smaller numbers of trials with fewer features of trial robustness compared with past approvals. A few key findings were that almost half of the pivotal trials used surrogate measures as primary end points, and only 20% used an active comparator.[8] The same group of researchers also published a systematic review, which confirmed the trend toward more frequent use of surrogate measures and less frequent use of randomization, double-blinding and active comparators in Food and Drug Administration drug approvals, which can be seen as a

Table 1
Recommended treatments with each level of evidence and each level of expected added clinical value.

Quality of evidence (n = 67)	Very low	Low	Moderate	High	NA
Number of treatments (%)	37 (55)	16 (24)	11 (16)	0 (0)	3 (4)

Added clinical value (n = 66)	Negative	Not documented	Small	Moderate	Large	Unknown added value	NA
Number of treatments (%)	0 (0)	12 (18)	12 (18)	17 (26)	3 (5)	6 (9)	16 (24)

sign of increasing flexibility in drug approval.[9] A study from 2017 evaluated the evidence of benefits in overall survival and quality of life for cancer drugs approved by EMA from 2009 to 2013. They found that most of these drugs did not have evidence of survival or quality of life benefits when approved by the EMA.[10] The findings of these studies correspond well to our findings for treatment recommendations by the DMC. We have not identified similar publications from a Scandinavian or Danish context.

Regarding the economic part of this study, the costs and savings estimated and reported are subject to large variations and inherent uncertainties, and typically, several sets of assumptions are made to present different estimations. Such assumptions are explicitly stated in the economic evaluation reports. In the context of this study, they should be viewed merely as a reference range for the economic implications of the recommendations made by the DMC. The economic analysis of the DMC is performed according to a Standard Operating Procedure as a cost-utility analysis. The results are presented as incremental cost-effectiveness ratio to inform the DMC on the final decision whether to recommend a specific drug for standard treatment. The DMC can decide that societal costs are prohibitive measured against the risk-benefit ratio. In case of dismissal, such drugs deemed "too expensive" may still be used in Denmark on an individual patient basis pending explicit authorization from the regional healthcare authorities.[11] The direct costs of drugs found in the recommendations may differ from the actual amounts, as these are based on official pricing by the manufacturer. The actual direct drug price is typically confidentially negotiated between Amgros and the manufacturers and not publicly available.

The average costs were slightly lower for the treatments recommended based on lower quality evidence, but due to the abovementioned limitations, this should be interpreted with caution. For treatments with no expected added clinical value, the budget consequences were generally smaller, and for half of these treatments, savings were expected, which is rational, as these treatments may indeed be recommended due to lower or comparable costs.

The main strength of this study is the complete access to assessments of all treatments recommended by the DMC from 2017 up until the end of 2021. These evaluations are made according to well-established methodology regarding the assessment of evidence quality and estimation of added clinical value.

The limitations of this study include some inconsistency in the reporting of different outcomes among the recommendations and the lack of some variables for some treatments. The economic variables of the present study must be assumed to be subject to considerable uncertainty.

In conclusion, the formal quality of evidence for most treatments recommended by the DMC, as assessed through GRADE criteria, is low or very low, and no recommendations were based on evidence rated as high quality.

The added clinical value of the treatments was often not documented and rarely large. This study provides incentive for continued attention to improve the clinical evidence upon which national recommendations are based.

Author statements

Competing interests

The authors declare no conflicts of interest. M.R.H. is currently employed by Novo Nordisk and holds shares in Novo Nordisk; at study initiation and planning and during data collection, he was employed by Odense University Hospital and not affiliated with Novo Nordisk. Novo Nordisk as an organization has not been involved in the present study, and no grants have been received by any author from or other companies.

Ethical approval

No ethical approval was required for this study.

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Original Research

Association between traumatic life events and vaccine hesitancy: A cross-sectional Australian study

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A B S T R A C T

Objectives: We sought to identify associations between the experience of traumatic life events and vaccination intention to inform whether trauma-affected individuals require targeted interventions when addressing vaccine hesitancy.
Study design: We conducted an online cross-sectional survey to identify whether direct or indirect exposure to various traumatic life events and the presence of post-traumatic stress disorder (PTSD) symptoms are associated with willingness to receive a COVID-19 vaccine in an Australian sample.
Methods: A national online questionnaire was administered to a representative sample of 1050 Australian adults in September 2021.
Results: Lower willingness to receive a COVID-19 vaccine was associated with direct experience of a fire or explosion (adjusted odds ratio [aOR]: 0.42; 95% confidence interval [CI]: 0.23–0.78; $P = 0.006$), direct experience of severe human suffering (aOR:0.39; 95% CI: 0.21–0.71; $P = 0.002$) and screening positive for PTSD symptoms (aOR:0.52; 95% CI: 0.33–0.82; $P = 0.005$). Conversely, higher willingness to receive a COVID-19 vaccine was associated with indirect exposure to severe human suffering (aOR: 2.0; 95% CI: 1.21–3.22; $P = 0.007$).
Conclusions: Our findings suggest that the experience of traumatic events and the presence of PTSD symptoms can contribute to vaccination decisions. Our work adds to the growing recognition of the need to effectively mediate the influence of traumatic experiences on encounters within the medical setting and supports the importance of addressing the needs of trauma-affected individuals in their vaccination experiences.

Introduction

Immunisation programmes rely on high vaccine uptake to be successful[1,2] not only for the sake of individual protection from vaccine-preventable diseases (VPDs) but also for the purpose of preventing transmission across the wider community.[3] While vaccination behaviour reflects a continuum of attitudes ranging from complete acceptance to outright refusal,[4,5] vaccine-hesitant individuals sit between these polarities. They may be opposed to vaccination or accept some vaccines over others, or plan to delay them, all the while being conflicted about their vaccination decisions.[4,6,7] Accordingly, vaccine hesitancy is a motivational state that encompasses intention and willingness to receive a vaccine.[8]

Despite their global prevalence and potential to influence decision-making, traumatic past experiences have been overlooked as a contributor to vaccine hesitancy. Most individuals will experience a traumatic event at some point in their lives,[9,10] and a smaller group who experience trauma will go on to develop post-traumatic stress disorder (PTSD), a psychiatric condition that may follow a traumatic event characterised by the experience of (1) intrusion symptoms such as flashbacks or nightmares of the traumatic event, (2) avoidance of reminders of the traumatic event, (3) cognitive and mood disturbances and (4) increased arousal or reactivity.[11] PTSD can have profound consequences for daily functioning and decision-making.[11] Perceptions and consequences of traumatic events are affected by alterations in threat appraisal.[12] People who have experienced trauma may overestimate the level of threat in day-to-day

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situations.[12] Similarly, threat assessments of VPDs influence vaccination decisions.[13,14]

While salient past experiences influence perceptions of vaccination,[15–17] the small body of literature regarding traumatic events, PTSD and vaccination decisions is mixed. While one study found no association between trauma history, PTSD symptoms and vaccine hesitancy,[18] other studies have found that decreased vaccine acceptance is associated with childhood trauma,[19,20] sexual abuse,[20] intimate partner violence[21] and PTSD history.[22] These studies were conducted in different contexts and with varying population groups, but there has yet to be a study within the Australian context. In this article, we investigate the relationship between trauma exposure, PTSD symptoms and willingness to receive a vaccine within a nationally representative Australian sample. We hypothesise that direct exposure to trauma will be associated with decreased vaccine willingness. Given that threat appraisal mechanisms are altered by direct exposure to a traumatic event, we hypothesise that direct vs indirect exposure to traumatic life events will differ in their associations with willingness to receive a COVID-19 vaccine. Accordingly, we also hypothesise that current PTSD symptoms will be associated with decreased vaccine willingness. Given the limited research on the topic, our aim is to quantify the prevalence of trauma types and their associations with vaccination decisions to inform whether affected individuals require targeted interventions when addressing vaccine hesitancy.

Methods

We conducted a quantitative, self-administered online questionnaire.

Survey development

In addition to demographic questions, the questionnaire comprised measures of (1) exposure to various traumatic events, (2) PTSD symptoms and (3) willingness to receive a COVID-19 vaccine. Exposure to traumatic events was primarily measured using the Life Events Checklist 5 (LEC-5) standard self-report.[23] This tool is designed to screen for exposure to 16 distressing life events that may result in PTSD. It also includes an additional item that assesses any significant event not captured by the 16 items. The LEC demonstrates satisfactory psychometric properties as an assessment of trauma exposure, including convergent validity with established trauma history measures.[24] The LEC-5 provided two measures of exposure for each distressing event: (1) direct exposure (event experienced by the individual directly) and (2) indirect exposure (the event was witnessed, learned about or part of someone's job).

We also added four exposure items based on a small but growing body of research, suggesting that negative experiences within the healthcare setting and previous vaccination procedures can influence vaccination decisions.[15,16,25–27] These questions asked whether participants were exposed to a particularly distressing medical procedure, negative interaction with a healthcare worker, negative vaccination experience or adverse event following vaccination (response options were identical to the LEC-5). These four items were chosen to represent potentially distressing procedural and social aspects of the medical setting, as well as potentially distressing events during and following vaccination.

We also used the CAIR Pandemic Impact Questionnaire[28] to measure exposure to pandemic-related stress. We used the exposure subscale of the CAIR Pandemic Impact Questionnaire to measure direct and indirect exposure to COVID-19 pandemic—related stressors. This subscale consisted of eight items that measure exposure to potential stressors (in the past 2 weeks) that directly result from the COVID-19 pandemic (e.g. losing a job or income or negative impacts on relationships). Response options for each item were ‘yes’ or ‘no’. Scores for direct exposure (‘happened to me’) and indirect exposure (‘happened to someone close to me’) were calculated by adding the ‘yes’ responses for each item. A score of 4 or more constituted moderate/high exposure to pandemic-related stress, whereas a score less than 4 was considered no/low pandemic-related stress.

Current PTSD symptoms were measured using the Post-traumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Short Form (PLC-5-SF). This is a 4-item, short-form version of the Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,[29] which generates measures that closely parallel the full-scale tool, making it appropriate for PTSD screening purposes.[30] Each item of the PCL-5-SF represents a type of symptom required for a PTSD diagnosis experienced within the last week (i.e. intrusion, avoidance, cognitive/mood alterations, hyperarousal). Participants screened positive for PTSD symptoms if they indicated moderate or high experience of all four measures.

The outcome measure, willingness to receive COVID-19 vaccine (for self), was measured with the question “How willing are you to get a COVID-19 vaccine? Would you say” and had four response options (not at all willing, a little willing, moderately willing and very willing). This item was taken from an early version of the World Health Organization's Behavioural and Social Drivers of Vaccination survey, intended to measure the extent of motivation to receive a vaccine.[8,31]

Study population and sample size

Australian adults aged >18 years who were eligible to receive a COVID-19 vaccine were eligible to participate in the survey. The sample size was determined using the most current national PTSD statistics, which find that prevalence in Australia is 12%.[32] A target sample of 734 was calculated to provide a 95% confidence interval (CI) within 10% of the point estimate. However, oversampling and the addition of data from pilot surveys resulted in a larger sample than targeted ($n = 1050$).

Participant recruitment

Recruitment of participants was outsourced to a national online fieldwork provider.[33] Their panel is by invitation only and derived primarily from offline sources. It is also frequently matched and compared with the Australian Bureau of Statistics and Census to ensure the best representation of Australian population. Sampling was Census stratified based on age, gender and location by state. Recruitment took place between 9 September and 22 September 2021. Eligible participants were invited to participate via email, which contained a link to the online survey. Regular sampling intervals were used throughout the study period, and regular reminders were used to give all respondents an equal chance to participate. Respondents received a modest monetary reimbursement commensurate to 15 min participation time, as dictated by the policies of the fieldwork provider, and agreed upon by participants when signing up to be part of the panel.

Data analysis

We used a logistic regression with a backwards step-wise approach to estimate odds ratios (ORs) with 95% CIs to determine factors associated with willingness to receive a COVID-19 vaccine. The response options ‘Moderately willing’ and ‘Very willing’ were combined, as were ‘not at all willing’ and ‘a little willing’ to form a dichotomous outcome. Direct and indirect trauma exposure and PTSD measures were also dichotomous in that participants reported either exposure or no exposure for each outcome. Factors with a P-value <0.2 in the bivariate analyses for willingness to receive the COVID-19 vaccine were included in the logistic regression model to adjust for confounders. Variables were removed sequentially from the model, beginning with those with the highest P-value, to leave only variables with a P-value <0.05. We used SPSS version 27 to extract data and execute the model.

Results

Participant characteristics

A total of 1050 Australian adults participated in the survey. Most respondents were from New South Wales (33%, $n = 345$), followed by Victoria (27%, $n = 288$) and Queensland (19%, $n = 201$), with the remaining 21% in other states and territories. Half of the participants identified as female (50%, $n = 529$), 49% ($n = 514$) identified as male, 0.5% ($n = 5$) identified as non-binary and 0.2% ($n = 2$) preferred not to say. Participants' age ranged from 18 to 87 years (mean = 48.7, standard deviation = 17.6). Approximately one-third (28%, $n = 293$) of participants indicated that they had a chronic illness, defined in the survey as 'obesity, diabetes, lung disease or another long-term illness'. Most participants (62%, $n = 648$) were in paid work, 24% ($n = 255$) were retired and 23% ($n = 247$) were not engaged in paid work at the time of the survey. At the time of data collection, Australia was in the midst of a major COVID-19 outbreak. New South Wales, Victoria and the Australian Capital Territory were under movement restrictions enforced under Public Health legislation. This affected the employment status of individuals usually employed in sectors ordered to close under the movement restriction laws. Participant age, location and employment characteristics are detailed in Table 1.

Prevalence of PTSD symptoms and traumatic life events

Seventeen percent ($n = 176$) of participants screened positive for PTSD symptoms. The frequency of symptoms associated with PTSD that were exhibited by participants is summarised in Table 2.

Table 1
Participant characteristics.

Characteristic	n (%)
Age group	
18–24	104 (10)
25–29	72 (7)
30–39	199 (19)
40–49	181 (17)
50–59	172 (16)
60–69	155 (15)
70+	167 (16)
Location by state	
New South Wales	345 (33)
Victoria	288 (27)
Queensland	201 (19)
Western Australia	90 (9)
South Australia	81 (8)
Tasmania	24 (2)
Australian Capital Territory	19 (2)
Northern Territory	2 (0.2)
Type of work during the pandemic	
Health worker	42 (4)
Essential services worker	179 (17)
Educator	60 (6)
Other workers	267 (25)
Retired	255 (24)
Not currently in paid work	247 (24)

Most respondents indicated exposure to at least one traumatic event (87%, $n = 915$). The most common traumatic events experienced directly by participants were COVID-19 pandemic–related stress (47%), distressing medical procedures (37%) and transportation accidents (33%). The most common traumatic events experienced indirectly by participants were transportation accident (37%), moderate/high COVID-19 pandemic–related stress (36.7%), life-threatening illness/injury (35%) and natural disaster (34%). The frequencies of all traumatic experiences are summarised in Table 3.

Willingness to receive a COVID-19 vaccine

Most of the 1050 study respondents (82%, n = 856) were very willing to receive a COVID-19 vaccine, 5% (n = 54) were moderately willing, 7% (n = 70) were a little willing and 7% (n = 70) were not at all willing. Most respondents (76%, n = 797) had already received at least one dose of a COVID-19 vaccine, and they indicated that they were moderately/very willing to receive a COVID-19 vaccine. Table 4 summarises the variables explored in the multivariate analysis. Variance inflation factors for the included variables ranged from 1.06 to 1.19, indicating no to very low correlation between variables. Lower willingness to receive a COVID-19 vaccine was associated with direct experience of a fire or explosion (adjusted odds ratio [aOR]:0.42; 95% CI: 0.23–0.78; $P = 0.006$), direct experience of severe human suffering (aOR:0.39; 95% CI: 0.21–0.71; $P = 0.002$) and screening positive for PTSD symptoms (aOR:0.52; 95% CI: 0.33–0.82; $P = 0.005$). Conversely, higher willingness to receive a COVID-19 vaccine was associated with indirect exposure to severe human suffering (aOR: 2; 95% CI: 1.21–3.22; $P = 0.007$). Direct exposure to a natural disaster and indirect exposure to injury or death caused to another were not statistically significant in the multivariate analysis.

Discussion

To our knowledge, this was the first study to explore associations between discrete traumatic life events, PTSD and willingness to receive a vaccine in a national sample of Australian adults. Most participants were willing to receive a COVID-19 vaccine, and these results are in line with national vaccine tracker estimates of hesitancy during our data collection period.[34] Direct exposure to a fire or explosion, severe human suffering or screening positive for PTSD symptoms were associated with less willingness. Indirect exposure to severe human suffering had the opposite effect, contributing to higher willingness. This validates our hypothesis that direct and indirect trauma exposures differ in their relationship to vaccine willingness. Contrary to other studies of traumatic events and vaccination,[20,21] sexual abuse and violence were not related to vaccine willingness in our sample. This may reflect how the consequences of trauma uniquely manifest within the Australian cultural context.

The finding that exposure to severe human suffering experienced by others was associated with higher willingness to receive a COVID-19 vaccine echoes research that has found an appeal to fear to be effective in increasing various health behaviours.[35,36] Such interventions are particularly effective when fear is paired with a feeling of efficacy for taking action to reduce the threat.[35] We suggest that being exposed to the potential for human suffering, paired with a belief that vaccines are beneficial for one's health increases willingness to receive a vaccine. On a broader level, this supports the notion that vicarious trauma can have an impact on vaccination decisions.

On the other hand, personal experience of severe human suffering was associated with lower willingness to receive a COVID-

Table 2
Frequency of PTSD symptoms.

Symptoms experienced in the last week	Frequency of responses, *n* (%) in the sample (n = 1050)				
	Not at all	A little bit	Moderately	Quite a bit	Extremely
Intrusion symptoms					
Suddenly feeling or acting as if the stressful experience were actually happening again	559 (53)	200 (19)	149 (14)	89 (8)	53 (5)
Avoidance symptoms					
Avoiding external reminders of the stressful experience	482 (46)	216 (21)	183 (17)	100 (10)	69 (7)
Cognitive/mood symptoms					
Feeling distant or cutoff from other people	404 (38)	234 (22)	202 (19)	132 (13)	68 (6)
Hyperarousal symptoms					
Irritable behaviour, angry outbursts or acting aggressively	515 (49)	251 (24)	169 (16)	68 (6)	47 (4)

PTSD, post-traumatic stress disorder.

Table 3
Frequencies of direct and indirect trauma exposure.

Trauma type	Direct exposure, *n* (%)	Indirect exposure, *n* (%)
Natural disaster	188 (18)	357 (34)
Fire or explosion	69 (7)	309 (29)
Transportation accident	350 (33)	388 (37)
Serious accident	113 (11)	291 (28)
Exposure to toxic substance	66 (6)	215 (21)
Physical assault	257 (25)	319 (30)
Assault with weapon	80 (8)	225 (21)
Sexual assault	122 (12)	232 (22)
Other unwanted/uncomfortable sexual experience	197 (19)	217 (21)
Combat or warzone	27 (3)	202 (19)
Captivity	18 (2)	172 (16)
Life-threatening illness/injury	161 (15)	366 (35)
Severe human suffering	66 (6)	291 (28)
Sudden violent death	31 (3)	323 (31)
Sudden accidental death	151 (14)	278 (27)
Serious injury/harm/death caused to someone else	28 (3)	136 (13)
Other stressful events	330 (31)	226 (22)
Negative interaction with healthcare professional	212 (20)	167 (16)
Distressing medical procedure	389 (37)	181 (17)
Distressing vaccination procedure	99 (9)	126 (12)
Distressing adverse reaction to a vaccine	46 (4)	151 (14)
Moderate/high COVID-19 pandemic–related stress	495 (47)	385 (37)

Table 4
Correlates of willingness to receive a COVID-19 vaccine.

Traumatic experience	Participants willing to receive a COVID-19 vaccine[a]/total participants in category, n (%)		Bivariate OR (95% CI)	*P*	Multivariate aOR (95% CI)	*P*
Direct exposure to severe human suffering	Yes	48/66 (73)	0.4 (0.21–0.75)	0.005	0.39 (0.21–0.71)	0.002
	No	862/984 (88)	1		1	
Direct exposure to fire or explosion	Yes	53/69 (77)	0.47 (0.25–0.89)	0.02	0.42 (0.23–0.78)	0.006
	No	857/981 (87)	1		1	
PTSD symptoms	Yes	142/176 (81)	0.53 (0.34–0.84)	0.006	0.52 (0.33–0.82)	0.005
	No	768/874 (88)	1		1	
Indirect exposure to severe human suffering	Yes	266/291 (91)	1.95 (1.18–3.2)	0.005	2 (1.21–3.22)	0.007
	No	644/759 (85)	1		1	
Indirect exposure to injury or death caused to another	Yes	125/136 (92)	2.08 (1.02–4.27)	0.045	2 (0.98–4.05)	0.56
	No	785/914 (86)	1		1	
Direct exposure to a natural disaster	Yes	156/188 (83)	0.73 (0.46–1.17)	0.19	0.74 (0.47–1.17)	0.19
	No	754/862 (87)	1		1	

aOR=adjusted odds ratio; CI=confidence interval; OR=odds ratio; PTSD=post-traumatic stress disorder.
[a] Includes response options 'moderately willing' and 'very willing'.

19 vaccine. Previous suffering can prime an individual to expect negative outcomes when making future decisions.[12] While appraisals of disease risk are associated with vaccine acceptance,[13,37] an individual who has experienced suffering may be more prone to an affect heuristic in their vaccine decision-making[38] related to an expectation of a negative outcome and an attempt to avoid it. Although affective appraisals can also influence disease risk–related motivation, the personal experience of severe suffering may inflate the perceived risks of a vaccination rather than a VPD. This further supports our hypothesis that direct trauma influences threat appraisal mechanisms in subsequent vaccination decisions.

Avoidance may also underpin the observed relationship between PTSD symptoms and decreased willingness to receive a

COVID-19 vaccine. Individuals with PTSD typically avoid situations that may bring about the associated feelings and physiological reactions of the precipitating trauma.[39,40] For example, following a traumatic medical experience, parents can feel so emotionally overwhelmed by the decision to vaccinate their children that they avoid it as a way to regain a sense of control.[41] The experience of the COVID-19 pandemic may also contribute to the development of PTSD symptoms.[42,43] The increase in daily stressors introduced by the pandemic movement restrictions may have exacerbated existing feelings of distress contributing to the higher-than-expected prevalence of PTSD symptoms in our sample and making vaccination decisions more difficult. Although this finding may reflect the timing of data collection, it may also be the case that PTSD is underrepresented in the current national statistics, as they are based on a national survey from 2007.[32]

Participants in our study were less willing to receive a COVID-19 vaccine if they had directly experienced a fire or explosion. This finding may be context specific. Southern parts of Australia were ravaged by bushfires in late 2019 and early 2020. Public health advice at the time urged Australians to stay indoors as smoke blanketed areas far beyond the immediate impact zone.[44] Almost immediately thereafter, pandemic movement restrictions were imposed nationally, and access to health and health services became more limited, given the increased demand. While consequences of trauma can be chronic, with supports in place, usually consequences can dissipate over time.[45] Moreover, non-vaccinating Australian parents who have experienced trauma may re-evaluate their vaccination decision if they feel heard and supported by health providers.[41] The recency of the Australian bushfires to the COVID-19 pandemic may have compounded the distress for those affected, and this along with the decreased access to supportive health services may have made their vaccination decisions more difficult, contributing to decreased willingness.

Our study has some limitations. We did not gauge each respondent's subjective interpretation of traumatic life events measured in the survey. This may have helped us understand participants' subjective definitions of severe human suffering by revealing the specific experiences encompassed by the term and the consequences of such events. Future qualitative studies may provide a more detailed understanding. We used willingness to receive a vaccine as the outcome measure, which does not necessarily reflect vaccination-related behaviour. Nevertheless, willingness was an appropriate outcome measure, given that our aim was to identify associations with the motivational state of vaccine hesitancy. Future research may seek to identify associations with vaccination behaviour for comparison. Finally, we did not collect sociodemographic information, such as income or education level or level of exposure to COVID-19, and as such, we could not adjust for these in our analysis. In addition, we did not have enough information about whether the employment status indicated by respondents represented their usual employment or their employment at the time of lockdown, so we could not reliably use this information. Future research can refine our findings by accounting for these potential covariates.

Our findings have implications for understanding vaccine hesitancy. We suggest that traumatic experiences can affect willingness to receive a vaccine, and the potential for the current COVID-19 pandemic to compound existing stressors, as well as the need for high COVID-19 vaccine uptake globally, make this an important consideration for interventions targeting hesitancy. Trauma-informed care is underpinned by foundational principles related to promoting understanding, safety, trust, autonomy, cultural competence, power sharing and integrated care.[46] Various trauma-informed communication approaches[47–49] have been developed in primary health settings to facilitate a person-centred approach. Further work is needed: trauma-affected vaccine-hesitant individuals might be consulted on how to improve the vaccination process for them, starting with the point at which they form attitudes and intentions to vaccinate or not. Vaccination services can be audited for quality improvement in trauma-informed care.[46] Our work adds to the growing recognition of the need to effectively mediate the influence of traumatic experiences on encounters within the medical setting[50] and suggests that strategies that address the needs of trauma-affected individuals with regard to vaccination may be useful.

Author statements

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Ethical approval

The approval was granted by The University of Sydney Human Research Ethics Committee. Informed consent was provided by all research participants.

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Competing interests

The authors have no competing interests to declare.

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Short Communication

Associations between prenatal exposure to power plants and birth outcomes across the United States

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ABSTRACT

Objectives: Although there is growing evidence that *in utero* exposure to power plants increases the risk of adverse birth outcomes, studies have focused on coal-fired plants and single US locations, limiting generalizability. We used birth certificate data from 50 states and DC to examine the associations between prenatal exposure to power plants and birth outcomes overall and by race/ethnicity.
Methods: We linked 2009–2018 county-level microdata natality files on 34,674,911 singleton births from 50 states and DC with 9-month county-level averages of power plant fuel consumption based on month/year of birth. We estimated linear regression models for birth weight and gestational age and probit models for the dichotomous outcomes of low birth weight, small for gestational age (SGA), and preterm birth. We subsequently examined interactions between plant fuel consumption and race/ethnicity.
Results: Overall, 69.1% of counties had any power plant fuel consumption. Although we found no overall effects of prenatal exposure to power plants on birth weight or SGA, a significant interaction (both $P < 0.01$) revealed that a 10% increase in fuel consumption was associated with infants born to White women having slightly lower birth weights (1.76 g; 95% confidence interval = −2.87, −0.65) and higher risk of being born SGA (0.0002; 95% confidence interval = 0.0002, 0.0002).
Conclusion: Power plants have negative effects on infant health, which exist independent of locality.

Introduction

There is a growing body of research demonstrating that *in utero* exposure to power plants increases the risk of adverse birth outcomes. Studies have found that plant emissions and proximity to power plants are associated with lower birth weight[1–3] and preterm birth[2,4] and contribute to racial/ethnic disparities in birth outcomes.[4] In contrast, reductions in exposure, such as through power plant closures, have been shown to reduce preterm birth.[5] However, studies to date have focused on coal-fired plants and single US states or regions, which have limited their generalizability.[2,3,5] To better understand the effects of power plants on birth outcomes, it is essential to take a broader perspective.

We linked county-level birth certificates from 50 states and Washington, DC, with power plant fuel consumption data from the Energy Information Administration (EIA) over a 10-year period. Our aim was to examine the associations between prenatal exposure to power plants and birth outcomes overall and by race/ethnicity.

Methods

We obtained the 2009–2018 county-level microdata natality files from the National Center for Health Statistics on all registered births.[6] On the birth certificate, women self-reported their race/ethnicity (White, Black, Hispanic, Asian, Other), education (0–11, 12, 13–15, ≥16 years), age (≤19, 20–24, 25–29, 30–34, ≥35 years), nativity (US born, foreign born), marital status at the time of delivery (yes, no), and prenatal smoking (yes, no). The birth facility recorded women's parity (1, 2, 3+), month of prenatal care initiation (none, first trimester, second trimester, third trimester), infant sex (male, female), and gestational age (weeks). We used National Center for Health Statistics–derived imputed data when available,

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and the remaining missing values were coded to be retained in analyses.[7]

Our dependent variables were continuous measures of birth weight (grams) and gestational age (weeks) as well as dichotomous outcomes: low birth weight (LBW; <2500 g), small for gestational age (SGA; <10th percentile for gestational age and sex), and preterm birth (<37 weeks). The analytic sample included 34,674,911 singleton births, 30–44 weeks' gestation, to 16- to 49-year-old women. The Boston College Institutional Review Board considered this study exempt.

Power plant fuel consumption data and geographic locations were derived from publicly available EIA records. Geocoded power plant data were derived from the EIA-923 Form, which includes self-reported monthly fuel consumption for each plant (metric million Btus).[8] Fuel consumption was used as a proxy for plant emissions due to missing data from Form EIA-860, which collects self-reported emission rates for each power plant.[9] Power plants were not stratified by fuel type as plants often had multiple sources of fuel listed in the data.

