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Original Research

Association between COVID-19 and subsequent vascular events in primary care patients in Germany

S. Zappacosta [a, b], A. Cascarano [c], M. Konrad [d], C. Tanislav [e], K. Kostev [f, *]

[a] Real World Solutions, IQVIA, Basel, Switzerland
[b] University of Paris Cité, Comparative Effectiveness Research, Paris, France
[c] Real World Solutions, IQVIA, Barcelona, Spain
[d] FOM University of Applied Sciences for Economics and Management, Frankfurt, Germany
[e] Department of Geriatrics and Neurology, Diakonie Hospital Jung Stilling Siegen, Germany
[f] Epidemiology, IQVIA, Frankfurt, Germany

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ABSTRACT

Objectives: The aim of this study was to investigate the relationship between COVID-19 diagnosis and the risk of developing a first-ever vascular event (VE) compared with the same risk in those with respiratory tract infection (RTI).
Study design: This was a retrospective cohort study.
Methods: This study using data from Disease Analyzer Database (IQVIA) included patients aged ≥18 years with at least one visit to a German practice during the index period. VEs were defined as cardiovascular or cerebrovascular events. Two cohorts were created: patients with a diagnosis of COVID-19 and those diagnosed with RTI. These were matched using propensity scores. Kaplan–Meier curves were created for the purposes of time to event analysis. A Poisson model was used to calculate incidence rates and derive incidence rate ratios (IRRs).
Results: A total of 58,904 patients were matched. There was no significant association between COVID-19 diagnosis and increased incidence of VE events among females (IRR [95% confidence interval (CI)]: 0.96 [0.82–1.11] and 1.30 [0.88–1.81]) or males (IRR, 95% CI: 0.91 [0.78–1.05] and 1.13 [0.80–1.62]). Overall, no significant association between COVID-19 diagnosis and incidence of VE was observed across age categories except for cardiovascular vascular events in the age category ≥70 years (IRR [95% CI]: 0.78 [0.67–0.94]).
Conclusions: Overall, our study suggests that COVID-19 diagnosis was not associated with an increased risk of developing VE compared with RTI diagnosis. However, further research in a variety of healthcare settings and regions is needed to confirm these preliminary findings from our cohort, which is a good reflection of routine clinical practice in Germany.

Introduction

Vascular disease is a group of non-communicable disorders of the heart and blood vessels including cardiovascular events (CDVE) such as coronary heart disease, peripheral arterial disease, and cerebrovascular events (CVE)[1] consisting of stroke and transient ischemic attack.[2] In 2019, an estimated 17.9 million people died from this group of diseases, which translates to 32% of global deaths.[1] More than 1.68 million of these deaths occurred in Europe alone. In many countries such as Germany, VEs are the leading cause of death and are also a significant cause of disability. This group of diseases accounted for 36% of all deaths in Germany in 2018, with a higher proportion of deaths observed in females vs males (38.8% vs 33.5%),[3] and consequently, places a considerable burden on healthcare systems, adding to the escalating costs of care.[4]

Previous research suggests that there may be a relationship between the recent COVID-19 pandemic and an increased risk of CDVEs and CVEs in different subpopulations.[5–7] The most common complications of COVID-19 include pulmonary and extrapulmonary symptoms, with frequent reports of fever, cough, and shortness of

* Corresponding author. IQVIA, Unterschweinstiege 2–14, 60549 Frankfurt am Main, Germany.
E-mail address: karel.kostev@iqvia.com (K. Kostev).

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breath among symptomatic patients.[8] It is estimated that among those who develop symptoms, approximately 80% recover without the need for hospital treatment or specialized care.[9] However, COVID-19 can also cause cardiac and cerebral injuries as a result of mechanisms currently under investigation, including a combination of direct viral injury and the immunological response of the patient acting as a host.[10] For example, cardiac and cerebral injury caused by COVID-19 may lead to the development of cardiovascular comorbidities such as myocardial infarction (MI) and other forms of CDVE including CVE.

A significant body of literature indicates that chronic systemic inflammation favors the development of atherosclerosis and predisposes individuals to clot formation by interfering with physiological hemostasis and by inducing a state of hypercoagulability.[11,12] It is therefore evident that acute inflammation facilitates the development of vascular events.[13,14] In particular, respiratory tract infections (RTIs), which evoke a broad systemic inflammatory reaction may be involved in the pathogenesis of cardiovascular complications.[15–17] Patients with a pre-existing VE might even be at a higher risk of vascular events than those without.[18] In the current debate, COVID-19 is suspected to have a different pathophysiological impact on the development of many disorders.[19] In this context, it could be surmised that the systemic inflammatory response caused by SARS-CoV-2 exposure may have a different effect on the immune reaction than other unspecified RTIs. If this is confirmed, this difference could render a different pathophysiological impact in causing VE.

Therefore, the aim of this retrospective cohort study was to investigate the relationship between COVID-19 diagnosis and the risk of developing CDVE or CVE among patients without pre-existing VE in general practices in Germany compared with a contemporary cohort diagnosed with RTI.

Methods

Database description

This retrospective cohort study used data from the Disease Analyzer Database (IQVIA). The Disease Analyzer contains de-identified electronic medical records from general and specialized practices in Germany including demographic, diagnosis (according to International Classification of Diseases, 10th revision [ICD-10]), and prescription patient data.[20] As data are collected in a non-interventional manner, the database offers an accurate reflection of routine clinical practice and real-world settings. Approximately 3% of all German practices are included in the Disease Analyzer Database. The validity and representativeness of the data have been described extensively, demonstrating the suitability of the Disease Analyzer Database for the conduction of pharmacoepidemiological and pharmacoeconomic studies.[21] In addition, the Disease Analyzer Database has previously been used in studies focusing on COVID-19 and cardiovascular outcomes.[22]

Study population

Patients aged ≥18 years with at least one visit to a German practice during the index period were included in the study. The index period was defined as March 1, 2020 (the start of the pandemic), to June 30, 2021. The study end was defined as December 31, 2021, allowing for a minimum follow-up time of 6 months. Patients for whom sex or age information was missing were excluded from the study. Two contemporary cohorts were defined: a cohort of patients with a diagnosis of COVID-19 (ICD-10: U07.1) and a cohort of patients with a diagnosis of acute lower or upper RTI (ICD-10: J06, J20, J21, J22). Any patient with a diagnosis of RTI who had also been diagnosed with COVID-19 during the index period was considered for inclusion in the COVID-19 cohort only. Care was taken to exclude patients with a diagnosis of COVID-19 before March 1, 2020, to avoid including patient records with a diagnosis code used to identify a disease other than COVID-19. Because this study does not include patients with pre-existing CDVE or CVE, all patients with pre-existing CDVE including CVE (see Appendix 1 for ICD-10 codes) up to 5 years before the index date were excluded from the study. Patient comorbidities, including diabetes, hypertension, obesity, and any type of cancer (see Appendix 2 for ICD-10 codes), were also retrieved for up to 5 years before the index date. After applying the inclusion and exclusion criteria, both cohorts were matched using a propensity score approach based on sex, age, index month of the infection, and identified comorbidities. The selection diagram for study patients is displayed in Fig. 1.

Outcomes

The primary outcome was the incidence of vascular events including CDVEs or CVEs. The secondary outcome was the time to first VE. A CDVE was considered to have occurred if the following diagnosis was recorded: angina pectoris, acute MI, subsequent MI, certain current complications following acute MI, other acute ischemic heart diseases, chronic ischemic heart disease, atrial fibrillation and flutter, and heart failure. A CVE was defined as stroke, cerebral infarction, or transient ischemic attack. A complete list of the ICD-10 codes used for the identification of these events can be found in Appendix 3.

Statistical methods

No statistical power calculation was conducted in this real-world study as the primary outcome was descriptive in nature. All study patients in the Disease Analyzer Database who met the inclusion and passed the exclusion criteria were included. Descriptive summary statistics (n [%], mean, standard deviation [SD], and interquartile range) were used to describe continuous variables. Counts and proportions were used to describe categorical variables. No imputation method was used for handling missing data as patients for whom age or sex information was missing were excluded from the cohort. Kaplan–Meier curves were used for the analysis of time to VE event, from index date until the first year of the follow-up period. Given the small proportion of events observed, a Poisson model approach was the preferred method for calculating the incidence rates of VEs per 1000 person-years and deriving incidence rate ratios (IRRs). P values <0.05 were considered statistically significant. Analyses were carried out using manufacturer is RStudio (Public Benefit Corporation) version 1.2.1235.