To link power plant fuel consumption data to county-level birth certificates, we used geocoded measures of the county population centroids. The minimum distances between the county centroid and each plant were calculated using trigonometry. The county-level fuel consumption for a given month was weighted by location using both inverse distance weighting (scaling the production level by the inverse linear distance between county centroid and plant) and inverse distance squared weighting (allowing for a nonlinear relationship between distance and weighting). Each plant's weighted consumption was summed at the county level. The county-month weighted consumption levels were averaged over the 9 months of gestation and merged with birth certificates based on month/year of birth.

We conducted a series of regression models to examine the associations between prenatal exposure to power plants and birth outcomes. We used linear regression models for birth weight and gestational age and probit regression models for LBW, SGA, and preterm birth. Models were adjusted for women's demographic and health-related information and birth year, with county random effects and clustering by county.

We subsequently included interactions between plant fuel consumption and women's race/ethnicity, tested using Wald tests. We calculated semi-elasticities among births exposed to any fuel consumption in their county (N = 29,816,062) from average marginal effects to estimate the effects of a 10% increase in fuel consumption on birth outcomes overall and race/ethnicity-specific semi-elasticities derived from the fully interacted model.

We conducted analyses using Stata statistical software, version 17.0 (StataCorp, College Station, TX), with robust SEs clustered at the county level.

Results

Across the 50 states and DC, 69.1% of counties had any power plant fuel consumption, used as an indicator of exposure to power plants, over the study period (see Supplemental Table 1). From 2009 to 2018, fuel consumption increased for 29 states by an average of 19.2% but decreased for 22 states by an average of 13.3%.

We found no overall effects of prenatal exposure to power plants on birth weight or SGA. However, an interaction by race/ethnicity (both $P \leq 0.01$) revealed that among infants born to White women, a 10% increase in fuel consumption was associated with a decrease in birth weight by 1.76 g (95% confidence interval [CI] = −2.87, −0.65) and a slightly higher risk of being born SGA (0.0002; 95% CI = 0.0002, 0.0002; see Table 1). Increased fuel consumption also slightly raised the overall risk of infants being born LBW (0.0001; 95% CI = 0.0000, 0.0002), particularly for those born to White women (0.0002; 95% CI = 0.0001, 0.0003).

Discussion

Although effect sizes were small, our research demonstrates that prenatal exposure to power plants heightens the risk of infants being born LBW and SGA. Our findings are consistent with prior research based on single states or regions,[1–3] which we have shown extends across US counties as well as how power plants more broadly are deleterious to infant health. We also observed greater effects for infants born to White women, similar to a prior study,[4] suggesting other factors besides power plants may influence racial/ethnic disparities in birth outcomes.

Several limitations are noted. Without home addresses, we were unable to calculate distances to plants and used county population centroids as a proxy, reducing specificity. Fuel consumption was used as a proxy for emissions, and the type of fuel could not be examined due to inconsistencies in reporting of EIA emissions data.

Table 1
Semi-elasticities (95% CIs) of the associations between prenatal exposure to a 10% increase in power plant fuel consumption (averaged over 9 months) and birth outcomes overall and by women's race/ethnicity (2009–2018).

Birth outcome	Overall	Interaction	White	Black	Hispanic	Asian	Other
Birth weight[a,b] (grams)	−0.63 (−2.00, 0.75)		−1.76 (−2.87, −0.65)	−0.14 (−2.41, 2.14)	0.65 (−1.25, 2.55)	0.26 (−2.92, 3.45)	3.11 (−9.16, 15.38)
P-value	0.4	0.004	0.002	0.9	0.5	0.9	0.6
Gestational age[a] (weeks)	0.00 (−0.01, 0.02)		−0.00 (−0.02, 0.02)	0.01 (−0.01, 0.03)	0.00 (−0.02, 0.02)	0.02 (−0.02, 0.05)	0.01 (−0.00, 0.02)
P-value	0.8	<0.001	1.0	0.5	0.9	0.4	0.2
Preterm birth[a] (yes/no)	−0.0003 (−0.0012, 0.0006)		−0.0002 (−0.0014, 0.0010)	−0.0006 (−0.0025, 0.0013)	−0.0003 (−0.0016, 0.0010)	−0.0020 (−0.0046, 0.0007)	−0.0005 (−0.0019, 0.0010)
P-value	0.5	0.4	0.7	0.5	0.7	0.1	0.5
Low birth weight[a,b] (yes/no)	0.0001 (0.0000, 0.0002)		0.0002 (0.0001, 0.0003)	0.0001 (−0.0001, 0.0004)	−0.0000 (−0.0003, 0.0003)	0.0000 (−0.0008, 0.0009)	−0.0008 (−0.0017, 0.0002)
P-value	0.04	<0.001	<0.001	0.3	0.8	0.9	0.1
Small for gestational age[a,b] (yes/no)	−0.0004 (−0.3021, 0.3014)		0.0002 (0.0002, 0.0002)	−0.0008 (−0.0016, 0.0001)	−0.0008 (−0.0015, −0.0002)	−0.0021 (−0.0051, 0.0008)	−0.0014 (−0.0040, 0.0012)
P-value	1.0	0.007	<0.001	0.07	0.01	0.2	0.3

[a] Model adjusted for women's race/ethnicity, education, age, nativity, marital status, parity, prenatal care initiation, prenatal smoking, infant sex, birth year; models included county random effects and clustering by county.
[b] Model also adjusted for gestational age.

This suggests that greater completeness of information will increase the utility of publicly available EIA data.

Our research provides further evidence for the downstream effects of power plants on infants, which exist independent of locality. Additional protections are warranted to safeguard women's and infants' health from the deleterious effects of power plants on a national scale.

Author statements

Authors contributions

S.S.H. and C.F.B. conceived the study. S.S.H. acquired the data. C.F.B. and H.S. analyzed the data. S.S.H., C.F.B., H.S., and C.S. interpreted the data. C.S. and S.S.H. drafted the article. C.S., H.S., C.F.B., P.J.L., and S.S.H. reviewed the article for important intellectual content. All authors read and approved the final manuscript of the paper. S.S.H. and C.F.B. are guarantors of the paper.

Ethical approval

This study was approved by the Boston College Institutional Review Board and considered exempt.

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Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.01.003.

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Original Research

Epidemiology of post-COVID conditions beyond 1 year: a cross-sectional study☆

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ABSTRACT

Objective: The aim of this study was to investigate the epidemiology of post-COVID conditions beyond 12 months and identify factors associated with the persistence of each condition.
Study design: This was a cross-sectional questionnaire-based survey.
Methods: We conducted the survey among patients who had recovered from COVID-19 and visited our institute between February 2020 and November 2021. Demographic and clinical data and data regarding the presence and duration of post-COVID conditions were obtained. We identified factors associated with the persistence of post-COVID conditions using multivariable linear regression analyses.
Results: Of 1148 surveyed patients, 502 completed the survey (response rate, 43.7%). Of these, 393 patients (86.4%) had mild disease in the acute phase. The proportion of participants with at least one symptom at 6, 12, 18, and 24 months after symptom onset or COVID-19 diagnosis was 32.3% (124/384), 30.5% (71/233), 25.8% (24/93), and 33.3% (2/6), respectively. The observed associations were as follows: fatigue persistence with moderate or severe COVID-19 (β = 0.53, 95% confidence interval [CI] = 0.06−0.99); shortness of breath with moderate or severe COVID-19 (β = 1.39, 95% CI = 0.91−1.87); cough with moderate or severe COVID-19 (β = 0.84, 95% CI = 0.40−1.29); dysosmia with being female (β = −0.57, 95% CI = −0.97 to −0.18) and absence of underlying medical conditions (β = −0.43, 95% CI = −0.82 to −0.05); hair loss with being female (β = −0.61, 95% CI = −1.00 to −0.22), absence of underlying medical conditions (β = −0.42, 95% CI = −0.80 to 0.04), and moderate or severe COVID-19 (β = 0.97, 95% CI = 0.41−1.54); depressed mood with younger age (β = −0.02, 95% CI = −0.04 to −0.004); and loss of concentration with being female (β = −0.51, 95% CI = −0.94 to −0.09).
Conclusions: More than one-fourth of patients after recovery from COVID-19, most of whom had had mild disease in the acute phase, had at least one symptom at 6, 12, 18, and 24 months after onset of COVID-19, indicating that not a few patients with COVID-19 suffer from long-term residual symptoms, even in mild cases.

Introduction

The COVID-19 has become a global pandemic, with greater than 617 million infections and greater than 6 million deaths worldwide as of September 19, 2022.[1] Early reports suggest residual effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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infection, such as fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia,[2–4] and decline in quality of life.[5,6] These post-acute sequelae of SARS-CoV-2 infection are known as post-COVID conditions, although there are several terms such as "Long COVID-19," "post-acute COVID-19," "persistent COVID-19 symptoms," "chronic COVID-19," "post-COVID-19 manifestations," "long-term COVID-19 effects," "post COVID-19 syndrome," "ongoing COVID-19," "long-term sequelae," or "long-haulers." While the epidemiology within 1 year of infection and the risk factors of post-COVID conditions are extensively investigated, epidemiology beyond 1 year and risk factors of their persistence are only partially understood.[7]

In this study, we explored the epidemiology of post-COVID conditions beyond 12 months and also identified factors associated with the persistence of each post-COVID condition in a cohort of patients recovering from COVID-19 at a tertiary care hospital designated for infectious diseases in Japan.

Methods

This study was designed as a single-center, cross-sectional survey in which a self-reported, online, or paper-based questionnaire was sent to eligible patients in February 2022 without any reminders. Participation in this survey was voluntary but not anonymous. Participants who had recovered from COVID-19 were requested to complete and return the questionnaire. Informed consent was obtained by marking a consent checkbox either online or on the paper-based questionnaire. This study was reviewed and approved by the institutional ethics committee.

Participants

Patients who had recovered from COVID-19 and who visited the outpatient service of the institution from February 2020 to November 2021 to undergo a predonation screening test for COVID-19 convalescent plasmapheresis were recruited.[8] Most of the participants had received acute-phase treatment for COVID-19 in other hospitals, and all participants in this study were Japanese because the screening test was designed only for Japanese patients.

Questionnaire

We developed the questionnaire through a literature review with reference to previous similar studies,[2,3,5,9–13] findings from our previous study on prolonged and late-onset symptoms of COVID-19,[4,7] and comprehensive discussions among the authors. We attempted to minimize the number of questions required to maximize the response rate. Six non-medical employees in National Center for Global Health and Medicine were included in a pilot study. They provided feedback on the content, clarity, and format of the items and on whether the survey questions were self-explanatory. Minor revisions were made in response to their feedback.

Items investigated

Patient characteristics, including COVID-19 vaccination status, information regarding the acute phase of COVID-19, and presence and duration of symptoms related to COVID-19, were investigated (Appendix 1). Disease severity was categorized as follows, according to previous literature:[3,14] (1) mild, no oxygen therapy; (2) moderate, oxygen therapy without mechanical ventilation; (3) severe, mechanical ventilation with or without extracorporeal membrane oxygenation. The post-acute phase symptoms related to COVID-19 included fatigue, shortness of breath, cough, dysosmia (including anosmia), dysgeusia (including ageusia), hair loss, depressed mood, brain fog, loss of concentration, and memory disturbance. This information was obtained using an online/paper-based questionnaire, as it was difficult to obtain this information from the medical records, given that many participants in this study were treated for the acute phase of COVID-19 at other hospitals.

Statistical analyses

The patient characteristics, presence of pneumonia, disease severity, and treatment in the acute phase of COVID-19 were expressed as median and interquartile range for continuous variables and as absolute values (n) with percentages (%) for categorical variables. The proportion of patients with prolonged symptoms, those with symptoms lasting for at least 2 months within 3 months of symptom onset, and those with symptoms lasting beyond 1 year have been described.

Linear regression analyses were performed to identify factors associated with the persistence of post-acute phase symptoms. The dependent variable was the duration of each symptom (days). The value of the dependent variable in the model was log-transformed because the duration of each symptom did not distribute normally. We included participants' characteristics and disease severity (age, sex, body mass index, smoking, high-risk comorbidity, COVID-19 vaccination status, severity) as independent variables according to clinical implications and previous literature.[3,13,14] Age and body mass index were analyzed as continuous quantitative variables, whereas the other variables were analyzed as categorical variables.

The level of significance for all statistical tests was set at $\alpha = 0.05$. Data were analyzed using SPSS Statistics for Windows, version 25.0 (IBM®, Armonk, NY, USA) and R, version 4.1.3 (R Foundation for Statistical Computing; 2018, Vienna, Austria).

Results

The self-reported questionnaire was sent to a total of 1148 patients who had recovered from COVID-19 (online: 958 patients; paper based: 190 patients), and 502 responses were obtained (online: 413 responses; paper based: 89 responses). The overall response rate was 43.7% (online: 43.1%; paper based: 46.8%). Among the 502 patients, 133 (31.5%), 205 (48.6%), and 84 (19.9%; 80 missing) became infected with SARS-CoV-2 between February and October 2020, November 2020 and June 2021 (alpha strains predominantly), and July and October 2021 (delta strains predominantly), respectively.[15,16] The demographic and clinical characteristics of the participants are summarized in Table 1. The median age was 48 years, and 59.8% of the participants were women. All participants were Japanese. A total of 234 patients (49.9%) did not have any underlying medical conditions. Eleven patients (2.2%) tested positive for SARS-CoV-2 at least 7 days after their second vaccination. Overall, 141 patients (33.3%) developed pneumonia. In terms of disease severity, 393 (86.4%), 58 (12.7%), and 4 (0.9%) patients had mild, moderate, and severe disease, respectively. The median number of days (interquartile range) from symptom onset or COVID-19 diagnosis to the questionnaire survey completion was 414 (279–563) days.

Participants with post-acute COVID-19 symptoms and symptom persistence

The proportion of patients with prolonged symptoms, those with symptoms lasting at least 2 months within the 3 months of symptom onset, and those with symptoms lasting beyond 1 year are described in Table 2. The frequency and duration of at least one symptom and of each prolonged symptom are summarized in

Table 1
Demographic and clinical characteristics of the participants ($n = 502$).

Characteristics	Value
Age, median (IQR), years	48.0 (42.0, 55.0)
Female sex, *n* (%) (1 missing)	300 (59.8)
Body mass index[a], median (IQR) (2 missing)	23.1 (20.7, 25.9)
Ethnicity, *n* (%)	
Japanese	502 (100)
Smoking history, *n* (%) (1 missing)	
Yes	206 (41.0)
Alcohol use, *n* (%)	
Yes	421 (83.9)
Individual comorbidity, *n* (%) (33 missing)	
No underlying medical conditions	234 (49.9)
Hypertension	70 (14.9)
Dyslipidemia	59 (12.6)
Diabetes	19 (4.1)
COPD	2 (0.4)
Bronchial asthma	69 (14.7)
Myocardial infarction	0 (0)
Malignancy	11 (2.3)
Immunodeficiency	2 (0.4)
Chronic kidney disease	2 (0.4)
History of pregnancy, *n* (%) (202 missing)	
Yes	166 (55.3)
Vaccination[b], *n* (%) (202 missing)	11 (2.2)
Acute COVID-19 characteristics, *n* (%)	
Pneumonia diagnosed (78 missing)	141 (33.3)
Highest severity during clinical course of COVID-19 (47 missing)	
Mild	393 (86.4)
Moderate	58 (12.7)
Severe	4 (0.9)
Pharmacological treatments	
Antiviral (72 missing)	56 (13.0)
Corticosteroids (75 missing)	58 (13.6)
Casirivimab/ imdevimab (13 missing)	2 (0.4)
Sotrovimab (15 missing)	2 (0.4)
Timing of the interview (77 missing)	
Days since symptom onset or diagnosis of COVID-19, median (IQR)	414 (279, 563)
The number and % of patients who were surveyed (108 missing)	
Within 3 months	2 (0.5)
3–6 months	8 (2.0)
6–9 months	92 (23.4)
9–12 months	59 (15.0)
12 months and longer	233 (59.1)

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; IMV, invasive mechanical ventilation.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Patients tested positive for SARS-CoV-2 at least 7 days after their second vaccination when immunity had developed.

Figs. 1 and 2a and b, respectively. The proportion and frequency were calculated using the number of patients who provided a response on the presence of post-acute COVID-19 symptoms as the denominator. Four hundred eighty-one participants (95.8%) experienced at least one symptom. The proportions of patients with fatigue, shortness of breath, cough, dysosmia, dysgeusia, hair loss, depressed mood, brain fog, loss of concentration, memory disturbance, and any of above symptoms lasting at least 2 months within the 3 months of symptom onset or diagnosis were 15.4%, 9.4%, 6.8%, 20.1%, 12.2%, 12.1%, 13.9%, 17.8%, 20.1%, 16.4%, and 53.4%, respectively. The proportion of participants with at least one symptom at 6, 12, 18, and 24 months after symptom onset or COVID-19 diagnosis was 32.3% (124/384), 30.5% (71/233), 25.8% (24/93), and 33.3% (2/6), respectively.

Factors associated with the persistence of post-acute phase symptoms

We identified the factors associated with the persistence of post-COVID conditions. After adjustment, the persistence of fatigue was associated with moderate or severe COVID-19 ($\beta = 0.53$, 95% confidence interval [CI] = 0.06–0.99); shortness of breath with moderate or severe COVID-19 ($\beta = 1.39$, 95% CI = 0.91–1.87); cough with moderate or severe COVID-19 ($\beta = 0.84$, 95% CI = 0.40–1.29); dysosmia with being female ($\beta = -0.57$, 95% CI = −0.97 to −0.18) and absence of underlying medical conditions ($\beta = -0.43$, 95% CI = −0.82 to −0.05); hair loss with being female ($\beta = -0.61$, 95% CI = −1.00 to −0.22), absence of underlying medical conditions ($\beta = -0.42$, 95% CI = −0.80–0.04), and moderate or severe COVID-19 ($\beta = 0.97$, 95% CI = 0.41–1.54); depressed mood with younger age ($\beta = -0.02$, 95% CI = −0.04 to −0.004); and loss of concentration with being female ($\beta = -0.51$, 95% CI = −0.94 to −0.09). No factors were associated with the persistence of dysgeusia, brain fog, and memory disturbance.

Discussion

This cross-sectional questionnaire survey is one of the few studies that explored the epidemiology of post-COVID conditions beyond 12 months. It also identified factors associated with the persistence of each post-COVID condition.

Importantly, we found that more than 25% of patients had at least one symptom at 6, 12, 18, and 24 months after symptom onset or COVID-19 diagnosis. This proportion of patients with any symptom appears to have remained high (more than 25%) 200 days after symptom onset or COVID-19 diagnosis (Fig. 1). In the early phase of the pandemic, there were no vaccines or established effective treatment for COVID-19, and several patients became severely ill. Because the acute-phase severity is a risk factor for post-COVID conditions,[17] it is presumed that a higher proportion of patients who contracted COVID-19 early in the pandemic would have post-COVID conditions. Hence, it is expected that the

Table 2
Number of participants with post-acute COVID-19 symptoms and the persistence of symptoms.

Symptoms	Number of patients with symptom (%[a])	Lasting at least 2 months within 3 months since the onset (%[a])	Lasting more than 1 year (%[a])
At least one symptom	481 (95.8)	212 (53.4)	71 (30.5)
Fatigue	394 (78.5)	61 (15.4)	9 (3.8)
SoB	183 (36.5)	39 (9.4)	14 (5.6)
Cough	299 (59.6)	28 (6.8)	3 (1.2)
Dysosmia	290 (57.8)	84 (20.1)	26 (10.3)
Dysgeusia	242 (48.2)	51 (12.2)	15 (5.9)
Hair loss	147 (29.3)	51 (12.1)	9 (3.5)
Depressed mood	147 (29.3)	58 (13.9)	19 (7.5)
Brain fog	186 (37.1)	74 (17.8)	23 (9.1)
LoC	185 (36.9)	84 (20.1)	29 (11.4)
MD	110 (21.9)	69 (16.4)	30 (11.7)

LoC, loss of concentration; MD, memory disturbance; SoB, shortness of breath.
[a] Calculated using the number of patients who could answer the presence of each post-acute COVID-19 symptom as the denominator.

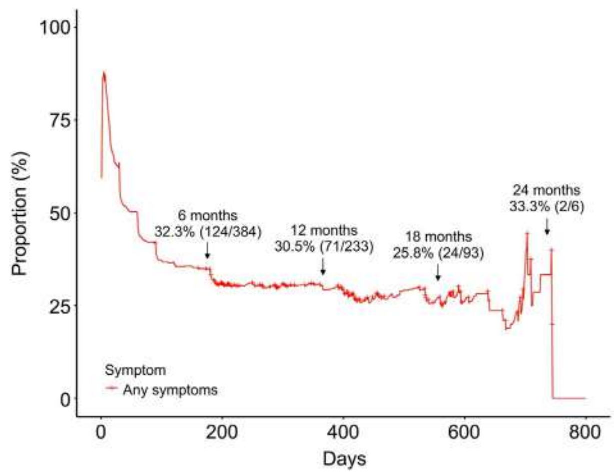

Fig. 1. Proportion of patients who had at least one post-COVID condition.

proportion of symptomatic patients will trend downward over time, even after 200 days. In addition, the number of patients at 24 months (6 patients) is too small to give a real information. Therefore, longitudinal follow-up surveys are required to better understand the natural history of post-COVID conditions.

Chronic fatigue is the symptom most frequently reported after recovery from acute COVID-19.[2,18,19] The persistence of fatigue was associated with moderate or severe COVID-19, compared with mild COVID-19 in the acute phase in this study. It is plausible because COVID-19 severity has been suggested as a risk factor of the development of fatigue.[17,20] Because fatigue is a subjective symptom and involves a complex set of factors,[21] objective evaluations such as the 6-min walk test with lung computed tomography scans do not necessarily correlate with fatigue.[22,23] Negative psychological and social factors associated with the COVID-19 pandemic have also been linked to chronic fatigue.[24,25] Important next steps are a comprehensive approach with mental and physical care for patients with chronic fatigue[26] and identification of measures that accurately correlate with subjective fatigue.

Female sex has been recognized as a risk factor for post-COVID conditions in a number of previous studies.[3,17,27] As it is in this study, being female was a risk factor of the persistence of dysosmia, hair loss, and loss of concentration. On the other hand, notably, absence of underlying medical conditions was associated with dysosmia and hair loss. Previous studies have reported that the majority of patients with alopecia after COVID-19 recovery had telogen effluvium,[28] a non-inflammatory alopecia involving diffuse hair loss. Proinflammatory cytokines including interleukin (IL)-1β, IL-6, tumor necrosis factor-α, and interferon types I and II (IFN-I/II), are proposed as activating factors of telogen effluvium.[29] Immunological abnormalities, such as levels of some circulating cytokines during or before the acute illness, have also been reported as predisposing factors.[30] Although these findings remain mostly unconfirmed,[30] robust immune response against the proinflammatory cytokines may contribute to chronic fatigue in patients without underlying medical conditions.

Clinically significant depression and anxiety were reported in approximately 30%–40% of patients following COVID-19.[31,32] The persistence of a depressed mood was associated with younger age in this study. The cause or pathophysiology of a depressed mood is complex and undetermined.[9] Younger people reported a significantly higher prevalence of generalized anxiety disorder and depressive symptoms[33] and reported more vulnerability regarding their mental health conditions.[34] Young people can be stressed easily, as they obtain information from social media[34] or are vulnerable to loneliness or lack of family support.[35] Loneliness or a sense of isolation among young patients may contribute to this; however, further studies are required to explore and clarify its mechanism.

In this study, we could not evaluate the efficacy of monoclonal antibody treatment and vaccination on post-COVID condition because only four patients were on either casirivimab/imdevimab or sotrovimab, and 11 patients completed two doses of vaccination before infection. A previous article reported that two doses of vaccination compared with no vaccination was associated with reduced odds of long-duration (≥28 days) symptoms of COVID-19.[13] This implied that vaccination may shorten the duration of post-COVID conditions in addition to its effects on preventing COVID-19-related morbidity and mortality. On the other hand, another article implied that vaccination before infection confers only partial protection in the post-acute phase of the disease; hence, reliance on it as a sole mitigation strategy may not optimally reduce long-term health consequences of SARS-CoV-2 infection.[36] The findings emphasize the need for continued optimization of strategies for the primary prevention of COVID-19. Further research on the treatment of post-COVID conditions is needed.

Our study has some limitations. First, this study was based on a self-reported questionnaire-based survey, which was subject to various biases, such as selection, volunteer, and recall biases. In particular, it is difficult to evaluate causality using this study design. Moreover, the study was limited to COVID-19 convalescent plasmapheresis patients who underwent the predonation screening test. It is unclear whether the results of this study can be applied to all patients recovering from COVID-19. Second, the enrolment period of patients infected was long, and some patients had

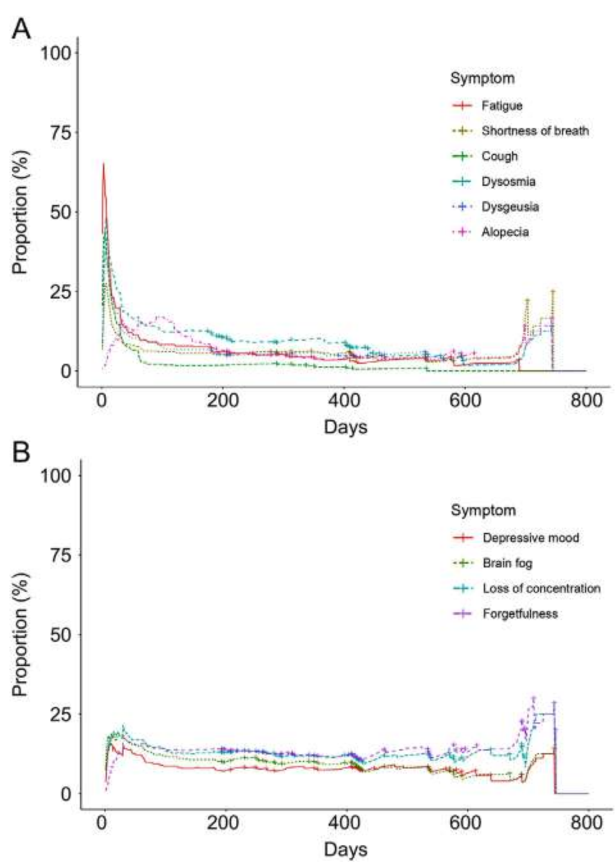

Fig. 2. (a) Proportion of patients with post-COVID conditions (fatigue, shortness of breath, cough, dysosmia, dysgeusia, alopecia). (b) Proportion of patients with post-COVID condition (neurocognitive symptoms).

persistent ongoing or chronic or late-onset symptoms at the time of the survey. In these cases, the actual durations of the symptoms were unclear, and it is likely that this study underestimated the durations of these symptoms. It may also affect the results of the linear regression analysis. Long-term observation is needed to better understand the duration of post-COVID conditions. Third, this was a single-center study with a small sample size. Fourth, the definition of post-COVID-19 condition in this study was similar to that of a previous study.[37] However, whether the symptoms could be explained by an alternative diagnosis remains unclear in this study. Therefore, our findings may have overestimated the prevalence of post-COVID-19 conditions. Fifth, only a few of the symptoms reported to occur as a post-COVID condition are included in the survey questionnaire of this study. Sixth, it was impossible to determine the type of variant. Considering that 31.5%, 48.6%, and 19.9% of the patients became infected with SARS-CoV-2 between February and October 2020, November 2020 and June 2021, and July and October 2021, respectively, it is likely that alpha (B.1.1.7) strains were most predominant.[38–40] The prevalence of the SARS-CoV-2 variants may have influenced the frequency of post-COVID conditions. Seventh, no information on the socio-economic level of the patients was obtained in this study. This should have been explored because a lower socio-economic status is a risk factor for post-COVID syndrome.[41] Finally, no information about reinfection has been explored in this study. This is a big bias because it can affect deeply the presence and persistence of post-COVID syndrome. In a previous study, compared with non-infected controls, cumulative risks and burdens of repeat infection increased according to the number of infections.[42]

In conclusion, our cross-sectional questionnaire survey revealed that after recovering from COVID-19, more than one-fourth of patients, most of whom had mild disease in the acute phase, had at least one symptom 6, 12, 18, and 24 months after symptom onset or COVID-19 diagnosis. The finding indicates that several patients with COVID-19 experienced long-term residual symptoms, even in mild cases. It also identified factors associated with the persistence of each post-COVID condition, which can help to predict the duration of each symptom, reducing patients' anxiety about its duration.

Author statements

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Ethical approval

This study was reviewed and approved by the ethics committee of the Center Hospital of the National Center for Global Health and Medicine (NCGM-G-004406-00). Informed consent was obtained from all the participants. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

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Competing interests

None declared.

Authors' contributions

S.M., S.T., M.T., S.S., M.A., C.K., Y.O., K. Tanaka, M. Suzuki, K.H., and N.O. conceptualized the study. S.M., S.T., T.M., S.K., and K.H. designed the study. S.M., Y.S., K. Takahashi, S.A., and M. Sanada conducted the research and investigation. S.M., S.T., T.M., M.T., Y.S., K. Takahashi, and M. Sanada were responsible for the data curation. S.M. and S.T. conducted the statistical analyses. S.M. and S.T. were major contributors in the writing of the original draft of the article. S.M. acquired funds for the study and supervised the project along with N.O. All authors read and approved the final article.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.01.008.

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Original Research

If you build it, will they come? Is test site availability a root cause of geographic disparities in COVID-19 testing?

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Objectives: The purpose of this study was to examine the relationship between test site availability and testing rate within the context of social determinants of health.
Study design: A retrospective ecological investigation was conducted using statewide COVID-19 testing data between March 2020 and December 2021.
Methods: Ordinary least squares and geographically weighted regression were used to estimate state and ZIP code level associations between testing rate and testing sites per capita, adjusting for neighbourhood-level confounders.
Results: The findings indicate that site availability is positively associated with the ZIP code level testing rate and that this association is amplified in communities of greater economic deprivation. In addition, economic deprivation is a key factor for consideration when examining ethnic differences in testing in medically underserved states.
Conclusion: The study findings could be used to guide the delivery of testing facilities in resource-constrained states.

Introduction

The United States has faced unprecedented challenges to its public health infrastructure over the last 3 years. The COVID-19 pandemic has caused and continues to cause large-scale impacts on households, communities and governments.[1] To date, hundreds of millions of people have received COVID-19 testing within the United States alone.[2] Modalities and delivery of testing vary between communities but typically relate to (1) presentation of a symptomatic patient or (2) population-level disease and preventive screening.[3] During the early phase of the pandemic, before COVID-19 vaccines, testing led to the implementation of control measures such as mask wearing and social distancing.[4–6] After rollout of the vaccine, testing reduced by one-third across the United States.[7] However, the reduction in testing was short lived, as utilisation of available testing services increased with the detection and surges in positive cases of the COVID-19 Delta variant in April and August 2021, respectively.[8] The high number of positive cases remained constant through to the end of 2021 for states such as West Virginia, and official reports of the Omicron variant were detected in December 2021.[9]

Testing inequities have received considerable research focus over the last 2 years. Studies highlight disparities in the rate of COVID-19 testing within communities of colour, urban and rural gradients, the level of food insecurity and economic deprivation.[10–13] Given that the objective of many studies is to identify areas of low testing (i.e. prevalence of testing), it is no surprise that most studies focus on future resource allocation as the primary end point.[14] Few studies have examined whether the addition of more testing resources (i.e. adding new testing sites) actually results in an increase in the testing rate within underserved communities. Uncertainty regarding the effects of test site availability on testing rate is a critical limitation to the current COVID-19 literature. Successful

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population-scale testing regimens rely on the use of testing sites, which can vary based on public trust and organisational and social factors, which can vary over space and time.[15]

West Virginia is an ideal location to explore the impact of test site availability on testing rate within medically underserved communities. Past research in the state has identified disparities in testing and positivity of tests for COVID-19 at the census tract level, with higher testing uptake seen in the Black/African American population, urban residents and within communities that were more food secure.[16] The present study builds on previous studies by examining whether geographic differences in test sites per capita contribute to disparities in the testing rate among medically underserved communities. Importantly, this research examines how neighbourhood-level factors, such as area deprivation and rural minority populations, influence the relationship between testing rate and test sites per capita. The results will provide an understanding of how social determinants of health impact test site utilisation. In addition, the findings will address the limited research on testing uptake and can be used to optimise the delivery of resources to slow the spread of the COVID-19.

Methods

Data mmanagement

ZIP code level testing data were obtained from the West Virginia Department of Health and Human Resources from March 2020 (when the first case of COVID-19 was detected in the state) to December 2021. Data contained unique patient identifiers, polymerase chain reaction (PCR) test results, the date test was performed, ZIP code of testing site and patient ZIP code of residence. Inconclusive tests were excluded from the analysis. The remaining testing data were aggregated so that each row of data represented a unique person who tested either positive or negative by month and ZIP code. Patients who were tested multiple times within a month and ZIP code were regarded as negative if all tests were negative and as positive if at least one test within the month indicated positivity. PCR testing data were joined to an Environmental Systens Research Institute, Inc. (ESRI) USA Zip Code Points shapefile containing 2019 estimated population data within ZIP codes.[17] Testing rate and unique testing sites per 1000 persons were estimated for each ZIP code using the US census population estimates contained within the ESRI USA ZIP codes shapefile. This study was approved by the West Virginia University Institutional Review Board (protocol # 2204554630).

Testing data were linked to five-digit ZIP code Area Deprivation Index (ADI) state-level rankings and 2019 census tract–level estimates of Black/African American population percentages. ADI rankings ranged from 1 to 10, with higher scores indicating higher disadvantage for a ZIP code relative to other ZIP codes in West Virginia.[18] The percentage of a ZIP code population identifying as Black/African American was obtained through intersecting the ZIP code level testing data with 2019 census tract–level estimates of Black/African American population percentages.[19] Covariates also included three continuous-by-continuous interaction terms, as follows: (1) testing sites per 1000 persons by ADI ranking; (2) testing sites per 1000 persons by Black/African American percentage of the population; and (3) Black/African American percentage of the population by ADI ranking. The outcome of this study was the log-transformed ZIP code–level testing rate.

Statistical analyses

Separate multivariable ordinary least squares (OLS) and geographically weighted regression (GWR) analyses were performed for each month from March 2020 to December 2021 (n = 22 months). OLS regression was used to identify statewide estimates, although GWR was incorporated to identify local differences in testing rate by testing sites per capita and adjusted for the Black/African American percentage of the population and ADI. Mathematical specification for OLS and GWR is presented in equation 1. For GWR, $i = 1 \ldots n$, γ_i is the model outcome at the i^{th} ZIP code, β_{i0} is the regression intercept, β_{ik} is the regression coefficient for the k^{th} covariate, x_{jk} is the observed value for the k^{th} covariate, P is the number of regression terms, and ε_i is the random error term for the i^{th} ZIP code.[20]

$$\textbf{OLS} \quad \gamma_i = \beta_0 + \beta_k x_k + \varepsilon_i$$
$$\textbf{GWR} \quad \gamma_i = \beta_{i_0} + \sum_{k=1}^{p-1} \beta_{ik} x_{ik} + \varepsilon_i \qquad (1)$$

Importantly, GWR was only conducted for 4 of 22 total months of the study. This was done to limit bias from multiple testing[21] while also highlighting the effects of testing sites per capita on testing rate at key time intervals across the study period. The four key months were (1) March 2020 (first COVID-19 case detected in West Virginia); (2) November 2020 (increased COVID-19 testing efforts and resources); (3) August 2021 (COVID-19 Delta variant surge); and (4) December 2021 (first COVID-19 Omicron variant positive patient detected).[22] The spatial window for GWR analyses was selected using an adaptive bandwidth and cross-validation scores in the ‘spgwr’ R package.[23] The resulting GWR coefficients representing the effect of sites per 1000 persons on the testing rate were mapped at the ZIP code level. Shading of points was determined based on the coefficient values as well as their corresponding t-values. t-values were used to determine if the local GWR coefficient was statistically significant at the 0.05 level. This approach aligns with previous research noting the importance of providing t-values side by side with local coefficients for proper interpretation of GWR results.[24]

Temporal trends were explored between the testing rate and model covariates by month using scatterplots. Scatterplots included y-axes to display variation in OLS coefficient and its corresponding t-value and month on the x-axes. The extent to which interaction effects influenced first-order effects for covariates were visualised by creating categorical ‘bins’ for ZIP code–level ADI ranking and Black/African American percentage of the population based on one standard deviation distance from the statewide average for each variable. For example, ZIP codes with an ADI ranking or Black/African American percentage of the population one standard deviation above the state average were categorised as ‘high’. Alternatively, ZIP codes with an ADI ranking or Black/African American percentage of the population one standard deviation below the state average were ‘low’. All others were categorised as ‘medium’.

Results

The results from the OLS models are summarised for each month (n = 22) from March 2020 (month 3) to December 2021 (month 24) in Fig. 1. The red line is the regression coefficient, the solid blue line is the corresponding t-value, and the dotted blue line is the threshold for statistical significance at the 95% confidence level (CI). The threshold was set at 1.96, given the large (n = 469) degrees of freedom in OLS regression analyses. Months where the solid blue line crosses above or below the dotted blue line indicate months where there was a statistically significant positive or negative effect, respectively, for that covariate on the testing rate. Overall, testing sites per 1000 persons and Black/African American

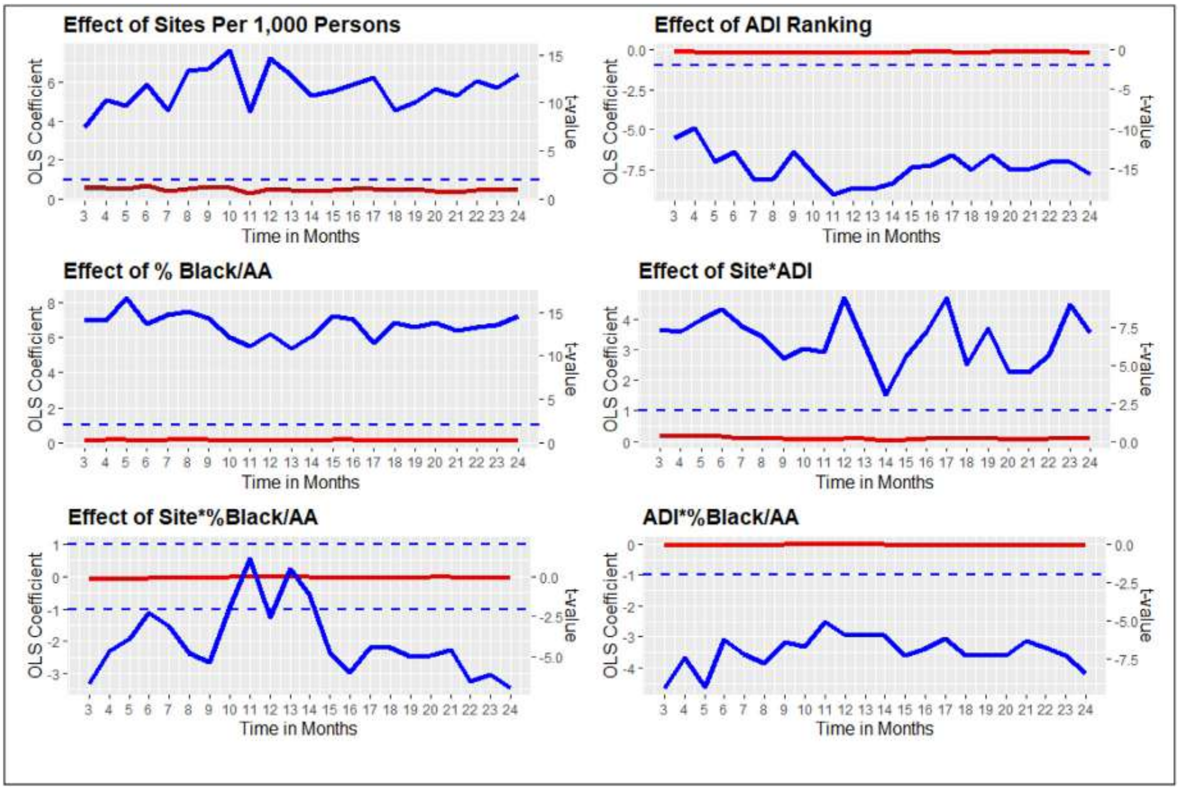

Fig. 1. Monthly change in statewide (ordinary least squares [OLS]) regression coefficients and their corresponding t-values for each covariate. Months on the y-axis start at 3 and end at 24 corresponding to March 2020 until December 2021. The red line is the regression coefficient, the solid blue line is the corresponding t-value, and the dotted blue line is the threshold for statistical significance at the 95% confidence level. ADI, area deprivation index; % Black/AA, Black/African American percentage of the population. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

percentage of the population have statistically positive effects on the testing rate across all months in the study. In contrast, ADI state-level ranking has a statistically significant negative effect on testing across all months. Interpretation of these results should be done with caution, given the statistically significant interaction effects in the OLS models. ADI ranking had a statistically significant positive interaction effect on the relationship between testing sites per 1000 persons and testing rate for all months (i.e. as ADI state ranking increased, the positive effect that the number of testing sites per 1000 has on the testing rate increases). However, Black/African American percentage of the population had a statistically significant negative interaction effect on the relationship between test sites per 1000 persons and the testing rates for all months, with the exception of months 10–14 (i.e. as the Black/African American percentage of the population increased, the positive effect of testing sites per capita on testing rate decreased). This result is complicated, as there is a statistically significant negative interaction effect for Black/African American percentage of the population on the relationship between ADI and the testing rate (i.e. as ADI increases, the positive effect that Black/African American percentage of the population has on testing is offset).

Mapped results from the GWR analyses for the four key months are shown in Fig. 2. ZIP codes where test sites per 1000 persons had no significant local effect on testing rate are shown as grey dots. ZIP codes where test sites per 1000 persons had a statistically significant local effect are displayed using a blue to red gradient, where lower effects are indicated in blue and higher effects are in red. It is important to note that any ZIP code with blue or red shading showed a statistically significant positive effect between the number of testing sites and the testing rate. The blue to red gradient is used to display the extent of the significant effect over time. Spatial trends within these 4 months suggest that the effect of sites per 1000 persons on the testing rate was highest in the northern and north-eastern regions of West Virginia, particularly during August and December 2021, when new COVID-19 variants were detected or surging.

Discussion

This study provides an empirical foundation to investigate the effect of test site availability on testing rate for COVID-19. Importantly, the impact of higher availability of testing sites on the testing rate was examined from a health disparities perspective during four key months of the pandemic for West Virginia. The findings indicated clear geographical differences in the extent to which test site availability impacts the testing rate across the state as a whole and within communities at the ZIP code level. Furthermore, the results suggest that the positive effects of site availability on the testing rate are influenced by neighbourhood-level social determinants of health. This is a critical finding within the context of the four key time intervals of the pandemic (March 2020, November 2020, August 2021 and December 2021), as it provides an opportunity to understand the impact of public health services during surges in cases and when new variants are detected.

Previous research in West Virginia has identified census tracts with higher Black/African American percentage of the population as a significant predictor for lower COVID-19 testing.[16] The present study results from March 2020 and December 2021 are in line with this conclusion, showing that the impact for sites per capita on testing is lower among communities with a higher Black/African American percentage of the population. However, caution must be taken in the interpretation of these results, as this was not true for

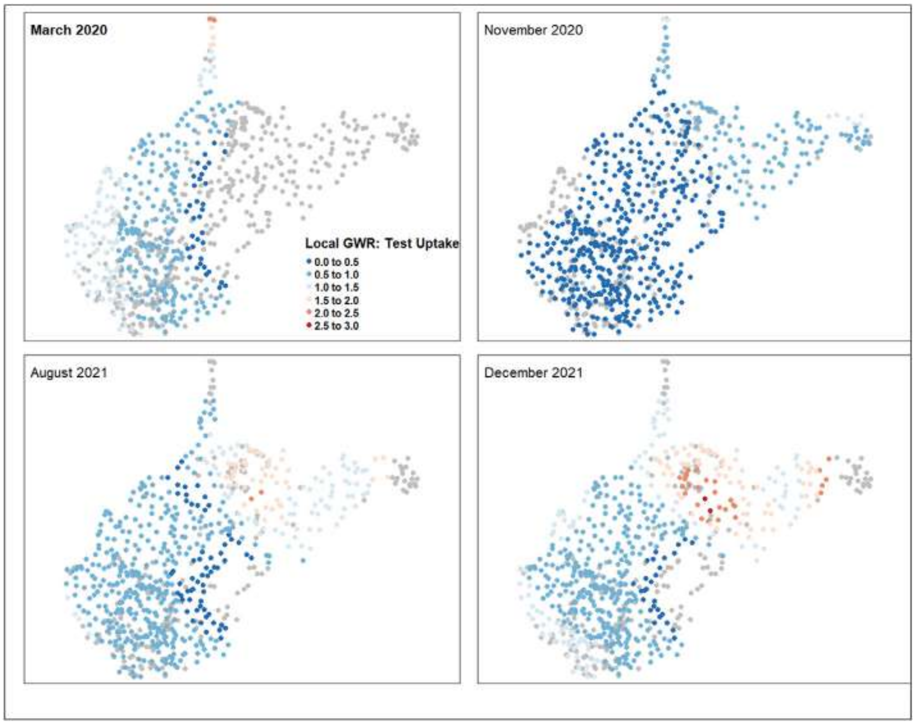

Fig. 2. Local coefficients from geographically weighted regressions (GWRs) examining the effect of testing sites per 1000 persons on the testing rate by ZIP code for March 2020, November 2020, August 2021 and December 2021. ZIP codes with grey dots indicate no statistically significant effect of test sites per 1000 persons on testing rate. ZIP codes where test sites per 1000 persons had a statistically significant local effect are displayed using a blue to red gradient, where lower effects are indicated in blue, and higher effects are indicated in red. It is important to note that any ZIP code with blue or red shading did observe a statistically significant positive effect between number of testing sites and testing rate. The blue to red gradient is used to merely display the extent of the significant effect over time. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article).

all key time intervals examined. No significant relationship was detected when extensive testing resources were available across the state. In November 2020, access to testing increased rapidly due to state-level mandates from the West Virginia Office of Governor.[25] In August 2021, a surge in testing was associated with the detection of the SARS-CoV-2 Delta variant, which was more transmissible and virulent than previous SARS-CoV-2 variants.[26] As such, a possible explanation is that during times of low testing, overall test uptake was lower among communities that also happened to have a higher Black/African American percentage of the population; thus, this does not infer that testing is lowest among Black/African American communities. The results from this study also showed a positive linear relationship between Black/African American percentage of the population and the testing rate, indicating an increase in testing among communities with a higher Black/African American percentage of the population. Therefore, this study suggests that the negative interaction effect identified between Black/African American percentage of the population and test sites per capita could be a result of the fact that the communities themselves had a lower testing rate. This potential theory was tested (results not shown), and it was found that the relationship between Black/African American percentage of the population and testing rate was modified by community deprivation. This is an important result, as the negative linear relationship between ADI and testing rate mitigated the positive effect that Black/African American percentage of the population had on the testing rate.

A previous study also examined the impact of ADI on disparities in COVID-19 testing and positivity within West Virginia but found no significant effect on testing or positivity.[16] On closer examination, the incidence rate ratio reported for ADI in this previous study was 1.31 (95% CI 0.99–1.75), indicating that for some census tracts, ADI had a weak negative effect and a strong positive effect on testing. In West Virginia, there are 484 census tracts and 851 ZIP codes (including PO Box addresses).[27,28] One possible explanation for the differences in these results is that the use of the more detailed ZIP code–level data reduced variability in ADI, which was estimated as the mean of census block group data in the previous study. The significance of ADI as a predictor of COVID-19 risk has been established in many studies across the United States.[29–31] The present study examined the impact of ADI on the use of testing resources, as opposed to COVID-19 risk, and found that testing sites per capita had a greater impact in communities of greater disadvantage. This is an important finding, as it informs decision-makers to direct limited resources to areas where they may have the highest impact on disease surveillance and control. Future studies should aim to understand how other social determinants of health impact the utilisation of testing resources for COVID-19 and other infectious diseases.

Some limitations of the present study should be noted. Perhaps most importantly, the trends identified are related to PCR testing data and do not include rapid antigen testing. This is a potentially important distinction, as higher or differing availability of rapid antigen results could bias the testing rate observed. In addition, the case definition for a positive COVID-19 test in the present study is prone to potential misclassification if samples were improperly handled or if patients were tested too early. That said, PCR testing data have been demonstrated to be more sensitive than rapid antigen testing[32] and samples, with few exceptions, were delivered to the laboratories within 24 h of the time the swab was obtained.

Conclusions

This study addresses gaps in the COVID-19 literature surrounding the impact of test site availability on population-level testing rates and explores how these relationships change when considering social determinants of health. The finding that higher test site availability increases testing uptake for areas of higher community deprivation could inform targeted testing regimens. The results provide critical information to inform future dissemination of testing resources within medically underserved and underrepresented rural groups. The current findings regarding higher Black/African American percentage of the population and lower uptake of testing reflect the challenges of delivering tests within underrepresented rural groups. This study found that it was not the Black/African American populations themselves that had lower testing, but that other neighbourhood-level factors, such as ADI, were partially responsible for the disparities observed.

Further research on health services delivery and use for testing for COVID-19 and other infectious diseases during the pandemic is warranted. For example, qualitative studies are ideally suited to better capture the lived experiences of community groups[33–35] and may determine other factors involved in the trends identified among communities with a higher Black/African American percentage of the population, particularly when factoring in community deprivation. The effects of test sites per capita on testing rate differed dramatically across West Virginia. Overall, higher impacts were noted for northern and north-eastern West Virginia, particularly after the detection of new SARS-CoV-2 variants. Finally, the consistent positive relationship for interaction between ADI and sites per capita on testing is encouraging, particularly given that previous research in West Virginia identified a positive, although not statistically significant, relationship between disadvantaged communities and SARS-CoV-2 testing rate.[16] Taken together, although within different temporal aspects, this suggests that disadvantaged communities take full advantage of testing resources when available, leading to higher testing rates.

Author statements

Ethical approval

This study was approved by the West Virginia University Institutional Review Board (protocol # 2204554630).

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Competing interests

The authors have no conflicts to declare.

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Original Research

Impact of tuberculosis on the incidence of osteoporosis and osteoporotic fractures: a nationwide population–based cohort study

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ABSTRACT

Objectives: Despite the high prevalence of tuberculosis (TB) and the disease burden of osteoporosis and osteoporotic fractures, there is still a lack of well-designed, large-scale studies demonstrating associations among them. We aimed to investigate the effect of TB on the incidence of osteoporosis and osteoporotic fractures.
Study design: This was a nationwide population–based cohort study.
Methods: This study was conducted using the National Health Insurance Service Database of South Korea. We included patients with newly diagnosed TB aged >40 years from January 2006 to December 2017. An uninfected control for each TB patient was randomly extracted by frequency matching for sex, age, income level, residence, and registration date at a 2:1 ratio. The primary outcome was the incidence of osteoporosis and osteoporotic fractures between the two groups, adjusted for sex, age, income level, residence, comorbidities, body mass index, blood pressure, laboratory tests, alcohol drinking, and smoking. The risk factors associated with osteoporosis or osteoporotic fractures were also investigated.
Results: A total of 164,389 patients with TB and 328,778 matched controls were included (71.9% males). The mean duration of follow-up was 7.00 ± 3.49 years. The incidence of osteoporosis in patients with TB was 6.1 cases per 1000 person-years, which was significantly higher than that in matched controls (adjusted hazard ratio [aHR] 1.349, 95% confidence interval [CI] 1.302–1.398, $P < 0.001$). The incidence of osteoporotic fractures was also higher in patients with TB than in controls (aHR 1.392, 95% CI 1.357–1.428, $P < 0.001$). Among fractures, the risk of hip fracture was the highest (aHR 1.703, 95% CI 1.612–1.798, $P < 0.001$).
Conclusions: TB independently contributes to the incidence of osteoporosis and osteoporotic fractures, particularly hip fractures.

Introduction

Tuberculosis (TB) is a common infectious disease and the second leading infectious cause of death worldwide in 2020, after COVID-19.[1] TB is a treatable and curable disease. However, even if properly treated, TB may lead to systemic complications, including both acute and chronic diseases.[2,3] Previous studies have reported that systemic inflammatory cytokines, such as interleukin 1, interleukin 6, and tumor necrosis factor α, are elevated in patients with TB.[7–9] These cytokines are important regulators of bone resorption and may be involved in bone loss and the pathogenesis of osteoporosis.[4–6] This suggests that the incidence of osteoporosis may increase in patients with TB.

Previous studies have investigated the association of TB with an increased incidence of osteoporosis or osteoporotic fractures.[10–12] However, as far as we are aware, no previous study has investigated which sites are most susceptible to osteoporotic fractures in patients with TB. Furthermore, no previous studies have investigated the influence of alcohol consumption, smoking, and body

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mass index (BMI) on the relationship between TB and osteoporosis and osteoporotic fractures nor matched participants with and without TB according to socio-economic status. As alcohol consumption, smoking, and BMI are the major risk factors for the development of osteoporosis and osteoporotic fractures,[13–16] not adjusting for their effects significantly limits evidence of independent contributions of TB to osteoporosis and osteoporotic fractures. Therefore, a study that adjusts for these variables is needed.

Despite the worldwide disease burden of TB, osteoporosis, and osteoporotic fractures, well-designed, large-scale studies are still lacking. Furthermore, as developing countries, such as India, Indonesia, and China, are significant sources of TB,[1] interest in chronic diseases such as osteoporosis will increase in these countries with the development of medical care in the future. Therefore, we aimed to investigate the risk of osteoporosis and osteoporotic fractures in patients with TB using a nationwide population–based database in a country with an intermediate TB burden through comparison with a control group that also considers socio-economic status.

Methods

Data sources

This study was conducted using the National Health Insurance Service-National Health Information Database (NHIS-NHID) of Korea.[19] In Korea, national health insurance is mandatory, and most of the Korean population (97.1%) subscribes to the NHIS. The remaining 3% of individuals with limited income and resources are categorized as Medicaid subjects, who receive medical cost support from the government. As the Medicaid population is also included in the NHIS-NHID, it can be considered to represent the entire Korean population. The NHIS-NHID includes the participants' identifiers, sex, birth date, income levels, residence, comorbidities, and treatment information, such as prescription drugs. Detailed diagnoses are coded using the *International Classification of Diseases, Tenth Revision* (ICD-10).

We also used the National Health Insurance Service-Health Screening (NHIS-HEALS) database.[20] In Korea, all insured citizens aged ≥40 years are required to participate biennially in the health screening program of NHIS, and the health screening rate was about 78.5% in 2017. Using this database, we obtained data on height, weight, BMI, blood pressure, fasting blood glucose, alcohol consumption, and smoking, which are not included in the NHIS-NHID. We merged the NHIS-NHID and NHIS-HEALS databases in this study. This study was approved by the Institutional Review Board of the National Health Insurance Service Ilsan Hospital (Institutional Review Board No: NHIMC 2020-03-072).

Study population

The study population was newly diagnosed with and treated for TB between January 2006 and December 2017. As the guidelines recommend evaluating osteoporosis from the age of 50 years for those with clinical risk factors,[21,22] among the patients with TB, we included those aged >40 years considering the follow-up period after TB diagnosis. Among those given an ICD-10 diagnosis code appropriate for TB, those who had been given a specialized claim code for TB or had been treated with two or more TB drugs for more than 28 days were defined as patients with TB. We used specialized claim codes for the NHIS's expanded benefit coverage service to better designate those with TB. Specialized claim codes guarantee coverage of 90% of the medical costs for patients. As untreated TB is highly contagious, the government subsidizes medical expenses by granting specialized claim codes to patients with TB to control transmission. As specialized claim codes benefit patients through government expenditure, evidence of TB diagnosis must be attached for issuance. Therefore, TB can be defined more strictly using specialized claim codes. The validity of the definition using specialized claim codes was verified in a previous study related to HIV, another infectious disease to which a specialized claim code is assigned.[23] The ICD-10 code, specialized claim code for TB, and TB drug code are described in Supplementary Table S1.

Patients with TB were classified into respiratory TB and non-respiratory TB groups according to related diagnosis codes. For those who had disseminated TB, patients with a co-existing diagnosis code for respiratory TB were classified into respiratory TB, and patients with only a co-existing diagnosis code for non-respiratory TB were classified as non-respiratory TB. The registration date of patients with TB was defined as the creation date of the TB diagnosis code.

The control group for comparing the incidence of osteoporosis and osteoporotic fractures in patients with TB was randomly extracted at a 1:5 ratio. Those diagnosed with osteoporosis or osteoporotic fractures before the registration date were excluded. In addition, those with the absence of the NHIS-HEALS data were excluded. After exclusion, the control group was re-extracted in a 1:2 ratio by matching sex, age, income level, residence, and registration date (Fig. 1).

Outcomes and covariates

The primary outcome of this study was the incidence of osteoporosis or osteoporotic fractures in the two groups during the follow-up period. The secondary outcomes included risk factors associated with osteoporosis or osteoporotic fractures in the entire population and in patients with TB. The diagnosis of osteoporosis and osteoporotic fractures was defined using ICD-10 codes (Supplementary Table S1). Each individual was followed up until the diagnosis of osteoporosis or osteoporotic fractures, date of death, or the end of the study period (December 31, 2017), whichever came first.

In addition to TB, the following variables that can affect osteoporosis and osteoporotic fractures were investigated as covariates: sex; age; income level; residence; and comorbidities, such as hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), ischemic heart disease, liver disease, cancer, and rheumatoid arthritis (RA). Comorbidities were defined according to the ICD-10 codes (Supplementary Table S1). Cases with either one diagnosis of comorbidities during hospitalization or more than twice at outpatient clinics during up to 2 years before the creation date of the TB diagnosis code were considered to have those comorbidities and were included in this study.