Results

Cohort description

In total, some 766,048 patients aged ≥18 years with at least one visit to one of 1255 general practices in Germany between March 1, 2020, and June 30, 2021, were available for inclusion, of which 1085 were excluded due to missing sex information. After applying further inclusion and exclusion criteria (including diagnosis of COVID-19 or RTI, no previous CDVE or CVE), 58,904 patients and 371,241 patients remained in the COVID-19 and RTI cohorts, respectively. These patients were matched using the propensity score approach, leading to a total of 58,904 patients diagnosed with COVID-19 and 58,904 patients with RTI for final inclusion in this study (Fig. 1). The mean (SD) age was 45.6 (17.4) and 45.4 (17.0)

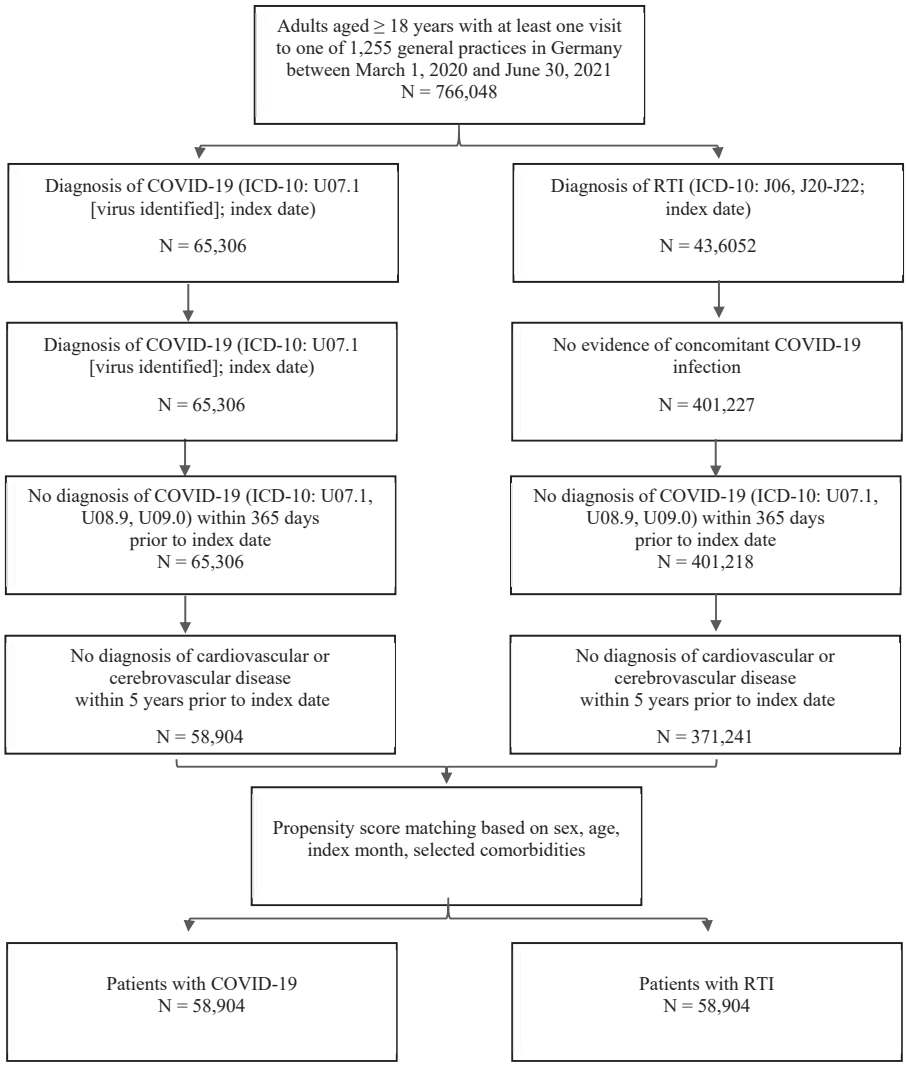

Fig. 1. Selection of study patients.

years, respectively, in the COVID-19 and RTI cohorts, with a higher proportion of females vs males in both groups (53.8% vs 46.4% in the COVID-19 cohort and 54.0% vs 46.0% in the RTI cohort). The mean (SD) follow-up time was 363.7 (17.3) days and 363.6 (16.8) days, respectively, in the COVID-19 and RTI cohorts, with a minimum follow-up time of 184 days for both. The baseline characteristics of both cohorts after 1:1 propensity score matching are summarized in Table 1.

Incidence rate and IRR

Table 2 presents the incidence of VE calculated per 1000 person-years (overall and stratified by sex and age category) and IRRs with a confidence interval (CI) of 95% for each of the cohorts. Overall, no significant association was observed between COVID-19 diagnosis and increased incidence of VE (IRR, 95% CI: 0.92 [0.84; 1.03] and 1.20 [0.93; 1.55]). Similarly, no significant association was observed between COVID-19 diagnosis and increased incidence of VE among females (IRR, 95% CI: 0.96 [0.82; 1.11] and 1.30 [0.88; 1.81]) or males (IRR, 95% CI: 0.91 [0.78; 1.05] and 1.13 [0.80; 1.62]). In addition, there was no significant association between COVID-19 diagnosis and increased incidence of VE by age category except for CDVE events in the oldest age category, ≥70 years (IRR, 95% CI: 0.78 [0.67; 0.94]).

Time to first VE

A total of 806 and 835 events were observed in the COVID-19 and RTI cohorts, respectively, accounting for less than 1% of events, with a higher proportion of CDVEs vs CVEs. The mean (SD) time to the first event was 412 (0.7) days for both cohorts (Table 3). A Kaplan–Meier analysis of the time to first VEs showed no significant differentiation of the overall survival probability between both cohorts as the curves crossed. Based on the log-rank test, there was no significant difference in the Kaplan–Meir curves for both cohorts for the time to first VE overall and by type of event in the first year of follow-up (Fig. 2).

Discussion

Main findings

This retrospective study, conducted in a real-world setting in German primary care practices, showed that overall, there was no significant association between COVID-19 diagnosis and increased incidence of cardiovascular or cerebrovascular outcome in comparison to patients suffering from a different RTI. However, these results need to be interpreted with caution as the

Table 1
Baseline characteristics of study patients after 1:1 propensity score matching.

Variable	Patients with COVID-19 (n = 58,832)	Patients with RTI (n = 58,832)
Age in database		
Mean (SD)	45.6 (17.4)	45.4 (17.0)
Follow-up (days)		
Mean (SD)	363.7 (17.3)	363.6 (16.8)
Age in database, n (%)	*N (%)*	*N (%)*
18–30	13,390 (22.8)	13,397 (22.8)
31–40	11,474 (19.5)	11,518 (19.6)
41–50	11,094 (18.9)	11,132 (18.9)
51–60	12,211 (20.8)	12,388 (21.0)
61–70	5697 (9.7)	5873 (10.0)
>70	4966 (8.4)	4524 (7.7)
Sex		
Male	27,165 (46.4)	27,066 (46.0)
Female	31,667 (53.8)	31,766 (54.0)
Index month		
March 20	412 (0.7)	412 (0.7)
April 20	1566 (2.7)	1551 (2.6)
May 20	838 (1.4)	834 (1.4)
June 20	640 (1.1)	645 (1.1)
July 20	809 (1.4)	797 (1.4)
August 20	1236 (2.1)	1249 (2.1)
September 20	1300 (2.2)	1308 (2.2)
October 20	4173 (7.1)	4187 (7.1)
November 20	8688 (14.8)	8604 (14.6)
December 20	10,187 (17.3)	9949 (16.9)
January 21	7172 (12.2)	7119 (12.1)
February 21	3617 (6.2)	3535 (6.0)
March 21	5810 (9.9)	5878 (9.9)
April 21	7223 (12.3)	7463 (12.7)
May 21	3856 (6.6)	4022 (6.8)
June 21	1305 (2.2)	1279 (2.2)
Comorbidities in the last 5 years (not mutually exclusive)		
Cancer	1839 (3.1)	1487 (2.5)
Diabetes	3999 (6.8)	3658 (6.2)
Hypertension	10,629 (18.1)	10,384 (17.7)
Lipid disorders	6589 (11.2)	7439 (12.6)
Obesity	4359 (7.4)	4278 (7.3)

RTI, respiratory tract infection.

incidence of CVE was much higher in the COVID-19 cohort but non-significant due to the small total number of events. The latter was observed in all age groups except for CDVE events in the oldest age category ≥70 years, where a significant association was found.