We also investigated data on height, body weight, BMI, blood pressure, fasting blood glucose, total cholesterol, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alcohol consumption, and smoking, all of which can affect osteoporosis and osteoporotic fractures. These health screening database variables were also extracted from records up to 2 years before the creation date of the TB diagnosis code. As health screenings are required every 2 years for all insured citizens aged ≥40 years in Korea, health screenings might be performed once during that 2-year period, and therefore, there could be one record of variables in the health screening database in that period.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation, and independent *t*-tests were used to compare patients with TB and controls. Categorical variables were analyzed using the Chi-

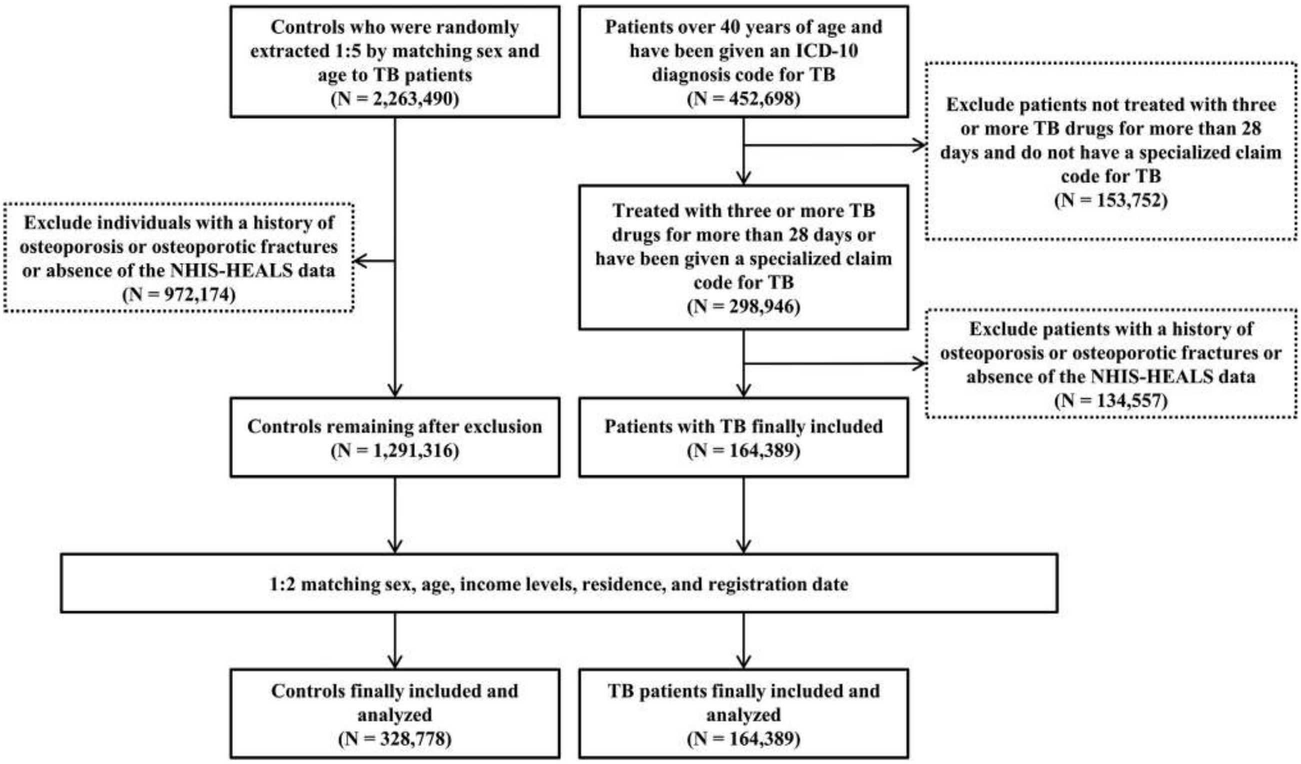

Fig. 1. Flow chart of the study population. NHIS-HEALS, National Health Insurance Service-Health Screening; TB, tuberculosis.

squared test. The incidence of osteoporosis and osteoporotic fractures are presented as the number of events per 1000 person-years. Cumulative incidences of osteoporosis and osteoporotic fractures were plotted, and the differences in the cumulative incidences between patients with TB and controls were evaluated using the log-rank test. Patients with TB were further divided into respiratory and non-respiratory TB, and the risks of osteoporosis and osteoporotic fracture were compared. To identify the independent risk factors for osteoporosis and osteoporotic fractures, Cox proportional hazards models were used to calculate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) after adjusting for sex, age, income level, residence, comorbidities, BMI, blood pressure, fasting blood glucose, total cholesterol, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alcohol consumption, and smoking. The hazard ratios for osteoporosis and various osteoporotic fractures in patients with TB compared with controls were also calculated after adjusting for these variables. A P-value of <0.05 indicated statistical significance. All analyses were performed in SAS, version 9.4 (SAS Institute, Cary, NC) or were conducted using R statistical software, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

A total of 164,389 patients with TB and 328,778 matched controls were included, and the mean follow-up duration was 7.00 ± 3.49 years. In both cohorts, the proportion of people aged >50 years was 70.0%, and 71.9% were males. The proportion of people with Medicaid was 9.5%, and 19.8% lived in the capital in both cohorts. DM, CKD, ischemic heart disease, liver disease, cancer, and RA were more prevalent in patients with TB than in the control group. In patients with TB, BMI was lower (22.29 ± 3.70 vs 24.02 ± 3.13, P < 0.001), but fasting blood glucose was higher (109.60 ± 45.76 vs 103.70 ± 30.41, P < 0.001). The proportion of current smokers (31.8% vs 28.6%, P < 0.001) and those who drank more than five times (20.4% vs 18.9%, P < 0.001) was higher in patients with TB (Table 1).

Incidence of osteoporosis and osteoporotic fractures in the TB and control cohorts

In patients with TB, the incidence of osteoporosis was 6.1 cases per 1000 person-years. In contrast, in the control group, osteoporosis incidence was 4.0 per 1000 person-years. Compared with matched controls, the aHR for osteoporosis in patients with TB was 1.349 (95% CI 1.302–1.398, P < 0.001). For osteoporotic fractures, patients with TB showed a higher aHR overall, compared with the control group (aHR 1.392, 95% CI 1.357–1.428, P < 0.001). This was also identified in vertebral fractures (aHR 1.523, 95% CI 1.476–1.571, P < 0.001), hip fractures (aHR 1.703, 95% CI 1.612–1.798, P < 0.001), and non-vertebral fractures (aHR 1.196, 95% CI 1.148–1.247, P < 0.001). Among patients with TB, those with non-respiratory TB showed a slightly lower risk of vertebral fractures than those with respiratory TB (aHR 0.922, 95% CI 0.859–0.992, P = 0.03; Table 2). The cumulative incidence curves for the incidence of osteoporosis and osteoporotic fractures among patients with TB and matched controls also showed that those with TB had a significantly higher incidence of osteoporosis (Fig. 2) and osteoporotic fractures (Fig. 3) than the matched controls (P < 0.001 by log-rank test, respectively).

Factors associated with osteoporosis and osteoporotic fractures

The factors associated with osteoporosis in the entire study population are presented in Supplementary Table S2. After adjustment, TB was identified as an independent risk factor for osteoporosis (aHR 1.349, 95% CI 1.302–1.398, P < 0.001). Female

Table 1
Baseline characteristics.

Variables		Controls, n (%)	Patients with TB, n (%)	*P*-value
Number of individuals		328,778 (66.7)	164,389 (33.3)	
Sex	Male	236,398 (71.9)	118,199 (71.9)	
	Female	92,380 (28.1)	46,190 (28.1)	
Age (years)	40–49	98,776 (30.0)	49,388 (30.0)	
	50–59	95,546 (29.1)	47,773 (29.1)	
	60–69	65,084 (19.8)	32,542 (19.8)	
	70–79	50,256 (15.3)	25,128 (15.3)	
	80–89	17,650 (5.4)	8825 (5.4)	
	≥90	1466 (0.5)	733 (0.5)	
Income levels	Medicaid	31,114 (9.5)	15,557 (9.5)	
	1–5	65,230 (19.8)	32,615 (19.8)	
	6–10	66,938 (20.4)	33,469 (20.4)	
	11–15	74,274 (22.6)	37,137 (22.6)	
	16–20 (highest)	91,222 (27.8)	45,611 (27.8)	
Residence	Seoul	65,232 (19.8)	32,616 (19.8)	
	Metropolitan	81,580 (24.8)	40,790 (24.8)	
	Urban	143,602 (43.7)	71,801 (43.7)	
	Rural	38,364 (11.7)	19,182 (11.7)	
Comorbidities	HTN	94,173 (28.6)	46,918 (28.5)	0.453
	DM	44,630 (13.6)	38,484 (23.4)	<0.001
	CKD	2351 (0.7)	3360 (2.0)	<0.001
	IHD	462 (0.1)	611 (0.4)	<0.001
	Liver disease	26,592 (8.1)	27,752 (16.9)	<0.001
	Cancer	11,164 (3.4)	16,815 (10.2)	<0.001
	RA	3414 (1.0)	3059 (1.9)	<0.001
Height (cm)	(mean ± SD)	164.10 ± 8.34	164.10 ± 8.45	0.021
Weight (kg)	(mean ± SD)	64.92 ± 10.96	60.14 ± 10.40	<0.001
Body mass index (kg/m2)	(mean ± SD)	24.02 ± 3.13	22.29 ± 3.70	<0.001
SBP (mmHg)	(mean ± SD)	126.40 ± 16.11	124.30 ± 16.75	<0.001
DBP (mmHg)	(mean ± SD)	78.15 ± 10.46	76.85 ± 10.68	<0.001
FBG (mg/dL)	(mean ± SD)	103.70 ± 30.41	109.60 ± 45.76	<0.001
Total cholesterol (mg/dL)	(mean ± SD)	195.80 ± 43.40	187.40 ± 42.24	<0.001
AST (IU/L)	(mean ± SD)	27.52 ± 23.37	29.76 ± 32.64	<0.001
ALT (IU/L)	(mean ± SD)	26.55 ± 25.56	25.15 ± 28.91	<0.001
Gamma-GT (IU/L)	(mean ± SD)	45.74 ± 66.61	58.27 ± 104.30	<0.001
Smoking	Never	139,810 (50.6)	62,652 (48.4)	<0.001
	Ex-smoker	57,508 (20.8)	25,613 (19.8)	
	Present smoker	79,142 (28.6)	41,120 (31.8)	
Drinking (days per week)	≤1	139,127 (51.1)	70,949 (55.6)	<0.001
	2–4	81,699 (30.0)	30,601 (24.0)	
	≥5	51,599 (18.9)	25,997 (20.4)	
F/U years (years)		7.57 ± 3.44	6.41 ± 3.70	<0.001
Total f/u duration, years, (mean ± SD)		7.00 ± 3.49		

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; DBP, diastolic blood pressure; DM, diabetes mellitus; F/U, follow-up; FBG, fasting blood glucose; Gamma-GT, gamma-glutamyl transferase; HTN, hypertension; IHD, ischemic heart disease; RA, rheumatoid arthritis; SBP, systolic blood pressure; SD, standard deviation; TB, tuberculosis.

sex, older age, Medicaid, HTN, liver disease, cancer, and living outside the capital were also identified as independent risk factors for osteoporosis. These results have also been observed in osteoporotic fractures. The aHR of TB for osteoporotic fractures was 1.392 (95% CI 1.357–1.428, $P < 0.001$), and DM, CKD, and RA increased the risk of osteoporotic fractures in addition to the variables identified above (Supplementary Table S3). In the TB cohort, female sex, older age, Medicaid, HTN, DM, CKD, liver disease, cancers, RA, and living outside the capital were identified as independent risk factors for osteoporosis and osteoporotic fractures (Supplementary Table S4).

Discussion

We found that the incidence of osteoporosis and osteoporotic fractures increased in patients with TB, compared with controls, matching sex, age, income level, and residence. This effect of TB remained significant after adjusting for other osteoporosis and osteoporotic fracture risk factors. TB was associated with an increased risk of osteoporotic fractures for all studied fracture sites, with hip fractures being associated with the greatest increase in risk.

Previous studies have reported that TB is associated with systemic inflammatory responses and that the levels of several inflammatory cytokines are elevated in patients with TB.[7–9] In addition, this systemic inflammatory response persists even after completion of TB treatment.[24,25] Proinflammatory cytokines are also involved in the pathogenesis of osteoporosis.[4–6] The expression levels of interferon-gamma, which is a cytokine that plays a crucial role in the immune response against TB,[26,27] were positively correlated with bone loss.[28] Interferon-gamma also stimulates neopterin release, which is associated with increased hip fracture risk.[29] This is consistent with the finding that the hazard ratio of hip fracture was the highest among osteoporotic fractures in our study.

Vitamin D deficiency has been reported as a risk factor for TB, and lower serum vitamin D levels have been reported in patients with TB.[30,31] Vitamin D deficiency can induce bone loss and secondary hyperparathyroidism, leading to osteoporosis and osteoporotic fractures.[32] Therefore, vitamin D deficiency could be another reason for the increased risk of osteoporosis and osteoporotic fractures in patients with TB. Although there is still insufficient evidence on vitamin D supplementation in patients with TB,[33,34] vitamin D supplementation might be considered for the

Table 2
Incidence of osteoporosis and osteoporotic fractures.

	Person-year	Event (N)	Rate (per 1000 person-year)	aHR (95% CI)[a]	*P*-value
Osteoporosis					
Matched control	2,579,176	10,353	4.0	1.000	
All tuberculosis	1,113,546	6809	6.1	1.349 (1.302–1.398)	<0.001
By infections site					
Respiratory	955,733	5719	6.0	1.000	
Non-respiratory	155,846	1074	6.9	1.015 (0.943–1.092)	0.692
Overall fracture					
Matched control	2,514,313	22,211	8.8	1.000	
All tuberculosis	1,073,528	14,260	13.3	1.392 (1.357–1.428)	<0.001
By infections site					
Respiratory	920,458	12,454	13.5	1.000	
Non-respiratory	151,185	1775	11.7	0.944 (0.890–1.001)	0.052
Vertebral fracture					
Matched control	2,560,617	14,661	5.7	1.000	
All tuberculosis	1,102,423	9984	9.1	1.523 (1.476–1.571)	<0.001
By infections site					
Respiratory	945,388	8814	9.3	1.000	
Non-respiratory	155,099	1145	7.4	0.922 (0.859–0.992)	0.030
Hip fracture					
Matched control	2,599,794	4865	1.9	1.000	
All tuberculosis	1,128,356	4208	3.7	1.703 (1.612–1.798)	<0.001
By infections site					
Respiratory	967,533	3812	3.9	1.000	
Non-respiratory	158,844	383	2.4	0.879 (0.769–1.004)	0.058
Non-vertebral fracture					
Matched control	2,575,627	8718	3.4	1.000	
All tuberculosis	1,119,382	5144	4.6	1.196 (1.148–1.247)	<0.001
By infections site					
Respiratory	960,417	4403	4.6	1.000	
Non-respiratory	156,985	733	4.7	0.949 (0.866–1.039)	0.255

CI, confidence interval; aHR, adjusted hazard ratio.
[a] Hazard ratios and 95% confidence intervals were calculated after adjusting for sex, age, income levels, residence, comorbidities, body mass index, blood pressure, fasting blood glucose, total cholesterol, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, alcohol drinking, and smoking.

prevention of osteoporosis and osteoporotic fractures in patients with TB, especially in those with multiple risk factors.

In addition to TB, female sex, older age, HTN, liver disease, and cancer were identified as independent risk factors for osteoporosis and osteoporotic fractures. Women and older age are major non-modifiable risk factors for osteoporosis and osteoporotic fractures.[35,36] Comorbidities, such as liver disease and cancers, are well-known risk factors for osteoporosis and osteoporotic

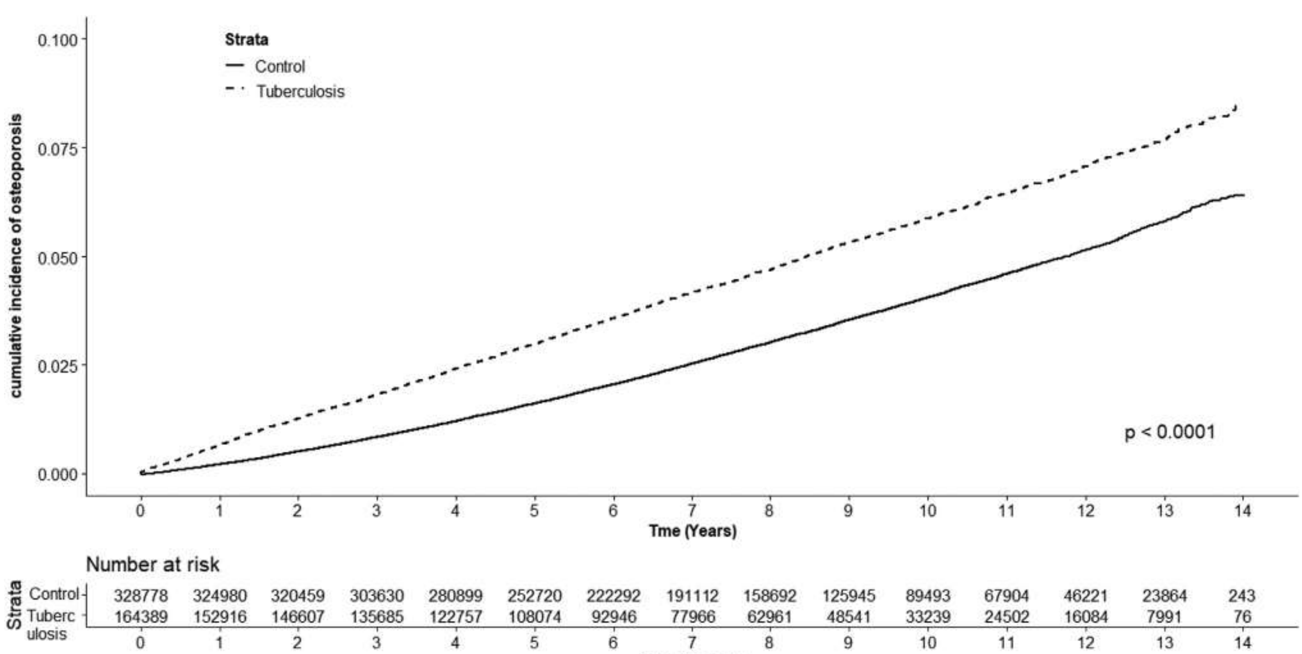

Fig. 2. Cumulative incidence curves for the incidence of osteoporosis among patients with tuberculosis and matched controls. Log-rank tests were performed to compare the two groups.

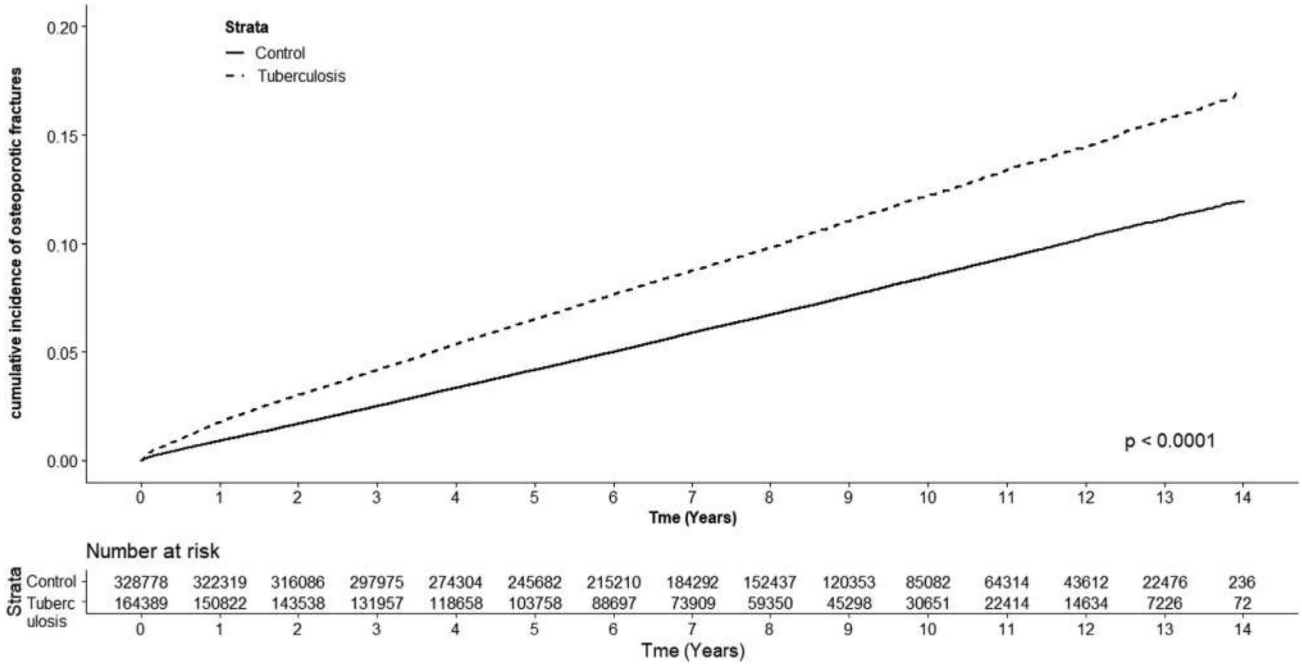

Fig. 3. Cumulative incidence curves for the incidence of osteoporotic fractures among patients with tuberculosis and matched controls. Log-rank tests were performed to compare the two groups.

fractures.[37,38] In the subgroup analysis of patients with TB in this study, these variables were also identified as risk factors. Therefore, among patients with TB, those with these risk factors should be more aware of the risk of osteoporosis and osteoporotic fractures in the future.

In this study, we matched not only sex and age but also income level and residence in the study groups. The incidence of both TB and osteoporosis may be influenced by socio-economic status.[17,18] Therefore, to verify the independent effect of TB on osteoporosis and osteoporotic fractures, it is necessary to match the socio-economic status between patients with TB and the control group. In fact, in a previous study on the association between TB and osteoporosis, both income level and proportion of urban residents with TB were lower than those of the control group.[12] This is a limitation to ascertaining the independent effect of TB on osteoporosis, as it may have influenced the outcome. We represented socio-economic status through income level and residence, and the controls were extracted by matching income level and residence with sex and age. As a result, we were able to present the independent effect of TB on osteoporosis and osteoporotic fractures. Our multivariable regression analyses showed that individuals with Medicaid and living outside the capital were independent risk factors for osteoporosis and osteoporotic fractures. These results were identified in the multivariable analysis of all patients and only patients with TB. Considering that developing countries, such as India, Indonesia, and China, are significant sources of TB, and interest in chronic diseases such as osteoporosis will increase in these countries with the development of medical care in the future, it is necessary to pay attention to osteoporosis and osteoporotic fractures that can occur in patients with TB. This is important in terms of reducing the global disease burden.

This study has several advantages. In addition to the previously mentioned matching of socio-economic status, this study was a well-organized, large-scale study. TB was analyzed by dividing it into pulmonary and extrapulmonary TB. We investigated not only the incidence but also the sites of fracture; consequently, we identified that the risk of hip fracture increased the most. Another important advantage of this study is that we presented the independent risk of TB more rigorously by adjusting for alcohol consumption, smoking, and BMI, which can significantly affect osteoporosis in the multivariable analysis. As alcohol consumption, smoking, and low BMI are major risk factors for the development of osteoporosis and osteoporotic fractures,[13–16] without adjusting for their effects, there is a significant limitation to suggesting the independent contribution of TB to osteoporosis and osteoporotic fractures. In particular, as suggested by the results of this study, the proportion of smokers and excessive drinkers was higher, and BMI was lower in patients with TB than in the controls; therefore, adjustment of these variables is mandatory. Without adjustment, it is difficult to determine whether TB is an independent risk factor for osteoporosis and osteoporotic fractures or whether low BMI and high rates of smoking and excessive drinking in patients with TB can cause osteoporosis and osteoporotic fractures. In this study, the effects of alcohol consumption, smoking, and BMI were adjusted by multivariable regression analysis; therefore, the independent risk of TB on osteoporosis and osteoporotic fractures could be well presented. To the best of our knowledge, this is the first time that we have adjusted for all of this in our analysis, and we consider this to be a major strength of our study.

Despite these advantages, our study has several limitations. First, variables that could affect the incidence of osteoporosis and osteoporotic fractures were not fully included because of the inherent limitation of the database. Information on some confounding factors, such as steroid use, asthma, chronic obstructive pulmonary disease, vitamin D, sun exposure, estrogen, a family history of osteoporosis, or patient activity, was not investigated. In addition, information regarding osteoporosis treatment has not been investigated. However, because the study population was large and other comorbidities and risk factors were adjusted, we think that it did not significantly affect the results. Despite the inherent limitations, many previous studies have been published through the corresponding database.[39–41] Second, our study did not include TB severity or duration of TB treatment. If TB is severe or treatment is prolonged, the risk of developing osteoporosis or osteoporotic fractures may increase. However, these effects could not be evaluated because information was not collected in this study. Third, this study was conducted in South Korea, a country with almost a single ethnicity of Asians. As it is known that ethnic differences play a significant role in the incidence of osteoporosis and osteoporotic fractures,[42] additional research is warranted to determine whether the results can be applied to other races and countries. Fourth, subjects who did not undergo health screening were not included in this study. Because a biennial health screening is required but not mandatory for all insured citizens aged $\geq$40 years, it is possible that subjects with relatively good healthcare adherence were mainly included in the study. Nevertheless, the analysis of this study included more than 160,000 TB patients, and we believe that it is crucial to include variables, such as BMI, alcohol consumption, and smoking, to identify the independent contribution of TB to osteoporosis.

In conclusion, TB was identified as an independent risk factor for osteoporosis and osteoporotic fractures, particularly hip fractures. The independent contribution of TB to osteoporosis and osteoporotic fractures was verified after adjusting for other factors. Considering the worldwide disease burden of TB, the incidence of osteoporosis and osteoporotic fractures among patients with TB is expected to increase. Because patients with osteoporosis and osteoporotic fractures are associated with high morbidity and mortality, careful follow-up is warranted in patients with TB, especially in high-risk patients with other risk factors.

Author statements

Ethical approval

This study was approved by the institutional review board of the National Health Insurance Service Ilsan Hospital (Institutional Review Board No: NHIMC 2020-03-072). The informed consent of the participants was waived because of the pure observational nature of the study.

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Competing interests

The authors declare there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.12.009.

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Original Research

Increased female political representation associated with lower county-level uninsured and preventable hospitalizations rates in the United States, 2013–2018

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A B S T R A C T

Objective: Although women comprise 50% of the population, females remain underrepresented in government. Inequitable female political representation, a form of structural sexism, may impact population health. Previous studies focused primarily on individual health behaviors and low- or middle-income countries. To date, no study has examined the association between female political representation and healthcare access and utilization, immediately policy-amenable outcomes, in the United States.

Study design: This was a repeated cross-sectional study.

Methods: This study uses 2013–2018 county-level data from the County Rankings. I performed multilevel analyses to determine the relationships between state-level female representation (% female state legislators) and two outcomes—the percentage of county-level population under age 65 years without health insurance (primary outcome) and the county-level preventable hospitalization rates (secondary outcome of interest). Potential confounders included county-level and state-level characteristics such as the unemployment rate. I also examined whether associations differed by political party control of the state legislature.

Results: In the fully adjusted model, one standard deviation difference in female political representation was associated with a decrease of 0.22 percentage points in county-level uninsured (95% confidence interval = −0.32, −0.12). The association between female political representation and preventable hospitalization rate differed according to state political party in control, with a decrease found only among counties in democratic/split controlled states (−80.51, 95% confidence interval = −149.65, −11.38).

Conclusions: The results suggest that policy intervention addressing the underrepresentation of women in government may help increase the proportion of uninsured and, under certain circumstances, decrease county-level unnecessary hospitalizations. However, further research is needed to better understand the role of political party control in modifying noted associations.

Introduction

Women comprise a little more than half of the US population. However, female political representation is only 30% of state legislation.[1] According to the 2019 World Economic Forum report, the United States compares poorly to other high-income countries in gender equality in politics.[2] This persistent underrepresentation of women in the US political institutions reflects the structural sexism inherent in our country—the social, economic, and political systems that support gender inequities.[3] Female political representation is a crucial indicator of structural sexism nationally and locally. Furthermore, the persistent underrepresentation of women in US political institutions may have immediate and long-term population health ramifications.[3]

As described in the ecosocial theory of disease distribution, social and political processes contribute to population health because they are significant determinants of material, social, psychological, and environmental exposures.[4,5] Female political

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representation reflects political processes in our society. The number of women in political office is often the effort of multiple interventions to bring more women into political office and change social norms.[6] For example, the introduction of quotas is a significant predictor of the level of a nation's women's representation today.[7] In addition, female political representation may also be an active instrument of change in the political system because they may be more accountable to their female constituents.

Previous studies have found important gender differences in political interests and concerns. Females generally prefer more public spending on social issues than men, leading to female legislators supporting these causes.[8–10] For example, increased female political representation in various South American, Asian, and European countries has been associated with increased social public spending on services such as education, drinking water infrastructure, and welfare.[10–14] Furthermore, political science studies have also found female politicians were more likely to promote policies that differed from their male politicians.[15] For example, the election of female politicians in local German systems led to an increase in public childcare provision.[16] In the United States, increased female representation in Congress has been associated with the passage of health, education, and women's health policies.[17] Therefore, in the US context, increasing female political representation may affect healthcare access and healthcare utilization outcomes either indirectly or directly. Greater female political representation may affect healthcare utilization indirectly through increased expenditures in social and passage of specific social policies, contextual factors that affect health outcomes.[10,13,18,19]

Previous studies have found greater female political representation to be associated with decreased child and infant mortality in Africa, Asia, Europe, and South America.[13,20,21] One study found that a 10 percentage point increase in female representation was associated with a two percentage point reduction in neonatal mortality.[22] This emerging body of literature on female political representation has primarily focused on children's health outcomes. Furthermore, there is limited research on the association between female political representation and population health in the United States.