Interpretation of results

The mean age in our study cohorts was approximately 45 years (equal to median age in our study), which is in line with that of the general German population (45.7 years in 2020).[23] A study using

Table 2
Incidence of CDVE and CVE per 1000 person-years in patients with COVID-19 and RTI.

Patient cohort	Incidence per 1000 person-years in patients with COVID-19 (n = 58,832)	Incidence per 1000 person-years in patients with RTI (n = 58,832)	Incidence rate ratio (95% CI)	*P* value
Cardiovascular events (CDVE)				
Overall	11.6	12.5	0.92 (0.84; 1.03)	0.1727
Female sex	10.7	12.7	0.96 (0.82; 1.11)	0.5425
Male sex	12.7	14.0	0.91 (0.78; 1.05)	0.1887
Age 18–30	1.3	0.9	1.42 (0.68; 2.99)	0.3429
Age 31–40	3.2	2.4	1.34 (0.82; 2.22)	0.2425
Age 41–50	5.9	6.8	0.86 (0.62; 1.20)	0.3793
Age 51–60	13.3	14.5	0.92 (0.74; 1.24)	0.4376
Age 61–70	25.9	26.4	0.98 (0.78; 1.24)	0.8686
Age >70	53.0	66.4	0.78 (0.67; 0.94)	0.0083
Cerebrovascular events (CVE)				
Overall	2.3	1.9	1.20 (0.93; 1.55)	0.1613
Female sex	2.1	1.7	1.30 (0.88; 1.81)	0.2012
Male sex	2.5	2.2	1.13 (0.80; 1.62)	0.4818
Age 18–30	0.3	0.1	4.62 (0.52; 41.35)	0.1318
Age 31–40	0.6	0.6	1.01 (0.35; 2.88)	0.9868
Age 41–50	1.0	1.4	0.74 (0.34; 1.61)	0.4465
Age 51–60	2.9	2.5	1.15 (0.70; 1.88)	0.5709
Age 61–70	4.1	4.5	0.90 (0.51; 1.61)	0.7358
Age >70	11.3	7.6	1.49 (0.96; 2.31)	0.0705

CI, confidence interval; RTI, respiratory tract infection.

Table 3
Time to first event by type of event.

Variable	Patients with COVID-19 (N = 58,832)	Patients with RTI (N = 58,832)
Time to first event (days)		
Mean (SD)	412 (0.7)	412 (0.7)
Type of event [a]	*N (%)*	*N (%)*
CDVE	674 (0.011)	725 (0.012)
CVE	132 (0.002)	110 (0.002)

CDVE, cardiovascular events; CVE, cerebrovascular event; RTI, respiratory tract infection.
[a] CDVE and CVE are mutually exclusive.

data from the Swedish Public Health Agency database previously described the association between COVID-19 and cardiovascular outcomes in a COVID-19 cohort with a median age of 48 years.[5] This study concluded that COVID-19 diagnosis was associated with a higher risk of developing an event. Although our overall results do not reflect those of the previous authors, it is important to highlight that our study cohorts excluded patients with a previous history of VE, which caused a lower number of events to be observed. When looking at the older age category ≥70 years, we observed an IRR of above one in the COVID-19 cohort (IRR, 95% CI: 1.49 [0.96; 2.31]), although this was still non-significant. This is comparable with the study of Modin et al., who used Danish registers to identify all patients diagnosed with COVID-19 in hospital settings.[6] They found that in a population cohort with a mean age of 77 years, incidence rates for ischemic stroke after COVID-19 diagnosis were significant, ranging between 6.6 (3.6–11.9) and 12.9 (7.1–23.5) depending on varying COVID-19 risk intervals. Our study results can be interpreted as a confirmation of the latter; nevertheless, the relationship with COVID-19 diagnosis might be confounded by the fact that the elderly population is already at increased risk of suffering from cerebrovascular complications as previously described in the literature.[24,25]

In our study, we also observed that the IRR among females was higher than in males but still non-significant. Several studies that have investigated how the risk of developing a CDVE or CVE can vary based on sex.[26–28] Although the evidence shows that females have a lower overall age-adjusted stroke incidence than men, they tend to experience more stroke events due to their longer life expectancy.[29] This could potentially explain the higher IRR of females vs males both for CDVE and CVE (IRR, 95% CI: 0.96 [0.82; 1.11] vs. 0.91 [0.78; 1.05] in patients with CDVE and 1.30 [0.88; 1.81] vs 1.13 [0.80; 1.62] in patients with CVE).

It is important to note that our study compared patients diagnosed with COVID-19 with a contemporary cohort rather than a historical cohort of patients. This would contribute to the discrepancy between our results and those of previous research conducted in the field.[5,30] However, as using a historical cohort might not account for changes in clinical practice and patient behavior since the start of the pandemic,[31,32] we considered the use of a contemporary cohort as a suitable comparator. Furthermore, the comparator cohort in our study included patients with a diagnosis of RTI rather than the general population. Literature findings

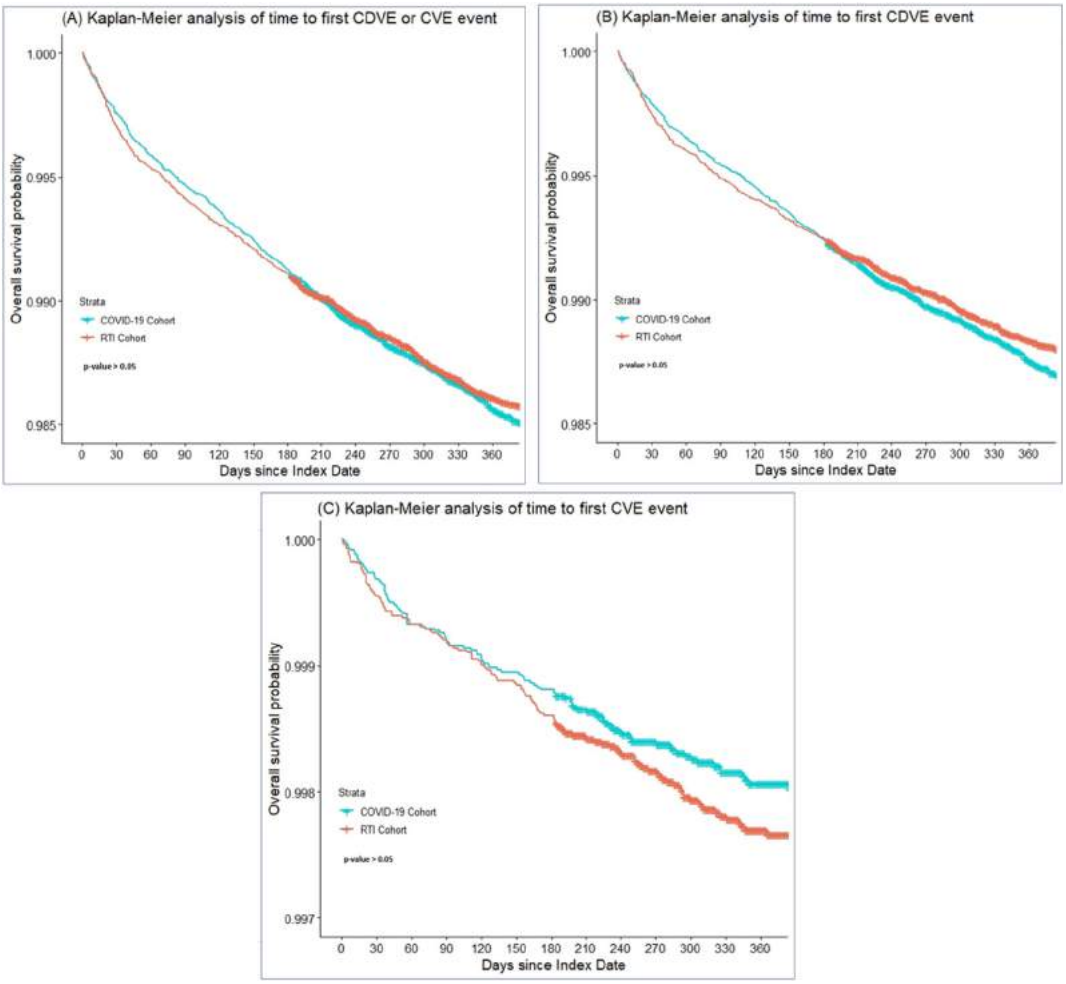

Fig. 2. Kaplan–Meier analysis of time to first event during first year of follow-up: (A) overall, (B) cardiovascular events (CDVE) only, (C) cerebrovascular events (CVE) only.

suggest that patients diagnosed with RTI have a higher incidence of developing a CDVE,[15,16] which would explain the resulting IRR of below one observed in the overall results for CDVE (IRR, 95% CI: 0.92 [0.84; 1.03]), although this value is non-significant.

Finally, the minimum follow-up time in this study was 6 months, with some patients having a follow-up time of over 1 year. We identified a non-significant difference in the time to first VE event during the first year of follow-up. These results should be interpreted with caution, however, given that in the presence of crossing survival curves (non-proportional hazards), the performance of the log-rank test might be affected by the type of crossing observed.

Public health implications

Previous research has confirmed the transient increase in the risk of cardiovascular and cerebrovascular complications following the diagnosis of several respiratory diseases, including influenza, pneumonia, acute bronchitis, and others.[15] To the best of our knowledge, this is one of the first studies to have compared the effects of COVID-19 diagnosis on VE outcomes with the effects of RTI diagnosis. Our preliminary findings help increase the pool of evidence focusing on RTI, considered prevalent in many countries and different healthcare settings.[33] The non-significant association between COVID-19 diagnosis and cardiovascular or cerebrovascular outcomes observed in our study can be interpreted in the context of the drop in hospital admissions due to acute coronary syndromes and stroke during the first wave of the pandemic.[34,35] Further research in varying healthcare settings and regions will help to confirm or disprove our preliminary findings. Notwithstanding the above, there should be a focus on the general prevention of respiratory diseases, as the complications resulting from respiratory failure have represented a great public health burden since the start of the pandemic.

Strengths and limitations

The main strengths of the present study are the large sample size used and the fact that the study reflects routine clinical practice in Germany, accounting for the shift in clinical practice and patient behavior with the use of a contemporary cohort based on data from the Disease Analyzer. In addition, the relatively large sample allowed subgroup analyses by age and sex to be performed.

In addition to these strengths, however, this study is also subject to a number of limitations, which need to be discussed. Because the real-world database used in this study does not cover hospital data including information on mechanical ventilation and does not capture mortality associated with hospitalization, no patients were censored before the end of the study period (December 31, 2021). As a result, the IRR calculated for VE may be biased. However, the magnitude of this bias may have been reduced by the fact that the study included a relatively young population (mean 45 years), as literature findings indicate that the case fatality rate of COVID-19 among patients younger than 50 years is less than 1%.[36] Similarly, the study did not account for database enrollment time or dropouts. Therefore, patients were assumed to have contributed person-time until the end of the study, which might have introduced additional bias by increasing the person-time denominator and thus leading to the underestimation of incidence rates. Because it is not necessary for COVID-19 cases to be confirmed in a primary care practice in Germany, the number of confirmed cases might have been underreported, which may also introduce bias to the results. The latter could have caused the number of patients in the RTI cohort also diagnosed with COVID-19 to be underestimated, thus decreasing the incidence of RTI patients, and resulting in IRRs of below one. Furthermore, given the general setup of the COVID-19 reporting systems in European countries, those patients who approached a primary care practice in Germany to receive care (either for COVID-19 or RTI) might have introduced additional selection bias. In addition, vaccination status (vaccination was broadly implemented in Germany starting in 2021, approximately 1 year after the pandemic started in March 2020)[37] was not considered for the propensity score matching in the present study because vaccination information is only captured by a subgroup of German practices included in the study.[38] Therefore, given that this study considers a continued index period extending from 2020 to 2021, patients included in the COVID-19 cohort could have had different levels of immunity, which could have influenced the outcomes observed. Similarly, with the identification of new COVID-19 variants[39] throughout the index period, patients in the COVID-19 cohort could have been exposed to variable infectiousness levels, which could have also affected the viral injury they suffered, influencing the primary outcomes observed.

Conclusions

Overall, our study suggests that COVID-19 diagnosis was not associated with an increased risk of developing a VE compared with RTI diagnosis. However, further research in a variety of healthcare settings and regions is needed to confirm these preliminary findings from our cohort, which is a good reflection of routine clinical practice in Germany.

Author statements

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Ethical approval

The database used includes only anonymized data in compliance with the regulations set forth in the applicable data protection laws. German law allows the use of anonymous electronic medical records for research purposes under certain conditions. In accordance with this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data. Because patients were only queried as aggregates and no protected health information was available for queries, no institutional review board approval was required for the use of this database for the completion of this study.

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Competing interests

The authors declare that they have no conflicting interests.

Author contributions

S.Z. and K.K. developed the study concept and design. S.Z. conducted the analysis and drafted the article. A.C. ensured the quality control for the programs. All authors contributed to the interpretation of data and critically reviewed the article for intellectual content. All authors were involved in the final approval of the article for submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.10.005.

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Original Research

Associations between 24-h movement behaviors and self-rated health: a representative sample of school-aged children and adolescents in Okinawa, Japan

A. Kyan [a, b, *], M. Takakura [b], M. Miyagi [c]

[a] Graduate School of Human Development and Environment, Kobe University, 3-11 Tsurukabuto, Nada-ku, Kobe City, Hyogo 657-8501, Japan
[b] Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan
[c] Faculty of Education, University of the Ryukyus, 1 Senbaru, Nishihara, Okinawa 903-0213, Japan

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ABSTRACT

Objectives: This study aimed to determine the associations between adherence to 24-h movement behavior guidelines and self-rated health (SRH) among Japanese adolescents according to their age group.
Study design: This was a cross-sectional study.
Methods: Probability proportional sampling data, which were collected from six regions of Okinawa Prefecture, Japan, considering the number of schools, included 2408 fifth-grade students (aged 10–11 years) in 31 elementary schools and 4360 eighth-grade students (aged 13–14 years) in 30 junior high schools. SRH, moderate-to-vigorous physical activity (MVPA), screen time (ST), sleep duration, and confounding factors (sex, weight status, family affluence, parental support, school satisfaction, and school demands) were self-reported.
Results: The logistic regression models showed that adherence to ST and sleep recommendations in elementary school students was associated with a high prevalence of good health only, whereas adherence to only MVPA, only sleep, ST and sleep, MVPA and sleep, and all three recommendations were associated with a high prevalence of good health among junior high school students. All combinations that included achievement of the recommended sleep duration were associated with SRH.
Conclusions: Achieving 24-h movement behavior guidelines, particularly sleep recommendations, is associated with better perceived health in school-aged children, especially in adolescents.