The impact of female representation on health outcomes in the United States may differ from other countries because of critical social, cultural, and political differences. Two recent systematic reviews on structural gender inequality found only a handful of articles that have examined the association between political representation and health in the United States.[23,24] This limited body of research on the health impact of female political representation in the United States had several limitations, including a focus on individual health behaviors or mental health and the use of composite measures of female empowerment. These studies have also reported mixed results. One ecological study with state-level exposure and outcome found that an increase in a composite measure of female status including political participation was associated with lower male and female mortality rates.[25] However, composite measures of female political participation did not find any association with anxiety, mood, and depressive symptoms for women[26,27] or any association with alcohol consumption in women or men.[28]

The mixed results from previous studies in the US context may also be because of the use of composite measures of female status and the focus on individual health behaviors and outcomes. Composite measures of female political participation may obscure associations between female political representation and health because it combines multiple indicators. For example, a previous study that found no association between female political participation and depression used a composite measure combining several indicators, including voter registration, voter turnout, women's institutional resources, and female elected officials.[26] The composite measure of female political participation may dilute any association related to female elected officials. In addition, previous studies may not have found any statistically significant association with individual health behaviors because it may be too distally related to political representation and influenced by multiple individual and contextual factors.[29]

The present study addresses several of these limitations. This study examines the association between state-level female political representation and two important population health indicators—healthcare access and utilization. The primary outcome is the county-level proportion of uninsured, and the secondary outcome of interest is preventable hospitalization rates. The county-level proportion of uninsured is policy amenable,[30] so it is likely to be sensitive to female political representation. Preventable hospitalization often reflects a lack of access to care[31] and is associated with changes in healthcare insurance access.[32] Given female legislators' presumed support of more liberal welfare policies and presumed more pronounced health and social services expenditures, I hypothesize that greater female political representation will lead to a lower county-level proportion of uninsured and lower county-level preventable hospitalization rates.

Furthermore, reflecting the growing influence of political ideology in US politics, I expect that the political party controlling the state legislature may affect this association. Republicans and Democrats have become increasingly divergent in the primary interest group sectors they represent and the type of policies their parties will support.[33,34] Therefore, I hypothesize that the association between female political representative and preventable hospitalization and insured rates will be greater when the democrat/split party control the state legislature.

Methods

This study uses information from the 2013–2018 County Rankings data set merged with annual state-level details from the US Census ($n = 18{,}663$). The primary exposure is annual female representation in state legislation from the Center for American Women and Politics Women Elected Officials Database.[35] The state level is an appropriate level to examine the role of female political representation because a primary function of the state legislatures in the United States is the appropriation of public funds. Similar to previous studies,[3] I operationalized structural sexism as the percentage of female legislators in the 2016 state legislature.

This study examines two different healthcare access–related outcomes. The primary outcome is the county-level proportion of uninsured. The secondary outcome of interest is the county-level preventable hospitalizations rate. Information from both outcomes was from the County Rankings trends data set. The county-level proportion of uninsured was calculated from the County Rankings data set as the percentage of the county-level population under the age of 65 years without health insurance. The preventable hospitalization rate is the number of hospital stays for ambulatory care–sensitive conditions per 100,000 Medicare enrollees.

The fully adjusted models included several county- and state-level potential confounders. These covariates reflect possible differences in the sociopolitical climate that explicitly influence female representation and the outcomes. County-level covariates from the County Health Rankings included the percentage of the county's children population who live in poverty, the percentage of the county population who are female, the percentage of the county population who are non-Hispanic White, and the percentage of the county, which is rural. Potential state-level confounders included the total population size, the percentage of the state population who are female, the female-to-male ratio of average income, and whether the state legislature political party control was republican or democrat/split control. The state-level covariates are from the Kaiser Family Foundation, with the exception of the female-to-male ratio of average income. The state-level gender-specific measure on the average income was from the American Community Survey (ACS) 1-Year Estimates-Public Use Microdata Sample. Information about party control of state legislature data for all years is from the National Conference of State Legislatures and categorized as a binary variable (republican or democrat/split/or non-partisanship) because of the small number of states, which were not republican controlled during the study period. Following the standard approach, I adjusted for age by including variables indicating the population's age distribution when the dependent and independent variables are crude population rates.[36] All the covariates besides the total population and the indicator variables for age, year, and political party were Z-transformed. I calculated correlation coefficients for all potential confounders and found no two variables with a correlation coefficient higher than 0.4.

Statistical analyses

Multilevel analyses were conducted to account for the multiple nested counties within states. I estimated a sequential series of multilevel random state-level intercept models to investigate the association between state-level structural sexism with county-level outcomes: (1) an unconditional model indicating variability between US states for each of the outcomes; (2) models adjusted for county- and state-level demographic characteristics; and (3) models with an interaction term to examine if associations differ according to the state political party in control. In a sensitivity analysis to examine whether there were lagged associations, I reran all models with a variable indicating the previous year's female political representation. All statistical analyses were conducted using Stata 15.0 (Stata Corp, College Station, TX) with statistical significance set at $P < 0.05$ (two tailed). Montclair Institutional Review Board reviewed this study and considered it exempt.

Results

The analytical sample consisted of six years of county-level data with complete information from 2013 to 2018. On average, an annual 3109 counties were in our sample (range 3093 in 2018–3123 in 2014), approximately 98% of all the counties. The mean county population size was 103,316 (range 262–1.02e+07). The county mean proportion of childhood poverty was 23%, non-Hispanic White was 77%, proportion female was 50%, and the proportion rural was 58%. The mean state population was 6,418,246 (range 577,601–3.95e+07). The average state-level ratio of female to male wages was 0.61 (range 0.44–0.79), and the average state-level proportion of females was 0.47 (range 0.11–0.52). The average female political representation was 0.25 (range 0.11–0.42) (Table 1).

In the unadjusted model, one standard deviation change in the proportion of females in the state legislation was associated with a statistically significant −0.15 decrease in the county proportion of uninsured (95% confidence interval [CI] = −0.25, −0.06). In the model adjusted for county- and state-level potential confounders, one standard deviation change in the proportion of females in the state legislation was associated with a decrease of 0.18 (95% CI = −0.30, −0.10) in the county proportion of uninsured (Table 2). This association did not differ by the political party controlling the state legislation (β for the interaction term = −0.08, 95% CI = −0.19, 0.02).

There was no statistically significant association between the proportion of females in the state legislation and county-level preventable hospitalization in the unadjusted or adjusted models (Table 2). However, the interaction term for female political representation and the state political party in control of the state legislation indicates political party in control of the state legislature was statistically significant, indicating heterogeneity in the association (interaction term β = −217.9, 95% CI = −387.8, −48.0). As shown in Fig. 1, the association between increasing female political representation differed according to the political party in control of the state legislature. Increasing female political representation was associated with decrease in preventable hospitalization if a non-republican party (i.e. democrat, split, or NA) controlled the state legislature. Using a one-year lagged variable for female political representation did not change the results associated with female political representation (Appendix Table 1).

Discussion

Female political representation is likely to impact the population that goes beyond its immediate symbolic social or cultural presentation of more females in the legislature. This study finds that increasing female political representatives is associated with decreased county-level uninsured. Although the proportion of females in the state legislation was not associated with a statistically significant difference in county-level preventable hospitalization in the overall sample, there were differences in this according to the political party in control of the state legislature. If a non-republican party controlled the state legislature, increasing female political representation was associated with a statistically significant decrease in preventable hospitalization. These findings suggest greater female political representation is associated with healthcare access and utilization, but the statistical significance of the association on utilization may depend on the larger political context.

Research on the association of female political representation with health in high-income countries is sparse, and previous efforts have found mixed results on individual health behaviors. Previous research has found structural sexism, including state political representation, to be associated with worse self-rated health and worse physical functioning among women,[3] greater risk cesarean sections among pregnant women,[37] and higher infant mortality.[19] This study is the first to examine the association of female political representation on healthcare access and utilization, two outcomes more proximal to policy and expenditure changes usually associated with female legislators.

During the study period, 2013–2018, 60% or more of the women serving in state legislation were democrats. This pattern mirrors what is occurring on the national level. There has been a growing partisan disparity in female representatives since the 1980s,[38] which may explain the heterogeneity found for preventive hospitalization related to party control. As most elected female representatives are non-republicans, they may be constrained when the republican party is in control because of differences in political ideology. Therefore, in an era of increasing partisan polarization and animosity, the associations between female representatives and population health may be muted and become increasingly drawn along partisan lines. Further research is needed to understand how the intersection of gender and political partisanship may affect support of difference policies and programs and, by extension, population health outcomes.

Study results should be interpreted in light of their limitations. First, the county-year data structure allowed us to control for annual variables that reflect overall states' social and health

Table 1
County-level and state-level characteristics of sample (n = 18,838).

Area-level characteristics	Mean	Median	Range
County-level characteristics			
Population size	103,316	26,159	262, 1.02E+07
Proportion non-Hispanic White	0.77	0.84	0.03, 0.99
Proportion child poverty	0.23	0.22	0.03, 0.75
Proportion of population female	0.50	0.50	0.27, 0.57
Proportion rural	0.58	0.59	0, 1
State-level characteristics			
Population size	8,748,800	6,040,715	577,601, 3.95E+07
Proportion female in legislation	0.25	0.25	0.11, 0.42
Female-to-male ratio of average income	0.61	0.61	0.45, 0.79
Proportion of population female	0.47	0.51	0.11, 0.52
States with republican control of state legislature (%)	28 (0.56)	–	–

Sample consisted of 18,838 counties (3140 counties in 2013, 3134 counties in 2014 and 3141 counties annually from 2015 to 2018).

Table 2
Multilevel models examining the association of female political representation and county-level percentage uninsured and preventable hospitalization rates, United States, 2013–2018.

Area-level characteristics	Preventable hospitalization rate			Percentage uninsured		
	Unadjusted	Adjusted	Includes interaction term	Unadjusted	Adjusted	Includes interaction term
n	18,663	18,654	18,654	18,819	18,798	18,798
State-level characteristics						
Proportion female in legislation Z-score	4.83 (−54.1, 63.8)	4.52 (−54.72, 63.76)	−80.51 (−149.65, −11.38)	−0.15 (−0.25, −0.06)	−0.20 (−0.30, −0.10)	−0.16 (−0.27, −0.04)
Female-to-male ratio of average income Z-score	–	−68.66 (−114.12, −23.21)	−56.46 (−102.17, −10.75)	–	−0.46 (−0.53, −0.39)	−0.47 (−0.54, −0.39)
Proportion of population female Z-score	–	20.3 (−4.06, 44.65)	12.62 (−11.93, 37.17)	–	0.01 (−0.03, 0.05)	0.02 (−0.02, 0.06)
Republican vs. non-republican control of legislature		9.06 (−66.29, 84.41)	51.7 (−25.69, 129.10)	–	−0.20 (−0.32, −0.08)	−0.22 (−0.35, −0.10)
Republican control of state legislature × proportion female political representation	–	–	153.99 (89.25, 218.74)	–	–	−0.08 (−0.19, 0.02)
County-level characteristics						
Proportion non-Hispanic White Z-score	–	−1.4 (−64.69, 61.90)	−1.3 (−64.55, 61.95)	–	−0.91 (−1.04, −0.79)	−0.91 (−1.04, −0.79)
Proportion child poverty Z-score		235.72 (192.69, 278.76)	234.79 (191.77, 277.81)	–	0.72 (0.65, 0.80)	0.72 (0.65, 0.80)
Proportion female Z-score	–	−44.27 (−86.34, −2.20)	−44.01 (−86.13, −1.99)	–	−0.08 (−0.16, 0.00)	−0.08 (−0.16, 0.00)
Proportion rural Z-score	–	23.81 (−25.94, 73.56)	23.59 (−26.17, 73.34)	–	0.88 (0.78, 0.98)	0.88 (0.78, 0.98)

All models also included fixed effects for year, state population, and state and county age distribution.

environments. However, it is still measured on the population level and subject to ecological bias. Second, this study focuses on a state-level measure of female political representation because most policies and expenditures are determined at the state level in the United States.[39] County-level female political representation may differ from the state level. Local county-level female representation may reflect more of the area-level social norms, which operate under different pathways than state-level mechanisms of policy and expenditures. While outside the focus of this study, future studies should examine the association between female political representation on both meso- and macro-levels at health. Third, missing values in the county-level data may have led to selection bias, but the negligible proportion of counties missing information (<2%) limits this bias. Finally, this study assumes the association between female representation and health is relatively immediate. Thus, there may be misclassification bias if such an association is lagged. However, the existence of such a misclassification bias would bias these results to the null.

To summarize, this study offers additional evidence that expanding female political representation is associated with positive changes in policy-amenable health outcomes—healthcare access and utilization. In addition, this study provides further evidence of the role of diverse and varied political representation in achieving equitable population health goals. In the United States, policies that affect health including taxation, access to health care, education are made on the state level.[39] By contrast, the responsibilities, number

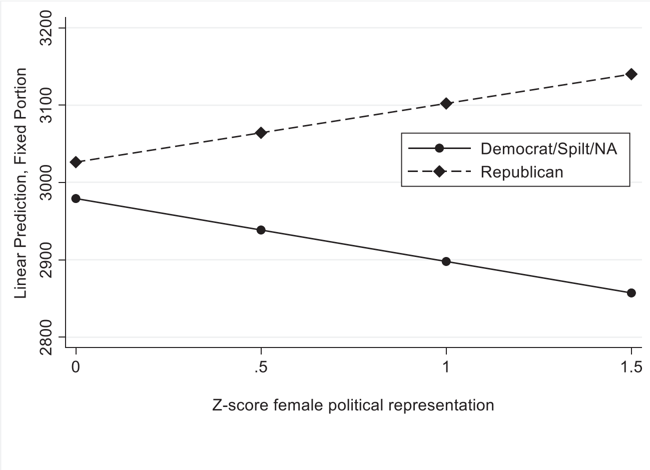

Fig. 1. Conditional average marginal effects of non-republican vs. republican control of state legislature with 95% confidence intervals.

and titles of elected county level, more commonly known as local officials, vary greatly by state. For these reasons, using state-level female representation may be a more accurate reflection of structural sexism that would affect policies and public expenditures. Nevertheless, this field remains understudied, and additional research is needed to identify mechanisms and contextual factors that may modify any association. Further research will need to elucidate whether possible mechanisms, such as support of Medicaid expansion and increased healthcare expenditures, are responsible for associations found in this study.

The recent election of Kamala Harris as the first female Vice President in the United States proclaims a new era of women in politics. Despite this achievement, female political representation in the United States continues to lag behind many other nations. Women's access to political office is determined by multiple contextual factors, including sociocultural norms, government policies, and the strategies of political parties. Nations in Europe, Asia, and Latin America have recognized the difficulty of individual action to address these barriers to achieving equal gender representation and have implemented policies as a policy response to increase female political representation at the local or national level.[7]

The support and level of female political representatives in a given nation reflect larger gender norms and attitudes in society. Gender remains one of several critical social determinants to access, power, and opportunities in our culture. Continuing inequality in female representation in the US may perpetuate adverse population health outcomes, especially those that could potentially be effectively addressed through policies.

Author statements

Ethical approval

This study was approved as exempt by the author's institutional review board and declared to be exempt.

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Competing interests

The author has no conflict of interest to report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.12.007.

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Original Research

Openness to church-based firearm safety interventions among Protestant Christian firearm owners

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ABSTRACT

Objectives: Protestant Christians are more likely to own firearms and not store them locked/unloaded compared to those from other religions. This study examines how Protestant Christians view the relationship between their religious and firearm beliefs and how that informs openness to church-based firearm safety interventions.
Study design: Grounded theory analysis of 17 semi-structured interviews with Protestant Christians.
Methods: Interviews, conducted August–October 2020, focused on firearms owned, carrying/discharge/storage behaviors, Christian belief compatibility with firearm ownership, and openness to church-based firearm safety interventions. Audio-recorded interviews were transcribed verbatim and analyzed using grounded theory techniques.
Results: Participant perspectives varied on firearm ownership motivations and compatibility of Christian values with firearm ownership. Variation in these themes and in openness to church-based firearm safety interventions resulted in clustering of participants into three groups. Group 1 owned firearms for collecting/sporting purposes and intricately connected their Christian identity with firearm ownership, but they were not open to intervention due to perceived high firearm proficiency. Group 2 did not connect their Christian identity to their firearm ownership; some believed these identities were incompatible, so were also not open to intervention. Group 3 owned firearms for protection and believed church, as a community hub, was an excellent location for firearm safety interventions.
Conclusions: The clustering of participants into groups varying in openness to church-based firearm safety interventions suggests it is feasible to identify Protestant Christian firearm owners open to intervention. This study presents a first step in coupling firearm owner characteristics with community-based, tailored interventions with promise for efficacy.

Introduction

Firearms account for 45,000 deaths and 86,000 injuries annually in the USA.[1] State prevalence of firearm ownership is strongly associated with rates of firearm-related injuries and deaths.[2–4] Studies since the 1970s have found firearm ownership and safety behaviors differ by religious affiliation. The 83.1 million religiously conservative Protestant Christian adults in the USA are more likely to own firearms and engage in riskier firearm behaviors than non-religious adults or those of other religions.[6–13] Yet, the effect of religious beliefs on practicing firearm safety behaviors, such as safe storage practices, is often ignored in public health interventions.

Several mechanisms explain the association between religious beliefs and firearm ownership/safety behaviors of Christians. Firearms symbolize identity, power, and self-determination.[14] Some Protestant Christians liken these symbols to sacredness[14] and the individualist tradition characteristic of their religion.[15] In addition, some beliefs specific to Protestant Christians, such as the

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punitiveness of God, biblical inerrancy, and moral convictions of sin, are associated with firearm ownership.[16,17] Protestant Christians' ethic—a set of moral principles—guides firearm owners to stress three duties: to protect others, defend self, and be diligent about safety.[18]

While research has begun to explain how Protestant Christians' religious beliefs influence their firearm ownership and safety beliefs, literature exploring how these beliefs may influence openness to safety interventions is lacking. Furthermore, Protestants may be particularly resistant to firearm safety interventions due to disparities in scientific literacy[19] and skepticism of public health messaging.[20,21] Furthermore, social network homophily, the degree of ideological similarity of one's social network, influences exposure and perceived credibility of public safety information.[22,23] For some individuals, the location of social networks within a homogeneous religious group suggests firearm safety interventions may be more effective at the organizational (i.e., church) than individual level. Church-based health promotion interventions for cancer screening, diet, and smoking cessation have been successful at modifying health behaviors.[24–27] This study therefore sought to explore in-depth how Protestant Christians view the relationship between their religious and firearm beliefs, focusing on how this relationship informs openness to church-based firearm safety interventions.

Methods

Sampling and recruitment

Eligibility criteria included self-identification as Protestant Christian, 18 years or older, lived in the USA, spoke English, and personally owned a firearm. A purposive sampling strategy was used to prioritize geographic diversity and gender balance. Beginning with researcher contacts, snowball sampling was used until saturation was reached (no novel themes identified within the last three participants). The interviewer described to participants motivations for conducting the study and questions to be asked; informed consent was obtained verbally. Participants were instructed that interviews would be kept confidential and were given a $20 gift card. All interviews were conducted over telephone by the lead author, who has extensive experience interviewing. Interviews lasted 30–90 min. Study procedures were approved by the Institutional Review Board.

Interview guide

The semi-structured interview guide was developed using literature and pilot tested with two community members who provided feedback. It included six domains: 1) types, number, and motivations for owning firearms; 2) firearm safety behaviors (concealed carry, discharge, and storage); 3) media, public, and private firearms discourse; 4) beliefs about the source and limits of the firearm rights; 5) compatibility of Christian beliefs and firearm ownership; and 6) openness to firearm safety interventions. For this last domain, participants were first asked, "What would you think about having a firearm safety training either at your church or with your church family but held somewhere else?" Depending on the participants' response, the interviewer then discussed specific aspects of a potential firearm safety training, such as the nature of the training (e.g., distributing lock boxes or trigger locks, beginning with a general injury prevention program such as Stop the Bleed[28] and transitioning the conversation into firearm safety) as well as preferred leaders (e.g., a church member who is an expert in firearms safety or an outside expert).

Data analysis

Interviews were audio recorded, transcribed verbatim, and analyzed using Dedoose software.[29] Drawing on grounded theory methods, the initial analytic phase included inductive thematic analysis involving a close reading of interview transcripts and open coding to identify key themes and questions that emerged to understand participants' perspectives. Three interviews were double-coded and disputes were discussed until consensus was reached. Once the codebook was agreed upon, the second phase of analysis involved axial coding to interconnect themes. Finally, the third phase used within-case and cross-case comparisons to identify patterns and counter-narratives.[30]

Reflexivity statement

Interviews and analysis for this study took place between August 2020 and June 2021 amid the COVID-19 pandemic, polarizing US presidential election, and social uprising against racial injustice in the aftermath of anti-Black police violence. These themes were prominent throughout the interviews, and the authors highlight them in the results where appropriate. The lead author engaged in memoing and peer debriefing with the author team to reflect on the influence of these events on interviews and analysis.

Results

Seventeen participants from 11 states completed interviews, and were nearly evenly split across gender, with nine men and eight women (Table 1). Participants reported denominations to be Methodist ($n = 5$), Baptist ($n = 4$), Non-denominational ($n = 2$), Presbyterian Church in America ($n = 2$), and Church of Christ ($n = 1$); three participants did not report their denomination.

We found participants were clustered into three groups based on their responses to several key themes (Table 2). Groups 1 ($n = 5$) and 2 ($n = 5$) were not open to church-based firearm safety interventions, whereas Group 3 (n = 7) reported enthusiasm at the

Table 1
Demographics of participants ($n = 17$).

	N	%
Gender		
Woman	8	47
Man	9	53
Race		
Asian	1	6
Black	2	12
White	14	82
State		
Alabama	5	29
California	1	6
Georgia	2	12
Florida	1	6
Kentucky	1	6
Mississippi	1	6
North Carolina	2	12
South Carolina	1	6
Texas	1	6
Virginia	1	6
Washington	1	6
Denomination		
Baptist	4	24
Church of Christ	1	6
Methodist	5	29
Non-denominational	2	12
Presbyterian Church in America	2	12
Not reported	3	18

same interventions. These three groups were also distinguishable based on several other themes, outlined in more detail below: characteristics of firearms owned and ownership motivations, compatibility of Christian values with firearm ownership and use, and Divine inspiration of duties as a firearm owner (Fig. 1).

Openness to Church-based firearm safety interventions

Openness to church-based firearm safety interventions was based on responses to questions about community changes to increase firearm safety. Some participants suggested a church-based intervention without prompting, while others reacted to interviewer-suggested programs such as lockbox distribution or integrating conversations about safe firearm storage/handling into existing first aid programs. Members of Group 1 were unwilling to participate in such interventions, as they viewed themselves as already proficient in firearm safety and not in need of additional trainings. One participant explained,

> "*I assume that people like me who have been dealing with guns all our lives feel comfortable carrying guns and feel confident. I've been around guns since I was 11 years old.*"

Some members of Group 1, however, did express interest in leading these trainings or had facilitated similar trainings. One participant described his role as a community expert,

> "*Now I have personally had probably 10 women, since the first of the year, want me to teach them how to shoot and recommend what they should buy and all that sort of thing. So I've actually taught first time gun owners how to use them safely, you know, marksmanship and all that sort of thing.*"

Similar to participants in Group 1, most participants in Group 2 reported being less open to such interventions (compared to Group 3); however, they emphasized their hesitancy was based in a belief that church was not an appropriate place to discuss firearms:

> "*For me personally, when I go to church, I don't look at things like having to face self-defense or anything like that. When I go to church, I want to go to be refilled spiritually and to learn and be taught and be led. So I would not be interested in something like that.*"

In contrast, most members of Group 3 expressed enthusiasm at the idea of a church facilitating a firearm safety intervention. One participant explained the church would be an appropriate venue because of its role as a community hub,

> "*I think that [church] would be a good place to have this, I sure do. As the church, you're going to talk about being a pillar in the community [it should be] your number one goal to make sure that these firearms that you have and talk about are safe within the community.*"

This group also emphasized the importance of these interventions being culturally tailored to rurality or gender. One participant explained the need for a female-led course,

> "*I would love to have a gun safety class for women because when I learned to swim, I had an instructor that was a male, and as a novice learner, he was very proficient, but he would miss little key details. [...] And I think that sometimes some of the terminology, some of the lingo, some of the things that men may say openly to women do not gravitate. So I would have a class that will be very safe for women. And they would feel comfortable asking questions and not feeling like it was not appropriate because they should know.*"

Characteristics and motivations for firearm ownership

Participants reported owning between two to more than 200 firearms; there were sizeable differences in numbers owned and motivations for owning firearms. Group 1 reported owning 50–200+ firearms. The principal ownership motivation for most of these individuals was for collecting or investment, followed by recreation. They also described firearm ownership as a method to preserve American values such as hunting. One participant explained,

> "*You know you have a right to defend yourself, and there's a hunting tradition in this country, recreational hunting. Which a lot of it I've taught my sons how to hunt responsibly and to not just kill an animal for no reason but prepare meat—that sort of thing. It could be important if there's some kind of a problem with the food chain, you know, to help provide for yourself, to be able to shoot deer, squirrels, and birds, and stuff.*"

Group 2 reported owning 5–50 firearms and often struggled to identify a single motivation for ownership. When asked why they purchased the firearms they owned, one participant responded,

> "*I don't know. I just thought they were cool. I mean, not for personal protection or anything like that. I just bought them to have them.*"

Some of these participants did report owning firearms for home defense but did not report regularly carrying them.

Finally, Group 3 reported owning 2–3 firearms, principally for protection. One participant explained,

> "*I grew up around hunters, all of my life from [rural area]. And my father hunted. I was uncomfortable because, you know, I didn't like the sound, But as I became an adult and I lived alone for a large*

Table 2
Differences in key themes by group membership.

	Group 1 NOT open ($n = 5$)	Group 2 NOT open ($n = 5$)	Group 3 Open ($n = 7$)
Number firearms owned	50–200	5–50	2–3
Motivations for ownership	Collect/invest Hunting/rural Carry for self defense	"Just to have them" Home defense	Protection Recreation
Tie firearm ownership to Christian beliefs	Extensively, thoughtfully	Christian beliefs are separate (and sometimes incompatible)	Mostly
Duty to be safe (diligent)	Divine	Not Divine, but responsibility of gun owner	Mixed between Divine and not Divine
Duty to protect/defend	Divine	More of a right than duty, not Divine	Divine
Duty to be vigilant	Divine	Not discussed	Mixed

Fig. 1. Conceptual model of how key themes influence openness to participate in church-based firearm safety interventions.

portion before I got married, I had it for home protection. And I went to a safety class to be educated on how to use the firearm properly."

Compatibility of Christian beliefs with firearm ownership

When asked how their Christian beliefs aligned with their beliefs on firearm ownership, most members of Group 1 provided extensive, thoughtful explanations, typically rooted in their identity as the protectors of their families and duty of self-defense. One participant explained,

"*Just because you're a Christian doesn't mean you can't defend yourself. I'm not saying be aggressive. That you've got to harm people or anything, but the first rule of a responsible patriarch or matriarch would be to defend your family.*"

Group 2 described their Christian beliefs as separate from their beliefs regarding firearm ownership, and sometimes explained these were incompatible. However, they believed the duty to protect their families to be of the utmost importance. One participant explained,

"*You know, one of the commandments says 'thou shall not kill.' So the use of weapons, I was thinking in Biblical times would be totally 100% against God's commandment. […] I don't know if God would be fine with it with self-defense, but either way, if I'm here in my house, me and my wife, and somebody's gonna break in the front door, I'm going to defend my wife and myself.*"

Most Group 3 participants were less likely to have a prepared response than Group 1 participants, while they often connected their firearm ownership to self-defense or protection of others as an act of Christian love. For example,

"*There's a quote that says, 'Do not fear' 365 times in the Bible […]. I believe that we shouldn't fear, but we should be prepared. So I believe the use of firearms, I think, can help show that you love other people.*"

Divine inspiration of duties as a firearm owner

Participants commonly referred to several duties as a firearm owner, although they differed in whether they described these as directives from God/Divinely inspired. These included the duty to be diligent with firearm safety (e.g., regular practice to maintain skill), duty to self-defense/protection, and the duty to be vigilant (e.g., aware of potential dangers). Most members of Group 1 described each of these duties as directives from God. One participant explained,

"*If somebody is attacking like at church, you know, everybody in the church is sitting there like fish in a bowl. If a crazy or mad or disturbed person comes in there and tries to hurt somebody, I feel like it's our Christian duty to try to protect those people. You know, women, kids, the preacher, innocent folks that's never hurt anybody.*"

Most members of Group 2 described safety not as a Divine duty, but as the responsibility of a firearm owner. In addition, they did not connect a duty to protect or defend to God, but rather described these as an inalienable right. For example,

"*I haven't seen anything in the Bible that should substantiate that you should have a firearm. […]. I haven't read anything that alluded to the fact that God said I can have a firearm and defend your family.*"

There was heterogeneity in Group 3 regarding whether duties to be diligent or vigilant were Divinely inspired, although there was agreement that the duty to protect/defend was directed. One participant explained,

"*Well, I do believe that the Bible tells us that we should be aware and be diligent at all times. I feel like God says that we should use tools to make us better and more faithful. That work is dead, but that does not mean to take a man's life because I feel more secure. That does not mean to say it's God's will that I'm selfish. Or that I overreact. And so I think that's where the line becomes blurred. God never prepared a place for us to cause harm against others to make ourselves feel more righteous.*"

Discussion

Church-based firearm safety interventions seeking to promote safe firearm behaviors have not been well-described in the literature, but the results of this study suggest some Protestant Christians are open to such public health interventions. Efforts should prioritize identifying those already willing. The clustering of participants into three groups indicates identifying those open to church-based firearm safety interventions is possible, although more work is needed to identify them consistently.