Introduction

Twenty-four-hour daily activities consist of physical activity (PA), sedentary behavior, and sleep, which are complementary such that if one increases, another will decrease.[1] The associations between each of the three behaviors and various adolescent health indicators have been recognized separately. Recently, they have been redefined as “Movement Behavior (MB)” when the three behaviors are combined,[2] and evidence of their health effects has been accumulating over the decade.[3] Canada and Australia have launched guidelines for children and adolescents that specify the recommended duration of each behavior: 24-hour MB guidelines (24-h MBGs).[2,4] These guidelines recommend having at least 180 min of PA daily, with 60 min of moderate-to-vigorous intensity PA (MVPA), no more than 2 h of screen time (ST) per day, and at least 8–10 h of sleep (9–11 h for those aged 5–11 years).[2,4] Asia-Pacific region is also discussing to develop the similar guidelines.[5]

According to a recent systematic review,[3] 20 studies from 14 countries (all Western countries except Korea, China, and India) have been published as of January 2020, and favorable associations between adherence to 24-h MBGs and adolescents' physical health (e.g. cardiometabolic health, physical fitness, obesity) and mental health (e.g. global cognition, health-related quality of life) have been reported. However, as exemplified by the fact that most studies in this review are from Western countries, evidence from Asian countries is lacking. In particular, only two studies have examined the association between 24-h MBGs and physical health

* Corresponding author. Graduate School of Human Development and Environment, Kobe University, 3-11 Tsurukabuto, Nada-ku, Kobe city, Hyogo 657-8501, Japan. Tel and Fax: +81 78 802-7721.
E-mail address: a-kyan@pony.kobe-u.ac.jp (A. Kyan).

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in Japan.[6,7] Although they have almost replicated Western countries' evidence, the combinations including ST recommendations were associated with a low risk of overweight/obesity,[7] and meeting the MVPA recommendation was associated with greater aerobic fitness and muscle endurance,[6] no study has reported the association between meeting 24-h MBGs and other health outcomes among the Japanese adolescent population. Accumulation of evidence on various health indicators as outcomes is necessary to determine whether it is appropriate to promote this guideline for Japanese adolescents.

Self-rated health (SRH) is an important epidemiological indicator of health status. It is well known that SRH reflects an individual's holistic or summarized self-concept based on social, psychological, and health aspects.[8] Moreover, SRH in young individuals have been suggested to be an independent predictor of mortality, despite the inclusion of numerous specific health status indicators and other relevant covariates known to predict mortality.[9] Therefore, identifying correlates associated with SRH in adolescents is important from a public health perspective. Even from a global research trend, some studies have reported that adequate MVPA and sleep and low ST are separately associated with better SRH,[8,10] yet only one study has examined the relationship between adherence to 24-h MBGs and SRH.[11] A Canadian adolescent study reported that those who achieved any of the recommendations were more likely to have good SRH than those who achieved none, dose-response gradient between an increasing number of MB recommendations met and better health indicators.[11] However, this study did not consider psychosocial factors, such as family, school climate,[12,13] and school demand, which can confound health status during this age period. It is debatable whether the same results were obtained after adjusting for crucial confounding factors. Moreover, because Japanese adolescent populations have different social, cultural, and health systems, personality traits, and physiques,[14–16] it is necessary to confirm the replication of evidence from Western countries.

Therefore, the present study aimed to examine the association between adherence to 24-h MBGs and SRH among Japanese adolescents. Because age-related increases in poor SRH have been observed during adolescence,[17] we examined whether the association differs according to age group and which combinations of 24-h MBGs were associated with poor SRH.

Methods

Study participants and procedures

This study included 2408 students (52.2% girls) who were enrolled in the fifth grade (aged 10–11 years) in 31 elementary schools and 4360 students (49.9% girls) who were enrolled in the eighth grade (aged 13–14 years) in 30 junior high schools in Okinawa Prefecture. Okinawa Prefecture is located in the southwesternmost part of Japan and has a population of 1.4 million people. The number of fifth-grade elementary school and eighth-grade junior high school students during the survey period were 16,339 and 16,922, respectively.[18] Okinawa Prefecture had 268 public elementary schools and 148 junior high schools during the survey period and was divided into six regions (four situated on Okinawa Island and two on remote islands).[18] The participants' data were collected through cluster sampling with schools as one unit. Schools included in this study were selected from each school-aged group with a probability that was proportional to the number of schools within the school-aged group and regions in the prefecture by the education board. A staff of the Okinawan Prefectural Board of Education selected the participating schools.

Classroom teachers distributed self-administered questionnaires following written instructions provided by the researchers. The questionnaire consisted of questions about sociodemographic attributes, psychosocial school environment, lifestyle, and health status. Anthropometric status data were obtained from school records at the end of the first semester in mid-July. Before conducting the survey, passive informed consent was obtained from parents or guardians. The students were requested to take home an informed consent form, which provided information regarding the ethical considerations of the study. Participation of the students was voluntary, and the confidentiality of the participants was ensured. The students were free to decline to participate in the study. The parents/guardians were given the phone number and email address of the principal investigator (M.M.) and had the opportunity to withdraw their children from the study by declaration. All assenting students who provided their parents' consent were requested to complete and return the questionnaire sealed in an unmarked envelope to ensure the confidentiality of their responses.

Self-rated health

SRH was assessed by answering five possible answers ("Strongly disagree," "disagree," "neither agree nor disagree," "agree," "Strongly agree") to "I'm healthy at present." Although measurement items for SRH vary and are not standardized,[19] questions almost identical to those used in this study are included in the standard Health Behavior in School-Children (HBSC) questionnaire, which is a reliable and validated measuring tool.[20] Similar questions are used in Japanese national surveys.[21] Participants' answer was recoded into dichotomous variable with categories that "strongly disagree," "disagree," and "neither agree nor disagree" were as "perceived poor health," whereas "agree" and "strongly agree" were as "perceived good health."

Physical activity

PA was measured using Patient-Centered Assessment and Counselling for Exercise plus Nutrition. This was developed to identify the extent to which young people achieved the current guidelines, which is a minimum of 60 min of MVPA per day of the week. The assessment tool has been confirmed to be valid and reliable for measuring PA in diverse populations, including Japanese adolescent.[22–28] In the questionnaire, PA refers to any activity that increased the heart rate and makes an individual feel out of breath for some time. PA can include sports, school activities, playing with friends, or walking to school. Examples of PA include running, brisk walking, rollerblading, biking, dancing, skateboarding, swimming, soccer, basketball, football, and surfing. To verify the consistency of the most recent PA, participants were dichotomized into either active or inactive based on whether they achieved seven days per week of 60 min MVPA based on the calculated average score of the responses for the last week and the typical week. Specifically, if the average number of days was less than daily, the participant was categorized as inactive.[2]

Screen time

ST was assessed by questioning television (TV) viewing and computer use separately. These questions were formulated as follows: "How many hours a day do you usually spend watching TV at home on weekdays?"; "How many hours a day do you usually use your personal computer (including smartphone or tablet), excluding the time when these devices were used for learning, to play computer games (such as TV game, computer game, and mobile game) at home on weekdays?" Possible answers to each

question were "never," "less than 1 h/day," "1–2 h/day," "2–3 h/day," "3–4 h/day," "4–5 h/day," and "more than 5 h/day." Although there are no standardized ST questionnaire items, many previous studies have adopted the items of time spent watching TV and using smartphones, tablets, and PCs as an indicator, which is comparable to our study.[29] Similar questions have also been used in national surveys in Japan.[30,31] The participants' answers were recoded in minutes of TV viewing and computer use per day using the midpoint method. We summed up both means and categorized the participants based on the cutoff of 2 h of recreational ST.[2]

Sleep duration

Sleep duration was assessed by questioning bedtime and awakening hours on weekdays. Participants were asked to report the times they typically turned out to go to sleep and when they woke up in the morning on weekdays. The question regarding bedtime hours was formulated as follows: "What times do you usually go to bed on weekdays?" Possible answers were "before 8 p.m." "9–10 p.m." "10–11 p.m." and "after 11 p.m." Regarding wake up time, the question was as follows: "What times do you usually go to bed on weekday?" Possible answers were "before 6 a.m." "6–6.5 a.m." "6.5–7 a.m." "7–7.5 a.m." and "after 7.5 a.m." Similar questions have also been used in national surveys in Japan.[32] The answer categories were recoded in minutes using the midpoint method. Sleep duration was calculated by subtracting wake up time from bedtime and then the participants were grouped based on whether or not they had a sleep duration that was within the recommended range (9.0–11.0 h/night for 6- to 13-year-olds; and 8.0–10.0 h/night for 14- to 17-year-olds).[2] Participants whose sleep duration was less than or greater than the recommended range were not considered to have met the recommended sleep duration.

Confounding factors

Sex, weight status, socio-economic status (SES; family affluence), parental support, school satisfaction, and school demand were considered as potential confounding factor.[33,34] We referred to the question items of family affluence, parental support, school engagement, and school demand used in the HBSC survey.[20]

Weight status was calculated using the height and weight data, which were obtained from school records taken by school nurse–teachers as part of the standard procedure carried out every April in Japan. Weight status was classified based on Japanese cutoffs for weight status that were established based on national reference data for Japanese children as normal weight, overweight/obesity (≥20%), or thin (≤−20%).[35] The calculation details are described in the appendix.

SES was assessed using the Family Affluence Scale Second Version (FAS-II). FAS-II is a measurement of family wealth used in the HBSC survey in 2009/2010.[20] The items, response categories, codes, and analysis strategy of FAS-II used in the present study are as follows: "Does your family own a car, van or truck?" Response categories were "No," "Yes, one" and "Yes, two or more." "Do you have your own bedroom for yourself?" Response categories were "No" and "Yes." "During the past 12 months, how many times did you travel away on holiday with your family?" The response categories were: "Not at all," "Once," "Twice," and "More than twice." "How many computers does your family own?" Response categories were "None," "One," "Two," and "More than two." According to a previous study,[36] a composite FAS score was calculated for each respondent based on their answers to these four items. Three groups were categorized in terms of the composite FAS score, in which FAS low (score = 0–3) indicated low affluence, FAS medium (score = 4, 5) indicated moderate affluence, and FAS high (score = 6, 7) indicated high affluence.

Parental support was measured using one question: "If I have problems at school, my parents are ready to help." The possible answers were "strongly disagree," "disagree," "neither agree nor disagree," "agree," and "strongly agree." Participants' answer was recoded into dichotomous variable with categories, such that "strongly disagree," "disagree," and "neither agree nor disagree" were as "unsupportive parents," whereas "agree" and "strongly agree" were as "supportive parents."

School satisfaction was measured by one question item: "How do you feel about school at present?" Possible answers to school engagement were, "I don't like it at all," "I don't like it very much," "I like it a bit," and "I like it a lot." Participants' answers were recoded into dichotomous variables with categories that "I don't like it at all" and "I don't like it very much" were as "unsatisfied with school," whereas "I like it a bit" and "I like it a lot" were "satisfied with school."

School demand was measured by one question: 'How pressured do you feel by the schoolwork you have to do?' Possible answers were "a lot," "some," "at little," and "not at all." Participants' answer was recoded into dichotomous variable with categories that "not at all" and "at little" were as "non-demanded," whereas "some" and "a lot" were as "demanded."

These school-related psychosocial measurements have confirmed their reliability and validity in capturing the social context of health in adolescents and have been included as part of an international standard questionnaire, that is, the HBSC survey.[20]

Statistical analyses

Students were classified into one of the following eight categories of guideline adherence: none, only sleep, only ST, only MVPA, sleep and ST, sleep and MVPA, ST and MVPA, or all three guidelines. Descriptive statistics were calculated for all the variables. Logistic regression models were used to examine the association between compliance with 24-h MBGs and SRH. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Sex, weight status, SES, parental support, school satisfaction, and school demand were included as covariates to adjust for potential confounding factors. For any specific combination of 24-h MBGs, those who did not meet the recommendation were placed in the reference group.[37]

Intraclass correlations, which indicate the proportion of the total variance in SRH attributable to schools, were 1.0% and 0.7% for elementary and junior high schools, respectively. Thus, we proceeded with the analysis without considering school variance.

Multivariable multiple imputation was used to complement the missing values, as the missing data were confirmed to have originated completely at random by the Little's missing completely at random test ($P < 0.001$). We generated five imputed data sets and combined the estimates using Rubin's rules.[38] Rubin's multiple imputation method is a statistical estimation of missing value data that creates multiple data sets with missing value imputations and integrates the results.

The variables in the imputation model were SRH, MVPA, ST, sleep, sex, height, weight, family affluence scale score, parental support, school satisfaction, and school demand.

Results

Table 1 lists the characteristics of the sample obtained using the imputed data set. The sample of junior high school students was larger than that of elementary school students because of the larger enrollment per grade. The prevalence of good health among

elementary and junior high school students was 91.3% and 88.4%, respectively. Elementary school students had a higher percentage of non-adherence to all recommendations (39.2%) than junior high school students (10.4%). In addition, adherence to the recommendation of only MVPA, only ST, and MVPA and ST was higher in elementary school students, and adherence to the recommendations of only sleep, MVPA, and sleep was higher in junior high school students. There were no differences in adherence to ST and sleep recommendations in each age group. The preimputed number of samples and the distribution of SRH depending on each independent variable are listed in e-Table 1 and e-Table 2, respectively (appendix).

Table 2 shows the results of the logistic regression model that examined the associations between the compliance of 24-h MBGs and SRH among elementary school students and junior high school students, respectively. The reference was the relationship between none of the adhered 24-h MBGs and the prevalence of good health. Among elementary school students, the adhered ST and sleep recommendation was associated with a high prevalence of good health (OR 2.24, 95% CI, 1.20–4.16). Among junior high school students, adherence to only MVPA (OR 3.41, 95% CI, 1.52–7.66), only sleep (OR 2.87, 95% CI, 2.22–3.72), ST and sleep (OR 4.12, 95% CI, 2.80–6.05), MVPA and sleep (OR 5.44, 95% CI, 3.72–7.93), and all three recommendations (OR 5.29, 95% CI, 2.83–9.88) were associated with a high prevalence of good health. These associations were continuously observed when taking into account confounding factors were considered.

Table 1
Participants' characteristics using the five imputed data sets.

Variables	Elementary school student		Junior high school students	
	Total		Total	
	n	%	n	%
Total	2408	100.0	4360	100.0
Sex				
Male	1152	47.8	2186	50.1
Female	1256	52.2	2174	49.9
Self-rated health				
Poor health	208	8.7	504	11.6
Good health	2200	91.3	3856	88.4
SES (FAS-II)				
Low	366	15.2	703	16.1
Middle	1152	47.8	2055	47.1
High	890	37.0	1602	36.7
Weight status				
Thin	66	2.7	84	1.9
Normal weigh	2076	86.2	3926	90.1
Overweight/obesity	267	11.1	350	8.0
School demands				
Non-demanded	1001	41.6	705	16.2
Demanded	1407	58.4	3655	83.8
Parental support				
Unsupportive parents	611	25.4	1654	37.9
Supportive parents	1797	74.6	2706	62.1
School satisfaction				
Unsatisfied with school	320	13.3	772	17.7
Satisfied with school	2088	86.7	3588	82.3
Compliance prevalence of 24-hour movement behavior				
None	944	39.2	454	10.4
MVPA	134	5.5	78	1.8
Screen time	242	10.0	77	1.8
Sleep	629	26.1	2227	51.1
MVPA and screen time	48	2.0	20	0.5
Screen time and sleep	276	11.5	555	12.7
MVPA and sleep	79	3.3	745	17.1
ALL three	57	2.4	203	4.7

FAS-II, Family Affluence Scale Second Version; MVPA, moderate-to-vigorous physical activity, SES, socio-economic status.

Discussion

This large-scale cross-sectional study, using a representative sample of adolescents in Okinawa, showed that achieving ST and sleep recommendations for elementary school students and all recommendations except ST, MVPA, and ST for junior high school students were associated with high SRH. It is noteworthy that the achievement of 24-h MBGs was often associated with SRH in junior high school students and that all combinations that included the achievement of the recommended sleep duration were associated with SRH. Based on these results, it can be interpreted that the achievement of 24-h MBGs, especially sleep duration, in junior high school students may be more important to their perceived health than that in elementary school students.

A Canadian adolescent study suggested that all of the recommendations are significant, but age-specific comparisons are impossible because this study analyzed adolescents aged 11 years to >20 years as pooled data.[11] In one study of US adolescents aged 6–11 years and those aged 12–17 years using depression as an outcome, older age was associated with the achievement of all recommendations, whereas younger adolescents showed only three recommendations (ST, ST and sleep, and PA and sleep).[39] Another study using data from 14 years in the United Kingdom also showed a significant association between meeting all three recommendations and depression.[40] According to 14 countries' global comparative study on the association between 24-h MBGs and health-related quality of life in children aged 9–11 years,[41] several counties did not detect the effect of achieving each recommendation. For example, none of the adhered recommendations was associated with health-related quality of life in China and Colombia, only sleep recommendations were associated with health-related quality of life in Brazil, and only ST and sleep were associated with health-related quality of life in Finland and India. Considering these previous findings and our results, the impact of the achieving 24-h MBGs on perceived health status, well-being, and quality of life might be more salient in older adolescents. Further research is needed, as few studies have discussed age-related differences.