Church-based public health interventions are effective at increasing health behaviors[24–26,31] due to the church's investment in members' health and ability to provide supportive networks.[26] In addition, churches often have a central role in communities, offering services to congregation and other community members.[26] Participants from Group 3 in our study also identified this role of the church as a central hub of the community as one reason it is appropriate for firearm safety interventions. Given participants' focus on the importance of overall safety for church members, public health interventionists may also consider embedding conversations about firearm safety into a more general safety promotion intervention, such as first aid or Stop the Bleed trainings.[28]

Church-based interventions are most effective when community-directed and designed as part of a collaborative partnership.[32] Peer-led interventions are a well-established method to increase the efficacy of health promotion programs because the shared identity between leaders and participants can increase trustworthiness of messaging.[33,34] While participants from Group 1 did not reflect openness to participating in church-based firearm safety interventions, they may be promising individuals to co-lead these interventions. Group 1 participants often described themselves as leaders in the church, so their investment in such programs may decrease skepticism and increase trust in interventions among other church members. Future research into such interventions may benefit from the train-the-trainer model of public health interventions, which increase sustainability.[35]

The clustering of participants suggests interventions should prioritize identifying individuals most open. Public health interventions sometimes use segmentation to increase effectiveness by tailoring aspects of interventions to individual characteristics. However, segmentation is often based on demographic characteristics such as gender or age rather than the behavioral and psychological factors more impactful in driving behavior change.[36] This assumption of homogeneity among demographics may unintentionally decrease effectiveness of tailoring attempts.[37] Psychographic profiling seeks to understand behavior motivations by characterizing the lifestyle, interests, and values of individuals.[36] The use of psychographic profiling as a future area of research to identify individuals most open to intervention is a strategy supported by our findings. Rather than grouping based on demographic factors such as age or race, participants instead clustered based on firearm and religious beliefs. However, because these beliefs are not easily observed, determining which individuals may be open for intervention based on such beliefs is unfeasible. Future research may use psychographic profiling to identify Protestant Christians open to church-based firearm safety interventions based on more readily observable characteristics, such as religious tradition or motivations for firearm ownership.

This study has limitations. First, while the snowball sampling technique allowed for accessibility to an otherwise challenging population to recruit, it may have led to homogeneity in participant attitudes and beliefs. In addition, only three of the 17 study participants identified as persons of color, which may also decrease diversity in participant responses. Finally, while we describe three distinguishable groups identified in our study, there was intra-group heterogeneity in the themes, which signals the need for further research

Conclusions

Findings from this study suggest only some Protestant Christians are open to church-based firearm safety interventions; more research is needed to make identifying these individuals based on psychographic characteristics feasible. Literature from peer-led and train-the-trainer interventions may provide lessons as these interventions are created.

Author statements

Ethical approval

This study was approved by the University of Washington Institutional Review Board.

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Competing Interests

None declared.

Author contributions

KMC, ARR, and MM contributed to the study conception and design. Data collection was performed by KMC. KMC led the analysis and all authors contributed to interpretation of findings. The first draft of the manuscript was written by KMC and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Original Research

Population-level impact of beliefs and attitudes on vaccine decision-making in South Africa: results from the COVID-19 Vaccine Survey (2021/2022)

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ABSTRACT

Objectives: In addition to being home to more than seven million HIV-infected individuals, South Africa also has a high burden of COVID-19 and related comorbidities worldwide. We aimed to identify the most influential “beliefs” and “attitudes” on vaccine decision-making behavior.
Study design: This study used panel data from cross-sectional surveys.
Methods: We used the data from Black South Africans who participated in the “*COVID-19 Vaccine Surveys*” (November 2021 and February/March 2022) in South Africa. Besides standard risk factor analysis, such as multivariable logistic regression models, we also used the modified version of population attributable risk percent and estimated the population-level impacts of beliefs and attitudes on vaccine decision-making behavior using the methodology in multifactorial setting.
Results: A total of 1399 people (57% men and 43% women) who participated in both surveys were analyzed. Of these, 336 (24%) reported being vaccinated in survey 2. Overall low perceived risk, concerns around efficacy, and safety were identified as the most influential factors and associated with 52%–72% (<40 years) and 34%–55% (40+ years) of the unvaccinated individuals.
Conclusion: Our findings highlighted the most influential beliefs and attitudes on vaccine decision-making and their population-level impacts, which are likely to have significant public health implications exclusively for this population.

Introduction

In addition to being home to more than seven million HIV-infected individuals, South Africa also has a high burden of COVID-19 and related comorbidities worldwide.[1–3] Furthermore, evidence suggests significant disparities in vaccine coverage in African countries.[4,5] Similar to other low- and middle-income countries, South Africa also experienced delays in vaccine allocation and delivery where vaccination programs officially started approximately 1 year after vaccine approval (February 2021). As of July 2022, only 37.3% of South Africans received at least one dose compared with 66.9% of the global average.[6] High vaccine coverage is crucial to reducing COVID-19-related severe adverse events.[7,8] This is particularly important in South Africa, where multiple variants of COVID-19 were prevalent, including Beta (B.1.351) and the fast-spreading Omicron and its subvariants (BA.4 and BA.5), which were first identified in the country in November 2021.[9–11]

Vaccine acceptability directly impacts vaccine uptake. There has been extensive research to investigate the potential barriers associated with the intention to get vaccinated and uptake of vaccination worldwide.[12–14] These studies, which were mostly conducted before the COVID-19 vaccines were approved and available for use, reported high acceptability rates, ranging from 67% to 91%.[15–17] In February/March 2021, more than 80% of adult South Africans reported that they “*they intend to get vaccinated*” when the vaccines become available. This proportion was 71% in a nationally representative cohort of South Africans in June 2021.[18] The most

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common reason for those who did not intend to get vaccinated was due to side-effects and concerns about the effectiveness of the vaccines.[14,19,20]

Despite undisputable evidence indicating that COVID-19 vaccines prevent severe adverse events, including hospitalization, and death, there is an emerging concern around vaccine hesitancy, which has increased over time in many countries.[3,14] Consequently, studies continue to collect timely data to track vaccine acceptability and uptake in many countries, including South Africa. Most recently, vaccine knowledge, beliefs, and attitudes were assessed in South African adults who participated in the "*COVID-19 Vaccine Surveys (CVACS)*". The *CVACS* was carried out twice, once in November 2021 and again in February/March 2022.[21,22]

This study aimed to investigate the population-level impacts of certain beliefs and attitudes and their interplay with vaccine decision-making in South African adults who participated in both "CVACS." After developing a risk scoring algorithm to predict individuals' vaccine decision-making behavior, we also quantified the degree to which the relative contributions of beliefs and attitudes influenced vaccination status. This is the first study to present empirical results for the most influential beliefs and attitudes on vaccine decision-making in the era of the widely available COVID-19 vaccines. Our findings collectively provide the most recent snapshot of the intention to get the vaccination and actual vaccination status and their significant contributors in Black South Africans. This information can potentially be used to improve the effectiveness of the current COVID-19 vaccine promotion and delivery programs/campaigns on vaccine uptake.

Methods

Survey population

The present study used the panel data from a cohort of the South Africans who participated in the "CVACS" from the nine provinces and 52 districts across the country. The surveys were implemented by the Southern Africa Labour and Development Research Unit. The details of the surveys and the populations were previously described.[21,22] Briefly, a multistage stratified cluster sampling was used to select the households. Respondents were interviewed telephonically in two time points. Survey 1 participants were unvaccinated as of November 2021 (i.e. approximately 9 months after the first dose of vaccine roll-out). A total of 3,510 adults (aged $\geq$18 years) participated in survey 1. A follow-up survey was conducted in February to March 2022 (survey 2). A total of 1,772 individuals participated in both survey 1 and survey 2. Of these, 1,399 (80%) identified themselves as Black South Africans and were included in the present study. Owing to the low response rates for the other ethnic groups, we only included (self-identified) Black men and women in this analysis.

Measurements

Data from the survey 1 and survey 2 were merged by unique participant identification numbers. Our analysis included age (<35, 35–49, 50–59, and $\geq$60 years), employment status (yes/no), education (grade 12 completed vs not), residential area (urban, traditional, farm), marital/cohabitation status, monthly household income (in quartiles), and medical aid/insurance (yes/no). In survey 1, participants' COVID-19 risk perceptions, beliefs, and attitudes were measured by asking (1) *Do you think you will get very sick with COVID-19 in the next* 12 months*?* (yes, no, don't know); (2) *Do you believe the COVID-19 vaccine will prevent you from getting COVID-19? (yes, no, don't know);* (3) *Do you believe the COVID-19 vaccine will help prevent you dying from COVID? (yes, no, don't know)*". In survey 1, participants were also asked their reasons for not getting vaccinated in survey 1. These questions included (4) "*I don't trust vaccine/ Vaccine has side effects*" and (5) "*Vaccine will kill (yes/no)*"; (6) "*Already had COVID-19*"; (7) "*Don't know where to go*"; (8) "*Vaccination site is too far*"; (9) *"Travel cost is high*"; (10) *"May not be able to work after vaccine* (yes/no); (11) "*Don't have time*". In addition, (12) religious and (13) health-related reasons for not getting vaccinated were derived from the participants' free text narratives for the question: *what is the single biggest reason that you are not yet vaccinated?* The study participants were also asked, *"Regarding the COVID-19 vaccine, do you plan to":* (a) get it as soon as possible, (b) going to wait, (c) only if required, (d) definitely not get it. The primary outcome was self-reported vaccination status in survey 2 (unvaccinated vs vaccinated).

Statistical analysis

Characteristics of the population were described by vaccination status using frequencies and percentages and compared using Chi-squared test. Using the data from the individuals who participated in both surveys, we developed a risk scoring algorithm to predict the vaccination status in survey 2. After adjusting for potential confounders identified in descriptive analysis, we fitted logistic regression model and presented the weighted-rounded regression coefficients (i.e. and multiplying the logarithms of the odds ratio by 10) for the self-perception, beliefs questionnaires reported in survey 1.[23] Total risk score for each participant was derived by adding up the final weighted scores for each item considered in the model. The total score was categorized using the deciles where "lowest" (1st decile) "to highest" (10th decile) risk for not getting vaccinated. We evaluated the internal validity of the primary outcome model using a bootstrapping analysis and generated 500 and 1000 test data sets by random selection with replacement (Stata 16.0 macro called rhsbsampler). The calibration of the model was visually assessed using pmcalplot and tested using the Hosmer–Lemeshow goodness-of-fit test, plotting the agreement between the predicted and observed probabilities of vaccination status. Statistically acceptable threshold was determined to predict those who would not get vaccinated with high sensitivity/specificity and discriminatory power. We also hypothesized that "*intention to get vaccination*" (i.e. as soon as possible vs other) in survey 1 and vaccine decision-making behavior in survey 2 will be strongly correlated. Therefore, it can potentially be considered as a proxy for vaccination status in survey 2. As a secondary analysis, we refitted the 7-item risk scoring algorithm to predict those who did not intend to receive the vaccine immediately in survey 1. Discriminative power of all models was assessed using the standard statistical measures, such as sensitivity, specificity, and area under the curve. The goodness-of-fits of our models were assessed using the Hosmer and Lemeshow test; non-significant p-values ($P > 0.05$) were interpreted as an acceptable fit. We also estimated the population-level impacts of these factors on vaccine decision-making behavior using the methodology in multifactorial setting.[24] This analysis was also conducted among those who were aged <40 and $\geq$40 years, which was identified as the cut-point for median. Methodology, SAS codes, and access to the Macro were presented in Appendix.

Results

A total of 1399 individuals (803, 57% men and 596, 43% women) who participated in both surveys were analyzed. Of these, 336 (24%) reported being vaccinated in survey 2. The overall mean age was 39 years (standard deviation: 16; median age: 36 years [interquartile range: 30–50]). The characteristics of the study population in survey 1 are compared by their vaccination status in survey 2 (Table 1). Age and gender distributions were not statistically significant between the two groups. Overall, 63% of the study population resided in urban areas, with significant difference between the vaccinated and unvaccinated groups. Unvaccinated survey participants had higher education and income levels, and they also more to report having medical aid and owning a vehicle compared with those who were vaccinated.

Reasons for being unvaccinated in survey 1

Overall, 60% of the study population indicated that they were not at risk of getting infected by COVID-19, which was the most common reason for not being vaccinated (Table 1). A significantly higher proportion of individuals in the unvaccinated group indicated that they were not at risk for COVID-19 compared with the vaccinated group (62% vs 54%, respectively, p-value = 0.007). Unvaccinated individuals were also more likely to believe that vaccine is not effective (i.e. would not prevent infections and death due to COVID-19) and not safe (i.e. severe side-effects and death). Religion and pre-existing health conditions were reported in <10% of the study population in survey 1; however, these two reasons were significantly more common in the unvaccinated group. Meanwhile, other factors including "*not knowing where to go for vaccination,*" "*travel costing and distance,*" and "*lack of time*" were all significantly more common among those who got vaccinated in survey 2. More than 60% of the vaccinated participants also indicated that "*they*

Table 1
Demographic and socio-economic characteristics of study population by vaccination status.

		Assessment at survey #2		
Assessments at survey #1	%	Vaccinated[a], $N = 336$ (24%)	Unvaccinated, $N = 1,063$ (76%)	p-value
Age				0.237
<35 years	46%	48%	45%	
35–49 years	28%	24%	29%	
50–59 years	15%	17%	14%	
≥60 years	11%	11%	12%	
Sex				0.194
Female	43%	46%	41%	
Male	57%	54%	59%	
Area of residency				0.037
Traditional	13%	13%	14%	
Urban	63%	57%	65%	
Farm	23%	28%	21%	
Level of education				0.015
Less than grade 12	40%	46%	39%	
Grade 12 or more	60%	54%	61%	
Tertiary education completed				0.031
No	55%	60%	53%	
Yes	45%	39%	47%	
Employment (last week)				0.212
No	59%	62%	58%	
Yes	41%	38%	42%	
Income (in quartiles)				0.100
First quartile (<1,700 ZAR[b])	25%	30%	24%	
Second quartile (1,700 to <3,000 ZAR[b])	27%	27%	27%	
Third quartile (3,000 to <8000 ZAR[b])	23%	25%	22%	
Fourth quartile (≥8,000 ZAR[b])	25%	18%	27%	
Medical aid/health insurance	21%	18%	22%	0.033
Water/pipe in dwelling	83%	80%	84%	0.196
Household has electronic device(s)	65%	62%	65%	0.436
Household has vehicle	39%	30%	43%	<0.001
Why didn't you get vaccinated?				
Self-perceived risk: no risk	60%	54%	62%	0.007
Vaccine will not prevent COVID-19	46%	29%	51%	<0.001
Vaccine will not prevent dying from COVID-19	48%	29%	54%	<0.001
Don't trust vaccine[c]	57%	43%	61%	<0.001
Vaccine may kill you	40%	32%	42%	0.012
Religious reasons	6%	3%	7%	0.004
Pre-existing health conditions[d]	8%	6%	9%	0.040
I already had COVID-19	47%	47%	47%	0.206
Don't know where to go	17%	20%	16%	<0.001
Vaccination site is too far	18%	24%	17%	<0.001
Travel cost is high	20%	24%	20%	0.012
May not be able to work after vaccine	48%	46%	49%	0.745
Don't have time	30%	39%	27%	<0.001
Are you going to get vaccinated?				<0.001
I will get it as soon as possible	38%	61%	30%	
I will wait	22%	19%	24%	
Definitely not get it	23%	6%	18%	
Other/missing	21%	14%	28%	

[a] At least one dose.
[b] 1 South African Rand; 1 ZAR = 0.064 US Dollar (January 2022).
[c] Vaccine has severe side-effects.
[d] Including diabetes, hypertension, allergy.

will get vaccinated as soon as possible" compared with 30% in the unvaccinated group.

A risk prediction model for vaccination status

In our risk prediction model, seven reasons for being unvaccinated from the survey 1 were identified as the most influential predictors for vaccination status in survey 2 (Table 2). Individuals with low perceived risk for COVID-19 were also significantly more likely to be unvaccinated compared with those who perceived themselves at high risk (adjusted odds ratio [aORs] from 1.74, 95% confidence interval [CI]: 1.24, 2.45). Similar trends were observed among those who did not believe in the vaccine's efficacy and safety. For example, those who believed that the vaccine will not prevent them from getting infected or dying from COVID-19 were more than three times more likely to be unvaccinated than those who believed in the effectiveness of the vaccine. These factors had the highest risk scores (11 and 12, respectively) to predict unvaccinated individuals because of their high odds ratios (aOR: 3.10 and 3.45, respectively). Individuals who believed that the vaccine is associated with severe side-effects and deaths in survey 1 were also significantly more likely to be unvaccinated in survey 2 (aOR: 2.10 and 1.55, respectively).

Fig. 1a presented the aORs across the deciles of the risk scores of being unvaccinated (Fig. 1a). There was a linear trend between the individuals' increasing risk score and the odds of being unvaccinated (P_{trend} <0.001). In our secondary outcome, similar increasing trends in odds ratios were observed to predict those who indicated not to get vaccinated in survey 1 (Fig. 1b). Performance of the risk prediction models for several cut-points is presented in Table 3 for the development and the internal validation data sets. A score of 12 or more had high sensitivity. Participants who scored 16–20 points were approximately four times more likely to be unvaccinated in survey 2. They were also almost nine times more likely to be vaccine hesitant in survey 1. Sensitivity/specificity and the discriminative power of those with a score ≥16 points, which requires at least two items from the risk prediction model and also falls into the sixth deciles of the total risk score, were statistically acceptable. Modifying of scores 12 or more would have prevented 71% of the unvaccinated individuals, and 80% of the vaccine-hesitant participants would also be prevented. (Fig. 2)

Population-level impacts of perceived risk and beliefs: age-specific analysis

In an age-specific analysis, we estimated the population-level impacts of all seven beliefs and attitudes on vaccine uptake when they were considered individually and collectively. Overall, three items: (1) *low perceived risk*, (2) *vaccine will not prevent COVID-19*, and (3) *vaccine will not prevent dying from COVID-19* were all identified as the most influential beliefs and attitudes on vaccine decision-making. After adjusting and accounting for their correlation structure, their population-level impacts ranged from 50% to 60% and 34% to 55% for younger (aged <40 years) and older (≥40 years). Modifying these three attitudes would have prevented (at least theoretically) 78% and 62% of the unvaccinated individuals in the younger and older groups, respectively (data not shown).

We also observed age-related disparities where 15% of the unvaccinated individuals in the older age group were exclusively associated with those who indicated to have had pre-existing health conditions, whereas only 2% of the unvaccinated younger individuals attributed to pre-existing conditions. The population-level impact of all seven items on vaccination status were estimated as 83% (95% CI: 79%, 87%; <40 years) and 72% (95% CI: 66%, 78%; ≥40 years all). These seven beliefs also had a substantial impact on vaccine hesitancy in both age groups, where lower self-

Table 2
Predictive model for unvaccinated participants: population-level impact of self-perception on COVID-19 uptake as reported in Survey #2 Black South Africans only (outcome: unvaccinated vs vaccinated).

Assessments at Survey #1	Adjusted[a] odds ratio (95% CI)	p-value	β×10	Score
Self-perceived risk for COVID-19:				
I am at risk for COVID-19	1		0	**0**
I am not at risk for COVID-19	1.74 (1.24, 2.45)	0.001	5.6	**6**
Don't know	1.40 (0.96, 2.05)	0.084	3.4	**3**
COVID-19 vaccine effectiveness:				
Vaccine will prevent COVID-19				
Yes	1		0	
No	3.10 (2.23, 3.89)	<0.001	10.8	**11**
Don't know	1.94 (1.34, 2.81)	<0.001	6.6	**7**
Vaccine will prevent dying from COVID-19				
Yes	1		0	**0**
No	3.45 (2.62, 4.56)	<0.001	12.4	**12**
Don't know	2.22 (1.50, 3.28)	<0.001	8.0	**8**
COVID-19 vaccine safety				
Vaccine is not safe[b]				
No	1			**0**
Yes	2.10 (1.63, 2.68)	<0.001	7.4	**7**
Vaccine may kill				
No	1			
Yes	1.55 (1.20, 2.03)	0.001	4.4	**4**
Other barriers				
Religious believes (txt)				
No	1		0	**0**
Yes	2.69 (1.37, 5.25)	0.004	9.9	**10**
Presence of health issues[c]				
No	1			
Yes	1.75 (1.05, 2.91)	0.031	5.6	**6**

CI, confidence interval.
[a] Odds ratios were adjusted for age, sex, area of residency, level of education, medical insurance.
[b] Severe side-effects.
[c] Including HIV, tuberculosis, diabetes, hypertension, and allergy.

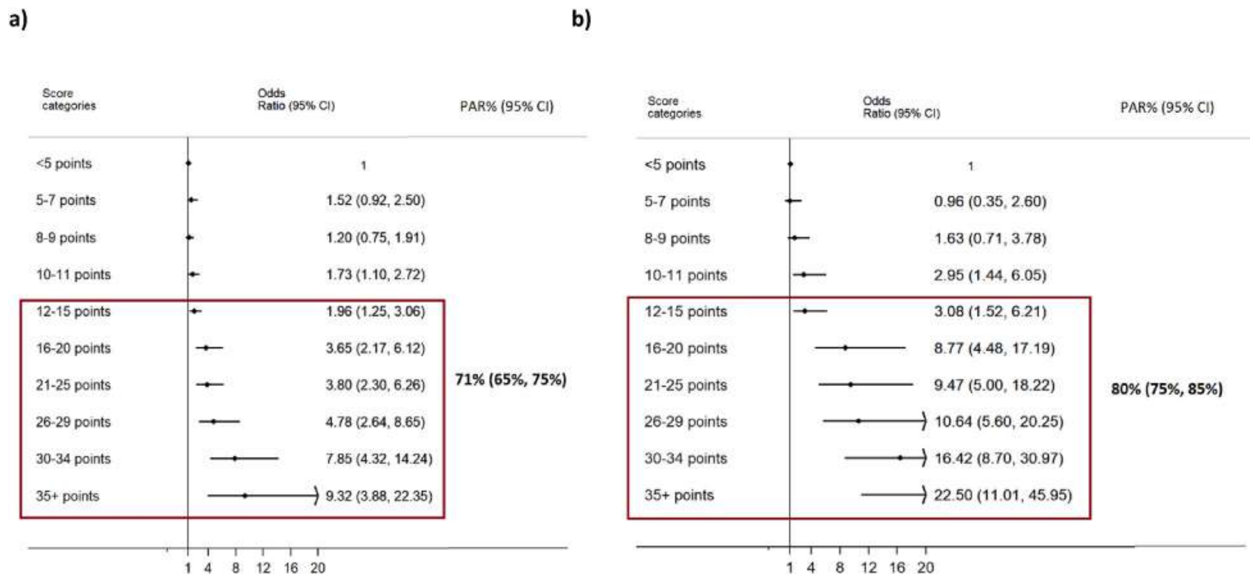

Fig. 1. Odds ratios (95% confidence intervals) of risk score (in deciles): test for trend in odds ratios were <0.001 (for both outcomes). (a) Primary outcome: unvaccinated vs vaccinated. (b) Secondary outcome: intention to get vaccinated (No vs Yes). PAR%, population attributable risk percent.

perceived risk and vaccine confidence were identified as the most influential factors in the decision-making process.

Discussion

Our findings provided compelling evidence for a high proportion of unvaccinated adults in a cohort of Black South Africans who participated in two consecutive rounds of national surveys conducted in November 2021 and February to March 2022. More than half of the survey 1 participants indicated that they would get vaccinated; however, only 24% of the study participants reported being vaccinated in survey 2. While age and sex distributions did not differ significantly by vaccination status, unvaccinated individuals appeared to have higher socio-economic status with higher levels of education and income. Some of these findings have been reported previously in other populations including South Africa. For example, vaccine acceptability was associated with higher education in South Africa.[18,20] However, this link was not consistently confirmed in other populations where higher socio-economic conditions and higher education were reported to be associated with high rates of vaccine acceptability.[26] This trend has been documented with childhood vaccination, where parents of higher socio-economic status were more likely to be hesitant in vaccinating their child.[27,28] These results may be interpreted as increasing vaccine hesitancy in adults who had higher socio-economic conditions.

Table 3
Performance of the risk scoring algorithm for different cut-points for not getting vaccinated: development and internal validation datasets.

Score	Model: outcome= unvaccinated vs vaccinated AUC [a] (95% CI): 75% (95% CI: 72%, 78%)	
Median (IQR)	25 (12-35) points	
Cut points	**Sensitivity (Specificity)**	**Correctly classified**
≥ 10 points	88% (29%)	72%
≥ 11 points	86% (30%)	72%
≥ 12 points	85% (36%)	71%
≥ 13 points	84% (39%)	70%
≥ 14 points	83% (40%)	70%
≥ 15 points	82% (41%)	69%
≥ 16 points	81% (43%)	68%
≥ 17 points	80% (45%)	67%
≥ 18 points	78% (45%)	66%
	Internal validation [b]= unvaccinated vs vaccinated AUC [a] (95% CI): 71% (95% CI: 69%, 74%)	
Score	**Sensitivity (Specificity)**	**Correctly classified**
≥ 10 points	94% (20%)	57%
≥ 11 points	91% (23%)	61%
≥ 12 points	88% (45%)	64%
≥ 13 points	87% (40%)	65%
≥ 14 points	85% (47%)	63%
≥ 15 points	81% (50%)	60%
≥ 16 points	78% (55%)	59%
≥ 17 points	76% (58%)	55%
≥ 18 points	76% (63%)	50%

[a] AUC, Area Under the curve.
[b] Internal validation was conducted using 500 test datasets generated with replacement.

The present study showed that COVID-19 vaccine hesitancy could be predicted by individuals' self-perceptions with statistically acceptable robustness and accuracy. We identified the seven most influential beliefs and attitudes for not being vaccinated and their combined population-level impacts and implications on vaccine uptake. In our risk prediction model, low-risk self-perception, lack of trust, and concerns around safety, religion, and pre-existing health conditions were all determined to be the most significant predictors of not being vaccinated, with weighted scores ranging from 4 to 12. Although these factors have been well recognized and reported as the most common reasons for vaccine hesitancy in other worldwide, their population-level influence on vaccine decision-making using weighted and clustering impacts are unique to the present study.