The results of junior high school students' increasing importance of achieving 24-h MBGs to SRH are slightly different from the Western evidence that all 24-h MBGs achievements are associated with SRH.[11] Adequate sleep time could be crucial for SRH rather than other recommendations in Japanese junior high school students because all combinations that included achieving the recommended sleep duration were associated with SRH in our results. In other words, it should be recommended that MB balances the promotion of MVPA and ST limitations during the day while focusing on getting adequate sleep at night. It has been recognized that sleep is an important factor for SRH.[42] A study of Japanese adolescents also showed that getting approximately 8 h of adequate sleep is associated with lower depression/anxiety.[43] Our findings extend the understanding of the importance of sleep by examining different combinations of meeting the 24-h MB recommendations.

Our result regarding the achievement of the MVPA and ST recommendation was not associated with SRH and was contrary to the findings of previous studies.[44] Although it supports that adequate sleep is paradoxically important, achieving ST only shows an insignificant effect. This may be due to different health effects depending on the type of ST. A recent Japanese study,[45] which examined the association between various types of ST (TV, social media, online games, and online videos) and depression, showed different results according to ST type: a negative impact was observed in social media use or playing online games, but a positive impact was shown in watching TV or online video. Currently, the differences in the health effects of different types of STs are already being discussed.[46] However, further evidence is required.

Table 2
Logistic regression examining the associations of movement behavior combinations with self-reported health.

Variables	Elementary school students				Junior high school students			
	Not adjusted model		Adjusted model		Not adjusted model		Adjusted model	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
None	Reference		Reference		reference		Reference	
MVPA	1.59	0.75–3.36	1.86	0.85–4.03	3.41	1.52–7.66	2.79	1.22–6.36
Screen time	1.33	0.77–2.28	1.19	0.68–2.08	1.48	0.79–2.76	1.52	0.80–2.91
Sleep	1.10	0.77–1.57	1.08	0.74–1.56	2.87	2.22–3.72	2.32	1.77–3.04
MVPA and screen time	2.38	0.57–9.99	2.51	0.58–10.87	2.68	0.60–11.88	1.88	0.42–8.48
Screen time and sleep	2.24	1.20–4.16	2.02	1.07–3.82	4.12	2.80–6.05	3.34	2.25–4.98
MVPA and sleep	6.89	0.92–51.43	6.92	0.91–52.96	5.44	3.72–7.93	4.14	2.80–6.12
All three	0.62	0.28–1.36	0.55	0.24–1.25	5.29	2.83–9.88	3.88	2.05–7.36
Sex			1.38	1.00–1.90			0.96	0.79–1.18
Weight status			0.64	0.42–0.97			0.65	0.48–0.88
SES			1.34	1.07–1.68			1.03	0.89–1.19
School demand			1.40	1.01–1.96			1.46	1.07–200
Family support			2.41	1.75–3.33			1.88	1.53–2.31
School satisfaction			2.71	1.89–3.88			2.63	2.11–3.29

OR, odds ratio; CI, confidence interval; MVPA, moderate-to-vigorous physical activity; SES socio-economic status.

Limitations

This study had several limitations. As the study participants were from only one prefecture, the generalizability of the present findings to adolescents in Japan as a whole may be limited. However, ST and sleep duration among elementary and junior high school students in Okinawa Prefecture were almost the same as the national averages, according to the 2015 national survey data.[31] The proportion of participants who reported good SRH in this study was also similar to the National Sports-Life Survey of Teens 2015, by the Sasakawa Sports Foundation[47] based on a nationwide two-stage stratified random sampling. In contrast, while comparable data for MVPA are only available for 2019,[48] the proportion of recommendation achievement is higher in our study. Further research is needed to confirm that our results can be replicated both nationally and internationally.

In addition, causality could not be drawn from the present study because of the use of a cross-sectional design. There may be those who cannot engage in these healthy behaviors because of poor health. Therefore, further longitudinal studies are required. Recent studies have pointed out the need for compositional analysis for isolating the time use characteristics of each behavior based on MB data measured quantitatively by accelerometers.[49] Future studies also need to examine the association between MB composition and SRH.

Conclusion

Our study found the importance of PA, ST, and especially sleep for SRH. These MBGs were more strongly associated with SRH than with sociodemographic and psychosocial environmental factors. This means that the daily MB may be one of the crucial signals of a child's subjective health status. To maintain and promote children's health, health behaviors should be monitored regularly, and key stakeholders, including public health authorities, health service providers, schools, parents, and adolescents themselves, should take necessary measures (developing laws, cultivating supportive communities, schools, and home environments, and providing education) without delay.

Author statements

Ethical approval

The Institutional Review Board of the University of the Ryukyus approved the study protocol (authorization number: 253).

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Competing interests

The authors declare no other conflict of interests.

Authors' contributions

A.K. performed the statistical analyses and drafted the manuscript. M.T. designed, reviewed, and edited the article and contributed to the discussion. All authors have read and approved the final article. M.M. designed and executed data collection and contributed to the discussion.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.10.012.

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Short Communication

Comparing the survival of adult inpatients with COVID-19 during the wild-type, Delta, and Omicron emergence

E. Murillo-Zamora [a, b], J. Guzmán-Esquivel [b, c], J.A. Bricio-Barrios [b], O. Mendoza-Cano [d, *]

[a] Departamento de Epidemiología, Unidad de Medicina Familiar No. 19, Instituto Mexicano Del Seguro Social, Av. Javier Mina 301, Col. Centro, C.P. 28000, Colima, Mexico
[b] Facultad de Medicina, Universidad de Colima, Av. Universidad 333, Col. Las Víboras, C.P. 28040, Colima, Colima, Mexico
[c] Unidad de Investigación en Epidemiología Clínica, Hospital General de Zona No. 1, Villa de Álvarez, Colima, Mexico
[d] Facultad de Ingeniería Civil, Universidad de Colima, Km. 9 Carretera Colima-Coquimatlán, Coquimatlán, C.P. 28400, Colima, Mexico

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ABSTRACT

Objective: This study aimed to compare the survival experience of adult inpatients with laboratory-confirmed COVID-19 during the first three waves (wild type, Delta, and Omicron) of the pandemic in Mexico.
Study design: A retrospective and nationwide study was conducted.
Methods: Data from 229,311 participants were analyzed using the Kaplan–Meier method, and estimates per each pandemic wave were obtained. A multivariate Cox proportional hazard regression model was fitted, and hazard ratios (HRs) and 95% confidence intervals (CIs) were computed.
Results: The overall mortality rate was 49.1 per 1000 person-days. Heterogeneous survival rates were observed during the analyzed emergences (log-rank test, $P < 0.001$), and the lowest survival functions were computed during the Omicron variant dominance. In multiple analyses and after adjusting by host characteristics and COVID-19 vaccination status, cases occurring during the Delta (vs wild type: HR = 1.03, 95% CI 1.01–1.05) and Omicron emergence were at increased risk for a fatal in-hospital outcome (HR = 1.17, 95% CI 1.13–1.22).
Conclusions: Our results suggest variant-related differences in the survival rates of hospitalized patients with laboratory-positive COVID-19. When compared with the wild-type virus, lower rates were observed during the Delta and Omicron emergence.

Background

The burden of the COVID-19 by the severe acute coronavirus (SARS-CoV-2) in Latin America has been high. In the region and by the end of April 2022, the cumulative mortality rate (per 100 thousand people) observed in Mexico (254) is only lower than the rates in Peru (654), Brazil (314), Chile (302), Argentina (286), Colombia (278), and Paraguay (267).[1]

Worldwide, several SARS-CoV-2 variants have been identified by genomic sequencing. In Mexico, and also by the end of April 2022, three COVID-19 waves had been registered: wild type (March 2020 to February 2021), Delta (B.1.617.2, May 2021 to November 2021), and Omicron (B.1.1.529, December 2021 to February 2022).[2]

Variant-related differences had been documented in terms of transmission risk, impacts on vaccine effectiveness, and illness severity.[3] To the best of our knowledge, no published data are evaluating the survival of hospitalized patients with COVID-19 in the function of the dominant SARS-CoV-2 variant at the time of symptoms onset. This study aimed to compare the survival experience of adult inpatients with laboratory-confirmed COVID-19 during the first three waves (wild type, Delta, and Omicron) of the pandemic in Mexico.