Despite undisputable evidence for vaccine protection against COVID-19-related adverse health outcomes and death, approximately half of the study population had concerns regarding the vaccine efficacy and lack of trust, that is, "*vaccine will not prevent COVID-19*" and "*Vaccine will not prevent dying from COVID-19.*" Meanwhile, 60% of the study population reported that they were not at risk of COVID-19. These three factors were identified as the most influential beliefs on vaccine decision-making and were collectively associated with 76% (<40 years) and 62% (≥40 years) of

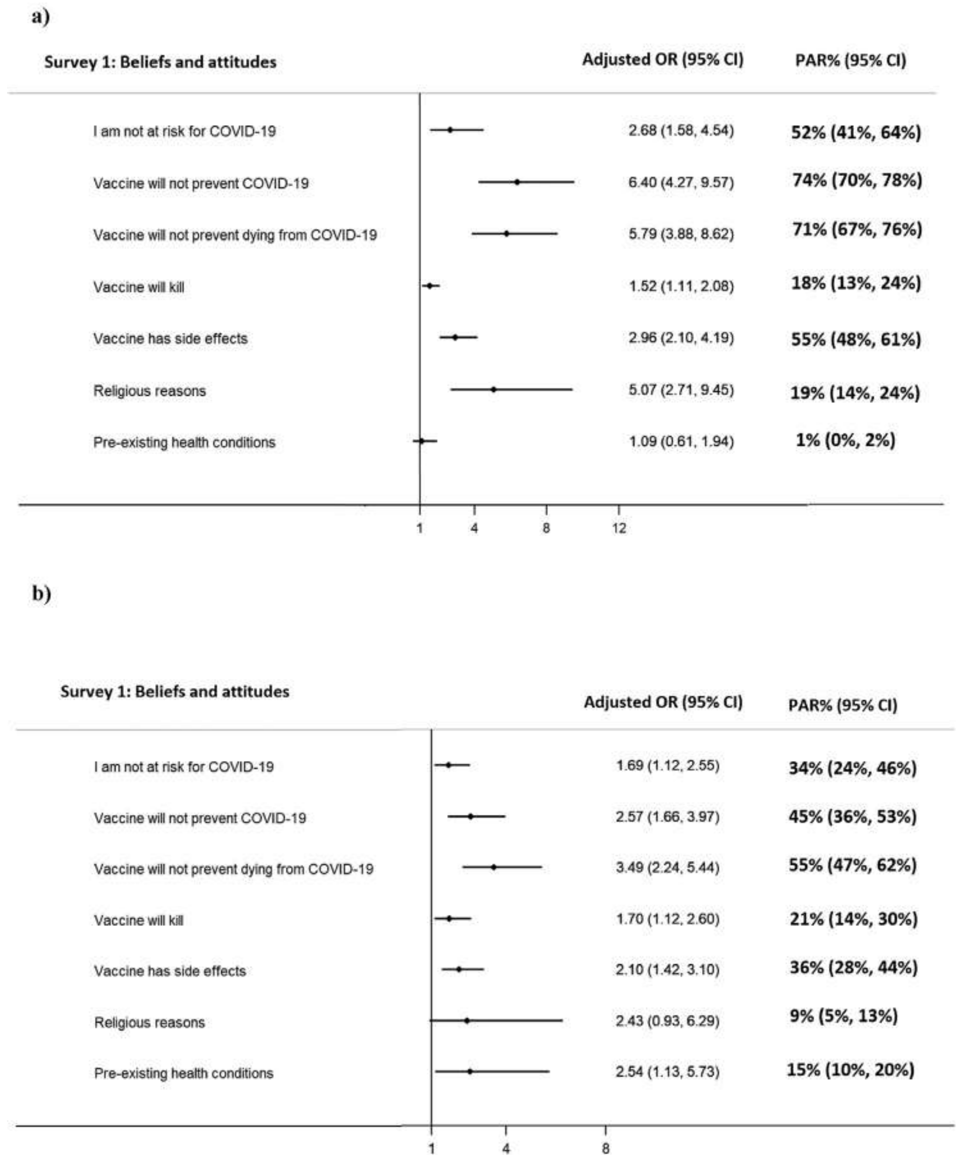

Fig. 2. Individual and population-level impacts of beliefs and attitudes on unvaccinated individuals: (a) Age: <40 years (full *PAR%*[§]: 83%, 95% CI: 79%, 87%). CI, confidence interval; PAR%, population attributable risk percent.

the unvaccinated individuals. Considering the impact of concerns around the safety of the vaccines and the other factors, including "*religion*" and "*pre-existing conditions,*" increased the population attributable risk percent to 83% (<40 years) and 72% (≥40 years), respectively. These relatively modest increases were primarily because of the strong correlations between these beliefs and attitudes, which is not surprising. Despite having significant odds ratios, the population-level impact of "*religion*" on vaccination status was substantially lower compared with the other factors. This was because of the very low prevalence (6%) associated with this factor. These estimates can be translated into 869 more vaccinated individuals (940 × 83% = 780 and 123 × 72% = 89 for <40 and ≥40 years, respectively). Therefore, if it was possible to change these factors (at least theoretically), the proportion of vaccinated individuals would increase from 24% (336/1399) to 86% [(336 + 869)/1399]. Meanwhile, "*pre-existing health conditions*" only had a modest impact among the older participants. Other factors including "*lack of knowledge where to go*" and "*travel difficulties and expenses*" were reported in ≤20% of the study population in survey 1; however, these individuals were significantly more likely to get vaccinated compared with those who knew where to go and did not indicate any difficulties in traveling.

Our findings provide empirical evidence for a substantial shift in vaccine acceptability over time in South Africa, which was also reported in other countries. For example, less than 40% of the survey 1 participants indicated that "*they would get vaccinated as soon as possible*" in survey 1, which is substantially lower than reported in national surveys conducted before vaccine development and availability. For example, 82% of the South Africans who participated to in the "*COVID-SCORE Global Survey*," which was conducted 3 months after the COVID-19 was declared as pandemic, indicated that "*they intend to get vaccinated when vaccines become available*" (June 2020) (Lazarus et al., 2020; NDoH 2021). High vaccine acceptability rates were also reported in *"The Council for Medical Schemes (CMS)"* (82%) and "*National Income Dynamic Survey-Coronavirus Rapid Mobile Survey*" (NIDS-CRAM)" (71%), which were both conducted before/during vaccine approval and roll-out in South Africa (February/March 2021).[31,32] These estimates were comparable with the other countries, including China (91.3%), the United Kingdom (79.2%), the United States (67%) and other European countries (74%) which were all reported approximately at the same time periods.[15–17,26]

More than two-and-half years into the pandemic, South Africa continues to have a high burden of infections where the country has already faced multiple variants of COVID-19 infections. However, as of July 2022, <40% of the South Africans had at least one dose compared with 66.9% global average.[6] The reasons for low vaccination rates in Black South Africans are likely to be different from other countries, with implications exclusively for this population. One of the marked results from our study is the impact of vaccine-related misconceptions, such as the vaccine will prevent getting "infected" and "dying" from COVID-19. Although these two concepts are different from each other, 83% of the study population who indicated that the vaccine would not prevent getting infected also believe that the vaccine would not prevent dying from COVID-19. There is an undisputable evidence for the vaccines' key role in reducing COVID-19 and preventing related severe adverse events, including hospitalization and deaths.[32,33] These findings have significant clinical and public health implications in South Africa where more than 300,000 excess deaths occurred over the past 12 months (June 2021 to June 2022) were reported to be primarily attributed to the COVID-19 infections.[30]

Limitations

Our study has several limitations. We only included the subset of the data from Black African men and women due to the low proportion of the other population groups. We were only able to analyze the available data. All the characteristics, beliefs, and attitudes were self-reported, including the vaccination status, therefore subject to recall bias. Risk scoring model was developed using cross-sectional data, which shares the same limitations associated with this design. Among those who participated in survey 1, only 1,772 (50%) of them also participated in survey 2. Therefore, the results cannot be generalized to the target population. However, our findings are exclusively unique to the Black South African men and women with the highest burden of other comorbidities, including HIV and tuberculosis.

Conclusion

The present study brings significant insight into the previous research and provides the associations between self-perceptions, beliefs, and attitudes on vaccine decision-making using the first and the most recent data from South Africans following the vaccine roll-out. Our findings particularly highlighted the most influential concerns around vaccine efficacy and safety and their population-level impacts on vaccine decision-making, which are likely to have significant public health implications exclusively for this population. One of the most significant results from this study was the considerable drop in vaccine acceptability since the vaccines have become widely available. This is particularly worrisome, given the high excess mortality rates that have been documented in the region. Given the ongoing nature of the pandemic, widespread misinformation and disinformation, factors contributing to variations in coverage are likely to be complex and nuanced for any vaccine; the COVID-19 vaccine is no exception. Taken together, our findings suggest that vaccine promotion and delivery programs should include a focus on the key role of vaccines in preventing COVID-19-related severe illnesses, hospitalization, and death.

Author statements

Ethical approval

Approval for the primary study was granted by the Ethics Committee of the University of Cape Town. The present study is used an open access (publicly available) data set and does not require further ethical approval.

Funding

The present study used the secondary data did not receive funding. However, the original study was funded by the Bill & Melinda Gates Foundation. Surveys were undertaken by the Southern Africa Labour and Development Research Unit (University of Cape Town).

Competing interests

None declared.

Participant's involvement/informed consent

CVACS data were collected using telephone surveys. Therefore, a verbal consent obtained from the participants by asking if they want to participate the survey. Those who said "yes" were included in the surveys.

Data availability

Publicly available data can be requested and accessed via https://www.datafirst.uct.ac.za/

Availability of data and material (data transparency)

Appendix 2a and b presented the methodology and the SAS Macro developed by the first author of the present article to estimate the "Population Attributable Risk" in multifactorial settings.

Author contributions

H.W., C.V., S.N., and J.M. prepared the concept sheet. H.W. and T.R. extracted database. H.W. and T.R. analyzed the data. H.W. and C.V. prepared the first draft. All authors interpreted the results. All authors approved the final version.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.01.007.

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Original Research

The association between experiences of being defrauded and depressive symptoms of middle-aged and elderly people: a cross-sectional study in China

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A R T I C L E I N F O

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Mental health
Ex post facto study

A B S T R A C T

Objectives: This study assessed the correlation between middle-aged and elderly fraud victimhood's experiences of being defrauded (EOBD) and depressive symptoms.
Study design: This was a prospective study.
Methods: Data from China Health and Retirement Longitudinal Study 2018 (N = 15,322, mean age = 60.80 years) were used. Logistic regression models were used to identify the association between EOBD and depressive symptoms. Independent analyses were used to examine the association between different types of the fraud and depressive symptoms.
Results: Among the middle-aged and elderly people, 9.37% of them have EOBD, and it was significantly associated with depressive symptoms. Among those with EOBD, fundraising fraud (3.72%) and fraudulent pyramid scheme and sales fraud (22.4%) were significantly associated with depressive symptoms, whereas telecommunication fraud (73.88%) had a limited role in inducing depressive symptoms in victimhood.
Conclusion: This study suggested that the government should make further efforts to prevent fraud, pay more attention to the mental health of the middle-aged and elderly victimhood, and provide timely psychological assistance to reduce the secondary harm caused by fraud.

Introduction

Fraud refers to the illegal acts that would cause financial losses other than robbery or theft.[1,2] In recent years, despite the Chinese government's increasing efforts to combat fraud, it is still at a high incidence. In 2020, Chinese public security authorities addressed 256,000 cases of telecommunication fraud alone.[3,4] The middle-aged and elderly people aged 45 years and above, who account for nearly 20% of China's total population, are heavily affected by various types of fraud such as telecommunication fraud and fundraising fraud, which have serious adverse effects on the healthy operation and development of the whole society.[5,6] In the United States, middle-aged and elderly people lose nearly $300 million annually to various types of fraud,[7] and the proportion of middle-aged victimhood had increased by nearly 50% in 1 year.[8] Fraud, as a crime targeting the victimhood's property, not only brings financial losses to the victimhood but also has a negative psychological impact on them.[9,10]

Existing research on fraud is spread across a variety of fields, including psychology, medicine, and law. In the field of psychology, the existing literature focuses more on the predictors of fraud, that is, the characteristics of people who are more likely to experience fraud. In the area of personality, most scholars have started with The Big Five to study the relationship between the five personalities and fraud susceptibility. Among them, openness and extraversion have been shown to have strong correlations with fraud susceptibility, but the specific relationships between different types of personalities and fraud susceptibility in different studies are still in disagreement.[1,11] Other scholars have explored the relationship between other factors, such as emotions,[12,13] self-control,[14,15] psychological

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vulnerability,[16] financial satisfaction,[2] perceived benefits,[17] and victimhood's experiences of being defrauded (EOBD).

Scholars have found a strong positive correlation between age and fraud exposure in their research, that is, fraud cases are highly prevalent in middle-aged and elderly people.[2,18–20] Academics have taken it as the research target for further exploration. Because of their cognitive ability, emotional regulation, and psychological vulnerability, middle-aged and elderly people are more likely to encounter consumer fraud,[21] financial fraud,[22] online deception,[12] and other types of fraud.[20] In addition, excessive trust[20,23,24] and fear of aging[20] are also strongly associated with fraud susceptibility. However, other scholars have argued that existing studies underestimated the role of possible protective factors associated with middle-aged and elderly people. Several scholars have pointed out that middle-aged and elderly people are more skeptical when face with email fraud.[8] O'Connor et al.[19] indicated that although middle-aged and older adults were at higher risk of fraud exposure, they were more sensitive to risk. Lichtenberg et al.[16] proposed that younger people were more likely to be defrauded than middle-aged and elderly people and that people with depressive symptoms were also at higher risk of being defrauded. Lichtenberg et al.[2] also implied a significant relationship between depressive symptoms and the EOBD in a previous study. DeLiema et al.[25] also reached similar conclusions in their study.

Interestingly, some scholars have also partially revealed in their studies that being defrauded could have a negative impact on mental health.[26,27] Rodriguez-Rodriguez et al.[28] suggested in their article that financial fraud could cause physical and psychological disorders, depression, and even suicide in victimhood. In addition, many scholars studying financial exploitation of middle-aged and elderly people have noted that financial exploitation negatively affects the psychological health of middle-aged and elderly people, causing anxiety and depression.[21,29,30]

Based on the existing literature, it can be found that some results have been obtained regarding the relationship between being defrauded and depressive symptoms, but there is a lack of targeted research on the question of "whether fraud has a significant correlation with depressive symptoms.". In addition, middle-aged and elderly people are exposed to various types of fraud, including telecommunications fraud, fundraising event fraud, and fraudulent pyramid scheme and sales fraud. However, few scholars have analyzed the variability of the effects of different types of fraud on depressive symptoms. In the existing studies on fraud and depressive symptoms, the types of the fraud are not systematically classified or only one or two types of the fraud are involved, and the focus is mainly on financial fraud in economic exploitation, without comparing the differences in the effects of different types of fraud on depressive symptoms. Existing studies have made limited contributions to the question of the relationship between being defrauded and depressive symptoms, and there is room for further exploration.

Therefore, this study investigated the association between EOBD and depressive symptoms in middle-aged and elderly people using data obtained from the China Health and Retirement Longitudinal Study (CHARLS) 2018. The main contributions of this study were (1) complementing and extending the psychological field of research on the relationship between EOBD and depressive symptoms and providing theoretical support for the investigation of the bidirectional relationship between being defrauded and depressive symptoms; (2) further explaining the differential effects of different types of the fraud on depressive symptoms in telecommunications fraud, fundraising event fraud, and fraudulent pyramid scheme and sales fraud; (3) providing a theoretical basis for reducing being defrauded in middle-aged and elderly people and providing some inspiration for psychological intervention after being defrauded.

Methods

Participants

The samples used in this article come from CHARLS 2018 questionnaire. It is a nationally representative baseline survey of Chinese families and individuals aged $\geq$45 years adopting a random sampling method and is launched by the Institute of Social Science Survey of Peking University, China. It included individual EOBD and was the first to investigate the types of the fraud in 2018. According to the World Health Organization's criteria for the classification of middle-aged and elderly people and the actual response ability, we selected samples of 19,092 respondents aged 45–90 years after merging different survey modules according to ID. Ultimately, 15,322 participants were used after excluding abnormal data (e.g. missing value, error value, etc.). The response rate is 80.25%.

Measures

Depressive symptoms were assessed by the 10-item Center for Epidemiologic Studies Depression Scale (CES-D10), which is a simplified version of CES-D20 scale. In CES-D10 scale, participants were asked, “Did you experience any of the listed situations last week,” which included (1) annoyance, (2) distraction, (3) being down in spirits, (4) feeling strenuous to anything, (5) being hopeful, (6) fear, (7) sleep deprivation, (8) pleasantness, (9) loneliness, and (10) feeling inability to continue life. Questions are measured by using 4-point Likert scale (0 = less than 1 day, 1 = 1–2 days, 2 = 3–4 days, and 3 = 5–7 days). The two questions assessing positive feelings (“being hopeful,” “pleasantness”) were reverse scored. The total score ranges from 0 to 30, and scores >10 on the CES-D10 indicated a clinical diagnosis of depression.[31–33] We used a dichotomized (yes/no) score as our outcome measure.

The survey on EOBD was that “Did you experience fraud in the past with property (material/financial) loss?” If participants experienced fraud with property loss, they would be regarded as having EOBD, and the corresponding variable was assigned a value of 1. Otherwise, the corresponding variable was assigned a value of 0.

For individuals who were defrauded within a year and had financial losses, CHARLS 2018 investigated the type of the fraud they encountered. The survey on the type of the fraud was that “What is the type of the fraud in the past year?” There were three types of fraud: telecommunications fraud, fundraising event fraud, and fraudulent pyramid scheme and sales fraud. Telecommunication fraud occurs in any situation, involving refund of online shopping, borrowing of money from friends, elimination of criminal suspicion, etc. Fundraising event fraud occurs when private wealth management companies absorb funds from middle-aged and elderly people in the name of high return on investment. Fraudulent pyramid scheme and sales fraud occurs when businesses lure middle-aged and elderly people to buy low-quality or even unqualified goods at a high price through free experience and other forms or give returns beyond the normal range in the form of pyramid selling.

Participants reported demographic data: *age* (45–64, 65–79, and 80–90 years),[34] *gender* (female and male), *marital status* (never married, married, and widow, separated, or divorced), *education level* (primary school or below, junior high school or above).

Individual income was measured by the total annual individual income; the unit is yuan/year. *Insurance* was derived based on responses to the question, “Are you the policy holder/primary beneficiary of any types of health insurance?,” with the response categories “yes” and “no.”

Health status indicators were assessed by questions as follows. *Disability* was measured by five questions: “Do you have (1) physical disabilities, (2) brain damage/intellectual disability, (3) vision problem, (4) hearing problem, (5) speech impediment?” with response categories “yes” and “no.” If the answer to any of the above questions was yes, the participant was considered to be disabled. *Self-rated health* was measured by the question “Would you say your health is.?” with response categories “very good,” “good,” “fair,” “poor,” and “very poor.” Chronic diseases were measured by 13 questions: “Have you been diagnosed with (1) hypertension, (2) dyslipidemia, (3) diabetes or high blood sugar, (4) cancer or malignant tumor (excluding minor skin cancers), (5) Chronic lung diseases, (6) liver disease (except fatty liver, tumors, and cancer), (7) heart problems (heart attack, coronary heart disease, angina, congestive heart failure, or other), (8) stroke, (9) kidney disease, (10) stomach or other digestive diseases (except for tumor or cancer), (11) memory-related disease, (12) arthritis or rheumatism, (13) asthma by a doctor?” with the response categories “yes” and “no.” *Number of chronic diseases* was measured by dividing the total number of the above diseases into 0, 1, 2–3, or ≥4.

Health behaviors were assessed by questions as follows. *Drinking frequency* was derived based on responses to the question, “Did you drink any alcoholic beverages, such as beer, wine, or liquor in the past year? How often?” with response categories “Drink more than once a month,” “Drink but less than once a month,” and “None of these.” *Sleep duration* was based on the question, “During the past month, how many hours of actual sleep did you get at night?” And it is categorized into (0, 5], (5, 6] (6, 8], or (8, 20] h/night according to the 25th, 50th, and 75th percentiles of the sleep duration in this study.[35]

Logistic regression models were used to identify the association between EOBD and depressive symptoms after controlling for sociodemographic variables, socio-economic variables, health status variables, and health behaviors variables. Adjusted for all measured covariates, we conducted an independent analysis for the association between different types of the fraud and depressive symptoms (telecommunications fraud, fundraising event fraud, fraudulent pyramid scheme and sales fraud, and depression).

Results

Characteristics of the study population

The descriptive statistics are presented in Table 1. It depicts univariate analyses of participants according to EOBD. It can be seen from the results that 9.37% of the participants had EOBD, which implies that frauds are quite common. In the participants, most of them (65.28%) were aged 45–64 years, followed by 65–79

Table 1
Demographic characteristics of participants (N = 15,322).

Variables	Total population[N = 15,322]	EOBD = 0 [13,887 (90.63%)]	EOBD = 1 [1435 (9.37%)]
Age (years)			
45–64	10,002 (65.28%)	9176 (59.89%)	826 (5.39%)
65–79	4853 (31.67%)	4290 (28.00%)	563 (3.67%)
80–90	467 (3.05%)	421 (2.75%)	46 (0.30%)
Gender			
Female	7838 (51.16%)	7134 (46.57%)	704 (4.59%)
Male	7484 (48.84%)	6753 (44.07%)	731 (4.77%)
Education level			
Primary school or below	9514 (62.09%)	8617 (56.24%)	897 (5.85%)
Junior high school or above	5808 (37.91%)	5270 (34.39%)	538 (3.52%)
Individual income (yuan/year)	12,393.42 ± 21141.11	12,362.11 ± 21087.61	12696.41 ± 21657.22
Marital status			
Never married	72 (0.47%)	60 (0.39%)	12 (0.08%)
Married	13,489 (88.04%)	12,270 (80.08%)	1219 (7.96%)
Widow, separated, or divorced	1761 (11.49%)	1557 (10.16%)	204 (1.33%)
Insurance			
Yes	14941 (97.51%)	13,550 (88.43%)	1391 (9.08%)
No	381 (2.49%)	337 (2.20%)	44 (0.29%)
Disability			
Yes	1694 (11.06%)	1484 (9.69%)	210 (1.37%)
No	13,628 (88.94%)	12,403 (80.94%)	1225(8.00%)
Self-rated health			
Very poor	547 (5.53%)	748 (4.88%)	99 (0.65%)
Poor	2863 (18.68%)	2535 (16.54%)	328 (2.14%)
Fair	7633 (49.82%)	6920 (45.16%)	713 (4.66%)
Good	2008 (13.11%)	1842 (12.02%)	166 (1.09%)
Very good	1971 (12.86%)	1842 (12.02%)	129 (0.84%)
Number of chronic diseases			
0	3247 (21.19%)	3022 (19.72%)	225 (1.47%)
1	1371 (8.95%)	1265 (8.26%)	106 (0.69%)
2–3	704 (4.59%)	635 (4.14%)	69 (0.45%)
≥4	10,000 (65.27%)	8965 (58.51%)	1035 (6.76%)
Drinking frequency			
None	9819 (64.08%)	8.948 (58.40%)	871 (5.68%)
≤1/month	1198 (7.82%)	1058 (6.91%)	140 (0.91%)
>1/month	4305 (28.10%)	3881 (25.33%)	424 (2.77%)
Sleep duration (h/night)			
(0, 5]	4385 (30.86%)	4260 (29.98%)	125 (0.88%)
(5, 6]	3247 (22.85%)	3163 (22.26%)	84 (0.59%)
(6, 8]	5378 (37.84%)	5279 (37.15%)	99 (0.70%)
(8, 20]	1201 (8.45%)	1185 (8.34%)	16 (0.11%)

(31.67%). Only 3.05% of the subjects were aged ≥80 years. The gender distribution of the subjects is relatively balanced (male vs female = 48.84% vs 51.16%). The educational level of most of the participants is low at the level of primary school and below. The income gap between the participants with EOBD and those without EOBD is small, and the income level of the participants with EOBD is slightly higher. Most of the participants were married, and few never married. In addition, almost all participants had insurance. Although most of the participants were not disabled, 65.27% of participants suffered from four or more kinds of chorionic diseases. But 75.79% of the participants thought their health was fair or above. Besides, there is differentiation in the drinking behavior of the subjects. A total of 64.08% of participants did not drink, and 28.10% of the people had more frequent drinking behavior. In addition, the night sleep duration of the subjects concentrated on 6–8 h, and 30.86% of the people were less than 5 h.

Experiences of being defrauded

Table 2 reports the association between EOBD and depressive symptoms. Compared with those who reported being defrauded, those who have been defrauded were more likely to have depressive symptoms (odds ratio [OR] = 1.612, 95% confidence interval [CI] 1.445–1.798, model 1). After adjustment for sociodemographic characteristics and socio-economic characteristics, EOBD was more strongly associated with depressive symptoms (OR = 1.661, 95% CI 1.484–1.859, model 2). Then we added health status indicators and health behaviors factors on the basis of model 2. The results of model 3 show that EOBD remained at a higher risk for depressive symptoms (OR = 1.478, 95% CI 1.309–1.669, model 3).

Results of independent analysis

We further explored the relationship between different types of fraud and depressive symptoms. According to the CHARLS 2018, there were three types of fraud: telecommunications fraud, fundraising event fraud, and fraudulent pyramid scheme and sales fraud. Table 3 presents the results of stratified analyses. Among participants, 3.72% suffered from fundraising event fraud, 22.40% suffered from fraudulent pyramid scheme and sales fraud, and 73.88% suffered from telecommunication fraud. And the average is loss as follows: (1) telecommunications fraud: 695.75 yuan, (2) fundraising event fraud: 33,096.15 yuan, and (3) fraudulent pyramid scheme and sales fraud: 2257.86 yuan. The results revealed that fundraising event fraud and fraudulent pyramid scheme and sales fraud were significantly related to depressive symptoms (all $P < 0.05$), but no obvious effect of telecommunications fraud on depressive symptoms in middle-aged and older adults was found.

Discussion

Fraud among the middle-aged and elderly has become an increasingly prevalent social problem in China. A total of 9.37% of

Table 2
Multiple logistic regression model on depressive symptoms.

Variables	(1)			(2)			(3)		
	OR	P	95% CI	OR	P	95% CI	OR	P	95% CI
EOBD (ref: no)	1.612	<0.001	1.445–1.798	1.661	<0.001	1.484–1.859	1.478	<0.001	1.309–1.669
Age (ref: 45–64 years)									
65–79				1.037	0.376	0.957–1.123	0.805	<0.001	0.737–0.879
80–90				0.971	0.779	0.791–1.192	0.800	0.045	0.643–0.995
Gender (ref: female)									
Male				0.654	<0.001	0.610–0.702	0.712	<0.001	0.654–0.775
Education level (ref: primary school or below)									
Junior high school or above				0.591	<0.001	0.548–0.638	0.659	<0.001	0.607–0.715
Individual income				0.949	<0.001	0.941–0.957	0.958	<0.001	0.949–0.967
Marital status (ref: married)									
Never married				2.248	0.001	1.402–3.605	1.822	0.024	1.082–3.067
Widow, separated, or divorced				1.482	<0.001	1.331–1.649	1.371	<0.001	1.221–1.540
Insurance (ref: yes)									
No							1.138	0.265	0.906–1.430
Disability (ref: no)									
Yes							1.563	<0.001	1.395–1.750
Self-rated health (ref: fair)									
Very poor							3.990	<0.001	3.378–4.711
Poor							2.385	<0.001	2.170–2.620
Good							0.590	<0.001	0.521–0.668
Very good							0.446	<0.001	0.389–0.512
Number of chronic diseases (ref: ≥4)									
0							0.732	<0.001	0.661–0.811
1							0.831	0.007	0.727–0.950
2–3							1.038	0.675	0.874–1.232
Drinking frequency (ref: none)									
≤1/month							1.069	0.353	0.929–1.230
>1/month							0.924	0.105	0.839–1.017
Sleep duration (ref: (6, 8], h/night)									
(0, 5]							2.322	<0.001	2.125–2.536
(5, 6]							1.187	0.001	1.075–1.311
(8, 20]							1.054	0.467	0.915–1.215
Pseudo R^2							0.146		
Sample size							15,322		

CI, confidence interval; OR, odds ratio.; EOBD, experiences of being defrauded.
Individual income was in logarithmic form. In model 1, the association between fraud and depressive symptoms was assessed; In model 2, the association between fraud and depressive symptoms was assessed when controlling for sociodemographic factors and socio-economic factors; In model 3, health status factors and health behaviors factors were added to the model 2.

Table 3
Independent associations between telecommunications fraud/fundraising event fraud/fraudulent pyramid scheme and sales fraud and depressive symptoms.

Variables	OR	P	95% CI
The type of the fraud (ref: none fraud)			
Telecommunications fraud (73.88%)	1.109	0.234	0.935–1.315
Fundraising event fraud (3.72%)	3.492	<0.001	1.731–7.048
Fraudulent pyramid scheme and sales fraud (22.40%)	1.611	0.003	1.160–2.056
Age (ref: 45–64 years)	0.995	0.037	0.990–0.999
65–79	0.800	<0.001	0.730–0.877
80–90	0.829	0.105	0.661–1040
Gender (ref: female)			
Male	0.720	<0.001	0.659–0.787
Education level (ref: primary school or below)			
Junior high school or above	0.662	<0.001	0.607–0.721
Individual income	0.957	<0.001	0.948–0.966
Marital status (ref: married)			
Never married	1.888	0.025	1.085–3.285
Widow, separated, or divorced	1.418	<0.001	1.256–1.602
Insurance (ref: yes)			
No	0.105	0.412	0.871–1.402
Disability (ref: no)			
Yes	1.591	<0.001	1.412–1.793
Self-rated health (ref: fair)			
Very poor	0.4.185	<0.001	3.516–4.980
Poor	2.453	<0.001	2.223–2.706
Good	0.590	<0.001	0.519–0.672
Very good	0.453	<0.001	0.394–0.522
Number of chronic diseases (ref: ≥4)			
0	0.759	<0.001	0.682–0.844
1	0.833	0.010	0.725–0.957
2–3	1.050	0.593	0.877–1.257
Drinking frequency (ref: none)			
≤1/month	1.109	0.168	0.957–1.285
>1/month	0.925	0.128	0.837–1.023
Sleep duration (ref: (6, 8], h/night)			
(0, 5]	2.318	<0.001	2.114–2.542
(5, 6]	1.190	0.001	1.074–1.320
(8, 20]	1.060	0.442	0.914–1.228

OR, odds ratio; CI, confidence interval.
Individual income was in logarithmic form.

the middle-aged and elderly people have EOBD. This result is similar to that of another study, which implies that frauds are quite common.[36] The Chinese government is increasing its efforts to combat all types of fraud, but the incidence of which is still at a high level. Therefore, current research on the relationship between EOBD and depressive symptoms in middle-aged and elderly victimhood remains to be added. In view of this, we attempted to explore it with the data obtained from CHARLS 2018. The main findings were as follows: (1) there was a statistically significant association between those who had EOBD and the development of depressive symptoms after controlling for other potential factors; (2) different types of fraud had different effects on the development of depressive symptoms in victimhood. Compared with people who had EOBD of telecommunications fraud, the victimhood of fundraising event fraud and fraudulent pyramid scheme and sales fraud were more likely to develop depressive symptoms.

We found that the middle-aged and elderly people were more likely to have depressive symptoms after being defrauded. EOBD has a negative impact on their finances, reducing their quality of life or even their ability to live, which significantly correlated with negative emotions such as self-blame and anxiety. These pessimistic feelings are exacerbated when they are blamed by family members, leading to depressive symptoms and even suicide.[21,37] In addition, different types of the fraud had different levels of impact on the triggering of depression in middle-aged and older adults. It may be because of different situations of different types of fraud. Specifically, telecommunications fraud was not significantly associated with depressive symptoms. Possible reasons are as follows. First, in reality, the amount of telecommunications fraud is generally low,[38,39] which is also reflected in the study (telecommunications fraud: 695.75 yuan, fundraising event fraud: 33,096.15 yuan, fraudulent pyramid scheme and sales fraud: 2257.86 yuan). And the economic loss of the fraud victimhood is not too serious. Second, telecommunications fraud is mostly committed by strangers,[40,41] which does not damage the interpersonal relationships of families, neighbors, and relatives. Therefore, telecommunications fraud has a limited impact on the health of middle-aged and elderly people in psychological aspect.

In contrast, fundraising event fraud and fraudulent pyramid scheme and sales fraud played a significant role in causing depressive symptoms in middle-aged and elderly victimhood. These two types of fraud often involve large amounts of money,[42,43] and the probability of acquaintance fraud or face-to-face fraud is extremely high,[44,45] which creates a shock to family relationships, material living standards, and socio-economic status.[46] This sudden change shocks victimhood psychologically and is more likely to promote the development of depressive symptoms.

According to our findings, first of all, after a fraud case occurs, the government should not only investigate the case in time to recover the economic loss for the victimhood but also arrange psychological counseling by psychologists immediately to minimize the psychological damage caused by the fraud to the middle-aged and elderly victimhood. If necessary, material assistance should be given to slow down the victimhood's negative emotional reactions. Second, the government should continue to increase its efforts to combat fraud cases, especially those involving large amounts of money, such as fundraising event fraud and fraudulent pyramid scheme and sales fraud. It is worth noting that the amount of telecommunications fraud has gradually increased in recent years and is more frequent because of its low cost of implementation, so the government still needs to combat telecommunications fraud. Finally, since antifraud warnings lose their effectiveness over time,[47] the government should regularize antifraud campaigns to keep middle-aged and elderly people alert and reduce the risk of being defrauded.

The strength of this study is that it uses a large sample size of data to complement research on depressive symptoms, a specific mental health symptom of fraud victimhood, providing theoretical support for action and policy development by public health and legal authorities. However, there are several limitations of this study that remain to be considered. First, the CHARLS 2018 survey used in this study classified types of fraud as telecommunications fraud, fundraising event fraud, and fraudulent pyramid scheme and sales fraud. However, this classification is still not sufficiently detailed. Future research could consider a more detailed classification of fraud types to improve the relevance of the findings. Second, some studies believe that when investigating the EOBD, it is more sensitive to describe the specific fraud situation to the respondent than to directly ask him/her whether he/she has experienced some kind of fraud. Unfortunately, CHARLS 2018 adopts the latter. Therefore, future studies can optimize the question to make the data more reliable. Third, all questions about depressive symptoms were reported by individuals, and because the respondents were middle-aged and elderly people, the data may be affected by their cognitive level and memory, resulting in reduced accuracy. Finally, the causes of depressive symptoms were diverse. Therefore, some other important factors may be overlooked. The contribution of other control variables to the cause of depressive symptoms may continue to be considered in subsequent studies. We strongly encourage scholars to conduct further research on the effects of fraud on depressive symptoms to reduce the secondary harm caused by fraud to victimhood.

Conclusion

The results of this study show that EOBD is significantly associated with the development of depressive symptoms in middle-aged and elderly victimhood, that is, middle-aged and elderly fraud victimhood are more likely to experience depressive symptoms. Second, there are differences in the effects of different types of fraud on depressive symptoms in middle-aged and elderly people. Fundraising event fraud and fraudulent pyramid scheme and sales fraud have a greater effect on depressive symptoms, whereas telecommunication fraud is not significantly associated with depressive symptoms. The results of this study may provide theoretical support for subsequent mental health interventions for middle-aged and elderly fraud victimhood. More importantly, the middle-aged and elderly are a target for frauds because they are likely to have lifelong savings, even if those savings may be small. This circumstance makes them generally vulnerable to frauds. So the government should make further efforts to prevent fraud.

Author statements

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Ethical approval

The Biomedical Ethics Committee of Peking University approved the study (approval number: IRB00001052-11015).

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Competing interests

None declared.

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Original Research

The relationship between loneliness and healthy aging indicators in Brazil (ELSI-Brazil) and England (ELSA): sex differences

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ABSTRACT

Objectives: This study aimed to estimate five harmonized healthy aging indicators covering functional ability and intrinsic capacity among older women and men from Brazil and England and evaluate their association with loneliness.
Study design: This was a cross-sectional study.
Methods: We used two nationally representative samples of men and women aged ≥60 years from the Brazilian Longitudinal Study of Aging (ELSI-Brazil) wave 2 (2019–2021; $n = 6929$) and the English Longitudinal Study of Aging wave 9 (2018–2019; $n = 5902$). Healthy aging included five separate indicators (getting dressed, taking medication, managing money, cognitive function, and handgrip strength). Loneliness was measured by the 3-item University of California Loneliness Scale. Logistic regression models stratified by sex and country were performed.
Results: Overall, age-adjusted healthy aging indicators were worse in Brazil compared with England for both men and women. Considering functional ability, loneliness was negatively associated with all indicators (ranging from odds ratio [OR] = 0.26, [95% confidence interval (CI) 0.13–0.52] in English men regarding the ability to take medication to OR = 0.49 [95% CI 0.27–0.89] in Brazilian women regarding the ability to manage money). Considering intrinsic capacity, loneliness was negatively associated with a higher cognitive function (OR = 0.72; 95% CI 0.55–0.95 in English women) and a higher handgrip strength (OR = 0.61; 95% CI 0.45–0.83 in Brazilian women). Lonely women demonstrated lower odds of a higher number of healthy aging indicators than men in both countries.
Conclusions: Country-specific social environments should be targeted by public policies to decrease loneliness and promote healthy aging later in life.

Introduction

In 2015, the World Health Organization defined healthy aging as developing and maintaining the functional ability that enables well-being later in life, comprising functional ability, intrinsic capacity, and environment components.[1] Since then, few proposed healthy aging scores emerged, using different indicators of functional ability and intrinsic capacity,[2,3] but not including data from Brazil. More recently, the World Health Organization proposed five harmonized indicators based on nationally representative data from 42 countries worldwide, including Brazil, and covering the same components.[4]

Common approaches to measuring healthy aging are essential in cross-country comparisons aiming at establishing the distinct impact of a particular environment on aging, especially between upper-middle-income and high-income countries. Due to a faster demographic change, upper-middle-income countries had to adapt

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more quickly to population aging than high-income countries despite having poorer health and social welfare infrastructures. Brazil and England, respectively, are good examples of those countries. They show a distinct aging process but with similar universal public primary care–oriented health systems with public participation, funded through general taxation and controlled by the Secretary of State for Health with decentralization at the local level.[5] In 2020, the Brazilian population aged ≥65 years was 10% of a 211,8 million population.[6] In England, this age group represented 18.5% of a 56,5 million population.[7]

The environment also encompasses the support and relationships related to the quality of support provided by people or animals at home and work and in other aspects of daily activities.[8] When there is a lack of support and relationships, loneliness, the subjective feeling of social isolation and not belonging,[9] can emerge.

Loneliness has been considered a global epidemic among the world's older adult population[10] and is associated with various adverse health outcomes, such as physical and mental health problems[11] and mortality.[12] About 11%–18% of depressive symptoms in England can be attributable to loneliness.[13] The mechanisms underlying poor health outcomes rely on a diminished capacity of self-regulation related to lifestyle and sleep quality,[11] neuroendocrine stress,[14] inflammatory responses, and immune deregulation.[11] However, few studies evaluated the impact of loneliness on positive outcomes, such as healthy aging. One study in Amsterdam did not find any association between loneliness and longevity (≥90 years) among men and women,[15] although longevity was not necessarily healthy. Other studies found that loneliness decreases the odds of 'aging well' in older German individuals (aged ≥40 years)[16] and in adults (aged ≥18 years) from Finland, Poland, and Spain.[17] However, studies comparing high-income with upper-middle-income countries are lacking. Therefore, this study aimed at estimating and comparing healthy aging indicators among older women and men from Brazil and England and evaluating the burden of loneliness on healthy aging indicators.

Methods

Data source

This is a cross-sectional analysis using data from wave 2 (2019–2021) of the Brazilian Longitudinal Study of Ageing (ELSI-Brazil) and wave 9 (2018–2019) of the English Longitudinal Study of Ageing (ELSA). Both studies are nationally representative of the community-dwelling population aged ≥50 years.[18,19] ELSI-Brazil sampling procedures included a probabilistic sample design, combining geographical stratification in clustering stages, covering 70 municipalities from the five great Brazilian geographic regions.[18] The final wave 2 sample comprised 9949 previous and refreshed participants.[20] Of those, 6929 had 60 years and over and were eligible for the current analysis. ELSA initial sample was drawn from the Health Survey for England in 1998/1999/2001, an annual cross-sectional survey[19] using a complex design with clustering effects. ELSA sample has periodically been refreshed to maintain the representation of younger older adults. The final wave 9 sample comprised 7289 core participants eligible for the nurse visit (i.e. an additional collection of biological samples and handgrip strength measures). Of those, 5902 were aged ≥60 years and were included in this analysis.

ELSI-Brazil has been approved by the Research Ethics Committee of the Oswaldo Cruz Foundation, Minas Gerais (protocol 34649814.3.0000.5091). The ELSA has been approved by National Research Ethics Service (London Multicentre Research Ethics Committee - MREC/01/2/91).

Healthy aging indicators

We included the five individual healthy aging indicators proposed by the World Health Organization.

- Functional ability: it included three basic daily activities. Participants were asked about having difficulties in (1) getting dressed, (2) taking medication, and (3) managing money. Participants were considered 'able of' when they did not report difficulties in any of the activities.
- Intrinsic capacity: it included cognitive and vitality subdomains. (4) Cognitive function was evaluated by the delayed word list learning test, where the interviewer read 10 words, and participants were asked to repeat as many words as they could after five minutes. Cut-offs considering the lowest 20th percentile were created for each country, stratified by sex, 5-year age group up to 85 years, and years of schooling (lowest or highest), to classify the absence of healthy aging. The lowest schooling level included incomplete formal education in each country (incomplete first level '≤7 years' in Brazil and 0 level or equivalent '≤11 years' in England). The vitality subdomain was evaluated by (5) handgrip strength. It was objectively assessed through the best of three attempts in the dominant upper limb by a handgrip dynamometer. Cut-offs considering the lowest 20th percentile were created for each country, stratified by sex, and 5-year age group, to classify the absence of healthy aging. All values used as cut-offs can be found in Supplemental Table 1. In England, handgrip strength was assessed during the nurse visit. The waves 8 (2016–2017) and 9 (2018–2019) nurse samples were designed to be analyzed as a whole, that is, 2837 from wave 8 and 2061 from wave 9.

Loneliness

Loneliness was measured by the 3-item University of California Loneliness Scale.[9] A valid scale in each country, containing three questions about how often the participant feels lack of companionship, left out, and isolated from others. Each question had three possible answers (i.e. hardly ever or never, some of the time, and often), generating a score ranging from 3 to 9. According to the final score, the participants were classified into 'no loneliness' (scores of 3–5) and 'loneliness' (scores of 6–9).[21]

Covariates

Covariates included sociodemographic characteristics (age groups [60–69, 70–79, and ≥80 years], wealth [quintiles]), living alone (yes or no), having a partner (yes or no), social network contact (infrequent or frequent), multimorbidity (yes or no), and depressive symptoms (yes or no). Wealth included the total non-pension household wealth and was measured differently in each country, considering its cultural peculiarities. In Brazil, wealth included any home or other property (less mortgage) and vehicle assets at the current value. In England, it included financial wealth (savings and investments), any home and other property (less mortgage), any business assets, and physical wealth such as artwork and jewels owned by the household minus any debt, comprising 22 components. A detailed description of the wealth variable can be found at http://elsi.cpqrr.fiocruz.br/en/guidelines-to-use/ for Brazil and http://bit.ly/1yrRgHd and http://bit.ly/1awp6iZ for England. In both countries, the components were either observed or imputed. Social network contact included the frequency of face-to-face meetings with children, family, or friends who do not live with the participant. Each category (i.e. children, family, and friends) used a 6-point Likert scale, ranging from less than once a year/never to three or more times a week. The final score combined the categories ranging from 3 to 18, higher scores indicating greater face-to-face contact frequency.[13] Infrequent social network contact included scores lower than 7, which means answering 'less than once a year/never' or 'once or twice a year' in at least two categories. Multimorbidity included a self-reported history of at least two medical diagnoses of cardiovascular disease (hypertension, stroke, heart attack, angina, or heart failure), high cholesterol, neurologic disease (Parkinson's or Alzheimer's disease), chronic obstructive pulmonary disease, diabetes, arthritis, asthma, or cancer. Depressive symptoms were measured by the validated 8-item Center for Epidemiologic Studies—Depression Scale[22,23] using the cut-off point of four or more as depressive symptoms.[24] The scale contains eight questions about depressive symptoms experienced during the week before interview.

Statistical analysis

We estimated and plotted in charts the prevalence of each functional ability indicator (i.e. ability to get dressed, ability to take medicine, and ability to manage money) and median of each intrinsic capacity indicator (i.e. cognitive function and handgrip strength) by country and sex at age groups. Covariates and loneliness age-adjusted prevalence were estimated by country and sex, allowing comparisons between Brazil and England. To examine the association between loneliness and each healthy aging indicator, we adjusted separate logistic regression models considering each healthy aging indicator as the dependent variable, including loneliness as the independent variable, and adjusting for other covariates. Considering the complex data design of ELSI-Brazil and ELSA, we incorporated the study design (i.e. cluster and stratification for ELSI-Brazil and cluster for ELSA) and weights using the Survey package (v4.0). All analyses were done separately by sex in the software R, RStudio, and Stata 17.0.

Results

In both countries, the included participants aged ≥60 years (6929 from ELSI-Brazil and 5902 from ELSA) had different missing data on each healthy aging indicator, and therefore, each model had different samples. Participants were younger in Brazil: 55% of the Brazilian participants were aged 60–69 years, whereas only 45% were the same age in England, justifying the age standardization approach used to compare prevalence. With regard to sex, in both countries, most participants were women (54.4% in Brazil and 53.9% in England).

Fig. 1 shows the prevalence of functional ability indicators [(A) ability to get dressed, (B) take medication, and (C) manage money] according to age and country. Of the abovementioned indicators, healthy aging was similar among women and men within countries. Overall, when comparing countries we observed that the prevalence of functional ability indicators was higher in England than in Brazil, mainly at 70–79 and ≥80 years, except for the prevalence of the ability to get dressed, which was higher in Brazilian women (98.1% vs 88.6% among Brazilian and English aged 60–69 years) and men (98% vs 89.5% among Brazilian and English aged 60–69 years).

Fig. 2 shows the median of intrinsic capacity indicators [(A) cognitive function and (B) handgrip strength] according to age and country. Median cognitive function and handgrip strength were higher among English than Brazilians for both men and women in all age groups, demonstrating higher intrinsic capacity indicators in England.

The age-adjusted prevalence of loneliness was similar across countries and sex: among women, the age-adjusted prevalence was 18.8% in Brazilians and 22.5% in English (Table 1). Among men, it was 14.7% in Brazilians and 16.2% in English. Overall, covariates were worse among women than men in both countries. However, they generally differed by country. Age-adjusted prevalence of older women who have a partner was lower among Brazilians than English (39.7% vs 56.3%, respectively); both women and men showed higher social network contact in Brazil than in England (94.7% vs 81.8% among women, respectively, and 93.8% vs 79.7% among men, respectively). The age-adjusted prevalence of men with multimorbidity was lower among Brazilians than English (34.9% vs 43.4%, respectively).

Table 2 presents the fully adjusted models of the association between loneliness and healthy aging indicators in older women and men from Brazil and England. Loneliness was negatively associated with a higher number of healthy aging indicators in women than men, irrespectively of nationality. Regarding functional ability, loneliness was negatively associated with all indicators among Brazilian women (get dressed: odds ratio [OR]: 0.37; 95% confidence interval [CI]: 0.22–0.64; take medication: OR: 0.37; 95% CI: 0.22–0.63; and manage money: OR: 0.49; 95% CI: 0.27–0.89), whereas in England, it was associated with the ability to manage money in women (OR: 0.38; 95% CI: 0.20–0.72) and take medication in men (OR: 0.26; 95% CI: 0.13–0.52).

Concerning intrinsic capacity, lonely individuals were less likely than non-lonely to have a higher cognitive function among English women (OR: 0.73; 95% CI: 0.55–0.95) and a higher handgrip strength among Brazilian women (OR: 0.61; 95% CI: 0.45–0.83).

Because depressive symptoms could also be a mediating path between loneliness and healthy aging, additionally, we tested the interaction effect between loneliness and depressive symptoms (Supplemental Table 2). Most of the models were not significant, demonstrating that loneliness might exert an independently effect on healthy aging, irrespectively of depressive symptoms.

Discussion

Our findings showed disparities in healthy aging indicators across countries, demonstrating better health among English women and men, except for the ability to get dressed, which was higher among Brazilians. The age-adjusted loneliness prevalence was similar across countries and sex. Nevertheless, consistently in both countries, loneliness is inversely associated with a higher number of healthy aging indicators among older women than men, demonstrating that the burden of loneliness decreases health more among women.

Comparing the prevalence of each healthy aging indicator is difficult because most of the previously published studies compared the prevalence of functional abilities according to categories of activities of daily living, such as basic or instrumental. In general, Brazil has worse functional ability based on basic activities of daily living[25] and instrumental activities of daily living (including taking medication and managing money) than England.[26] However, in 2015, a study found comparable age- and sex-adjusted prevalence in six basic activities of daily living (including getting dressed; 82.1% in Brazil vs 83.7% in England).[27] In the present study, the higher ability to get dressed in Brazil could be attributable to warmer weather, where comfortable, soft, and fewer clothes are needed.

Although intrinsic capacity was worse in Brazil, the same pattern did not occur for all functional ability indicators, reinforcing that functional ability derives from the interaction between intrinsic capacity and environment. Therefore, healthy aging also depends on the social, economic, political, and built environments where older adults live and should be targeted to build age-friendly communities. Studies comparing countries with different contexts

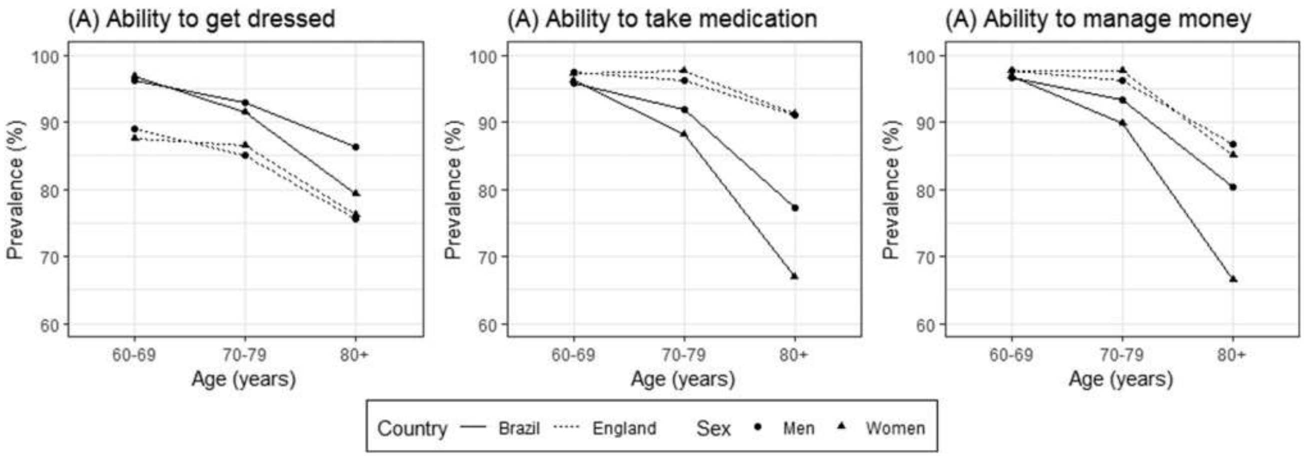

Fig. 1. Prevalence of functional ability indicators, (A) ability to get dressed, (B) take medication, and (C) manage money, according to age and country—ELSI-Brazil (2019–2021) and ELSA (2018–2019).

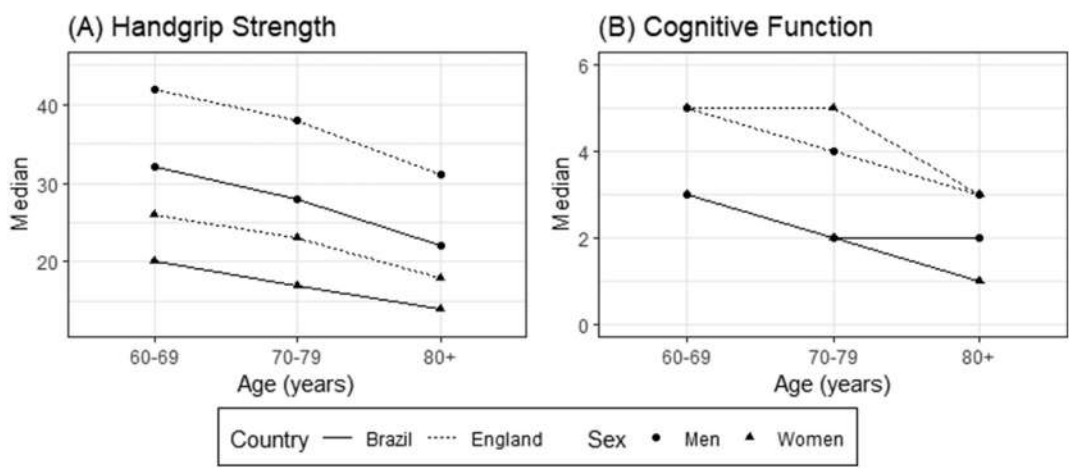

Fig. 2. Median of intrinsic capacity indicators, (A) cognitive function and (B) handgrip strength, according to age and country—ELSI-Brazil (2019–2021) and ELSA (2018–2019).

Table 1
Age-adjusted prevalence of healthy aging indicators and other participant's characteristics among women and men from Brazil and England—ELSI-Brazil (2019–2021) and ELSA (2018–2019).

Variable (%)	Age-adjusted prevalence							
	Women				Men			
	Brazil		England		Brazil		England	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Other participant's characteristics								
Loneliness	18.8	16.2–22.0	22.5	20.7–24.0	14.7	11.4–19.0	16.2	14.5–18.0
Living alone	28.6	24.1–34.0	32.2	30.4–34.0	20.3	17.4–24.0	19.4	17.6–21.0
Having a partner	39.7	37.0–43.0	56.3	54.4–58.0	71.7	69.2–74.0	72.2	70.1–74.0
Frequent social network contact	94.7	93.5–96.0	81.8	80.0–83.0	93.8	92.2–95.0	79.7	77.7–82.0
Multimorbidity	50.8	46.6–55.0	44.6	42.7–47.0	34.9	32.1–38.0	43.4	41.2–46.0
Depressive symptoms	33.3	30.1–37.0	32.7	30.8–35.0	20.9	17.7–24.0	22.1	20.3–24.0

CI, confidence interval.

are needed[28] mainly because the social environment, often measured by the satisfaction of personal relationships and frequency of social network contact, seems to be more essential in achieving well-being in later life among women and men than the built environment.[29] Positive aspects of personal relationships have been reported to decrease the risk of poor functional ability among Brazilians[30] and English.[31]

In our study, loneliness was associated with all healthy aging indicators, independently of depressive symptoms. As mentioned earlier, comparisons between studies that investigated the association between loneliness and functional ability indicators should be made with caution because these indicators have been indirectly measured in the literature, differently from this study. Longitudinal studies that included 'difficulties in getting dressed'[16,32] or 'poor

Table 2
Fully adjusted models of the association between loneliness and healthy aging indicators in older women and men from Brazil and England—ELSI-Brazil (2019–2021) and ELSA (2018–2019).

Healthy ageing indicators	Women				Men			
	Brazil		England		Brazil		England	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Ability to get dressed								
No loneliness	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Loneliness	**0.37**	**0.22–0.64**	0.80	0.57–1.31	0.67	0.23–1.95	1.23	0.80–1.90
Ability to take medication								
No loneliness	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Loneliness	**0.37**	**0.22–0.63**	0.91	0.37–2.21	0.76	0.35–1.67	**0.26**	**0.13–0.52**
Ability to manage money								
No loneliness	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Loneliness	**0.49**	**0.27–0.89**	**0.38**	**0.20–0.72**	0.96	0.39–2.34	0.78	0.31–1.95
Higher cognitive function								
No loneliness	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Loneliness	0.86	0.63–1.15	**0.73**	**0.55–0.95**	1.06	0.71–1.57	0.77	0.54–1.10
Higher handgrip strength								
No loneliness	1.00	Ref.	1.00	Ref.	1.00	Ref.	1.00	Ref.
Loneliness	**0.61**	**0.45–0.83**	1.12	0.80–1.56	0.60	0.34–1.05	1.06	0.70–1.61

CI, confidence interval; OR, odds ratio; Ref., reference.
Models were made separately by each healthy aging indicator (i.e. getting dressed, taking medication, managing money, cognitive function, and handgrip strength) and adjusted for age group, wealth, living alone, having a partner, social network contact, multimorbidity, and depressive symptoms.
The bold values are represented as p <0.05.

handgrip strength'[33] as one item of the outcome consistently found a positive association with loneliness. These results suggest that inflammatory responses[11] caused by loneliness may generate sarcopenia, which is a major contributor to the risk of functional ability decline and physical frailty.[34] Furthermore, cross-sectional and longitudinal evidence indicated that loneliness was negatively associated with cognitive function.[35] The linked mechanisms were unclear and warranted further investigation.[35] Nevertheless, there is some evidence that this relationship could be associated with too much or too little activity of certain neurotransmitters and hormones,[14] probably leading to brain damage.

Some implications emerge from our findings for public policies: irrespectively of the social context, promoting healthy aging encompasses organizations that enable people's relationships and an infrastructure that empowers social connections.[36] In the health sector, we encourage multiprofessional teams to track loneliness with simple questions and to provide group activities to support and increase the sense of belonging. Recently in the United Kingdom, general practitioners have been offering a social prescribing that links those in need to a range of services that support social, emotional, and practical needs.[37] Intersectionally, age-friendly environments that enable tackling loneliness include having access to community spaces to get together and accessibility when going outside, such as street infrastructure and public transport network.[36] Further research can evaluate the effectiveness of these actions on healthy aging.

Although longitudinal studies reported being a woman as a determinant of loneliness,[38] we did not find that women suffer more from loneliness than men. However, our results demonstrated that the burden of loneliness unequally decreases healthy aging among older women than men in Brazil and England, corroborating previous results in England.[39] Distinctively from our results, longitudinal[32] association between loneliness and cognitive impairment[35] or items of difficulties in getting dressed/cognitive impairment[32] was increased among older men but not women in China. Some possible explanations could be speculated. First, differences might be attributable to a lack of uniformity in measuring loneliness. Second, different loneliness patterns occur in each country even when showing similar overall loneliness scores using the 3-item University of California Loneliness Scale. English more often answer that they hardly ever feel a lack of companionship than Americans.[40] In the present study, older Brazilian women were more likely not to have a partner than English, which can be compensated by the higher social network contact. These are social environment variables previously described to be associated with loneliness. Third, worse social determinants in women, such as living alone and not having a partner, may have a higher buffering effect on healthy aging.

This study has some strengths and limitations that must be considered when interpreting our results. We highlight the inclusion of recent data from two nationally representative samples of older adults as a strength that ensures external and internal validity, along with the methodological studies' rigor and comparative procedures. As a potential limitation, analyzing healthy aging indicators separately limited interpretations. However, healthy aging scores are a new approach, and their wide use depends on further investigations. Another potential limitation relates to the wealth measurement consistency, a significant covariate in countries' comparisons, that was limited due to countries' particularities. Finally, the cross-sectional design limits establishing the associations' direction, not ruling out reverse causality bias.

In conclusion, despite having different contexts, consistently in Brazil and England, lonely women were less likely to age healthy than men. The environment in which older adults live should be targeted by public policies to empower social connections, decrease loneliness feelings, and promote healthy aging in later life, mainly among women.

Author statements

Acknowledgments

Both ELSI-Brazil and ELSA followed all ethical requirements.

Ethical approval

ELSI-Brazil has been approved by the Research Ethics Committee of the Oswaldo Cruz Foundation, Minas Gerais (protocol 34649814.3.0000.5091). The ELSA has been approved by National

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Competing interests

All authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.01.005.

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