Methods

A nationwide retrospective cohort study was conducted in Mexico. Eligible subjects were adult (aged ≥20 years) inpatients with laboratory-confirmed (reverse transcription polymerase chain reaction) COVID-19 and symptoms onset from March 2020 to February 2022. They were identified from the nominal records of a normative system for the epidemiological surveillance of respiratory viral pathogens (SINOLAVE, the Spanish acronym) that belongs

* Corresponding author. Tel.: +52 (312) 3161167.
E-mail address: oliver@ucol.mx (O. Mendoza-Cano).

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to the Mexican Institute of Social Security (IMSS, the Spanish acronym). The IMSS is an employer-based health scheme that provides medical and social services to 64% (≈83 million people) of the total population of the country. Patients with missing clinical or epidemiological data of interest were excluded.

We used the dominant variant at the time of illness onset as an approximation of the etiological variant for each case. This latter was made by using genomic sequencing data from the General Directorate of Epidemiology of Mexico.[3] Enrolled subjects were then classified as follows: wild type, March 2020 to February 2021; Delta (B.1.617.2), May 2021 to November 2021; Omicron (B.1.1.529), December 2021 to February 2022.

Clinical and epidemiological data were retrieved from the audited surveillance system, which primary sources are the medical files and death certificates, when applicable. Vaccinated subjects were those who had received, at 15 or more days before illness onset, at least one shot from any COVID-19 vaccine.[4] Pneumonia patients were those with clinical (fever, cough, and dyspnea) and radiographic findings (ground-glass opacities in computed tomography scanning or X-ray) suggestive of this abnormality.

The main outcome was in-hospital death due to any immediate cause. We used the Kaplan–Meier method to compute survival functions and 95% confidence intervals (CIs). The log-rank test was used to evaluate variant-related differences in survival rates. The association of the dominant SARS-CoV-2 variant at symptoms onset on the risk of death was evaluated through hazard ratios (HRs) and 95% CI, which were calculated by using proportional hazards models. The multiple model was adjusted by patients' age and gender, the COVID-19 vaccination status (unvaccinated/vaccinated), body mass index (≥30 kg/m^2, no/yes), pneumonia diagnosis at admission (no/yes), and days elapsed from symptoms onset to healthcare seeking.

Results

Data from 229,311 adult inpatients were analyzed for a total follow-up of 2,279,854 person-days. A total of 111,893 deaths were registered (49.1 deaths per 1000 person-days). The viral-stratified in-hospital mortality rates were as follows: wild type, 49.8% (n = 91,993/184,860); Delta, 45.3% (n = 17,085/37,740); Omicron, 42.0% (n = 2815/6711). The characteristics of enrolled patients for selected variables are presented in Supplementary data 1.

At any cutoff, the survival functions during the Omicron variant emergence were lower than those from the wild-type and Delta variant, particularly on the fifth day of in-hospital stay and later (Fig. 1). The curves from the wild-type and Delta variants were quite similar.

The computed survival functions, according to the days elapsed since hospital admission, were 1 day (wild type, 95.4% [95% CI 95.3–95.5%]; Delta, 96.5% [95% CI 96.3–96.7%]; Omicron, 95.3% [95% CI = 94.8–95.8%]); 3 days (wild type, 90.9% [95% CI 90.8–91.0%]; Delta, 92.7% [95% CI 92.5–93.0%]; Omicron, 90.1% [95% CI 89.3–90.8%]); 7 days (wild type, 74.2% [95% CI 74.0–74.4%]; Delta, 77.2% [95% CI 76.7–77.6%]; Omicron, 71.1% [95% CI 69.9–72.3%]); 15 days (wild type, 49.4% [95% CI 49.1–49.6%]; Delta, 52.5% [95% CI 51.9–53.1%]; Omicron, 48.4% [95% CI 47.0–49.8]); and 30 days (wild type, 25.5% [95% CI 25.2–25.8%]; Delta, 27.3% [95% CI 26.5–28.0%]; Omicron, 23.8% [95% CI 21.6–26.2%]). The follow-up endpoint was discharged from the hospital.

In the multiple analysis, cases occurring during the Delta and Omicron emergence were at increased risk for a fatal in-hospital outcome (vs wild type: Delta, HR = 1.03 [95% CI 1.01–1.05]; Omicron, HR = 1.17 [95% CI 1.13–1.22]). These estimates were adjusted by the COVID-19 vaccination status, which reduced in about 12% the risk of dying (HR = 0.88 [95% CI 0.86–0.91]). They were also adjusted by other conditions that were associated with reduced survival probabilities, namely, male gender (HR = 1.12 [95% CI 1.10–1.13]), age (per each additional year: HR = 1.02 [95% CI 1.01–1.03]), body mass index of ≥30 kg/m^2 (vs no: 1.13 [95% CI 1.11–1.14]), pneumonia diagnosis at admission (vs no: HR = 1.19 [95% CI 1.17–1.20]), and days elapsed from symptoms onset to healthcare seeking (per each additional day: HR = 1.003 [95% CI 1.002–1.005]).

Discussion

Our study characterized the survival experience of a large set of adult inpatients with COVID-19 during the first 2 years of the pandemic in Mexico. We documented that after adjusting by host characteristics and vaccination status, adults who were hospitalized during the Omicron variant emergence had lower survival rates than those from the previous waves.

A smaller involvement of the lower respiratory tract has been documented in cases of the Omicron variant infection and therefore to a reduced risk of hospital admission.[5,6] This latter results from the specific entry pathway of the Omicron variant, which is endocytic rather than through the transmembrane serine protease 2 (TMPRSS2).[7] The TMPRS22 is highly expressed in alveolar cells.[8] In our study and as presented in Supplementary data 1, cases occurring during the Omicron emergence were less likely to develop pneumonia (28.2%) than those from the previous waves (wild type, 39.0%; Delta, 34.7%). In addition, recently published data found that the viral load of Omicron infections is not higher than that of previous variants; therefore, its increased infectivity is more likely to be related to increased affinity to cell receptors or immune escape.[8]

We observed high in-hospital mortality rates during the dominance of the analyzed SARS-CoV-2 variants (wild type, 49.8%; Delta, 45.3%; Omicron, 42.0%). One factor that might be determining this scenario is that 4 of 10 analyzed hospitalized patients had pneumonia at admission. We also observed a decreasing trend in the frequency of severe pulmonary manifestations of COVID-19 and when from 39.0%, 34.7%, and 28.2% during the dominance of the wild-type, Delta, and Omicron variants, respectively.

The heterogeneous survival rates that were documented in our study could not be explained by host characteristics that had been consistently associated with a poorer in-hospital prognosis (i.e. high body index or increasing age).[9] It is important to emphasize that we evaluated the factors associated with the survival of hospitalized patients and not the determinants of hospitalization. The risk of hospitalization during the dominance of the Omicron variant was lower than the risk of its predecessors.[10] As presented in Supplementary data 1, enrolled patients during the Omicron dominance and when compared with previous waves were older, were less likely to be COVID-19 vaccinated or obese (body mass index of 30 or above), and had a higher prevalence of pneumonia at hospital admission. These factors may be determining, at least partially, the observed scenario. If replicated in other populations, further research is needed to elucidate the factors determining these heterogeneous survival rates.

The potential limitations of our study must be cited. First, low hospitalization rates were registered all over Mexico during the Omicron emergence. Therefore, the case fatality rate would be low when compared with the wild-type or Delta emergence. Second, no genomic sequencing was performed on all the enrolled subjects, and we are unable to ensure the pathogenic strain for each case. However, and as observed in other regions of the world, a high dominance of each variant was observed in Mexico during the study periods. By August 22, 2022, nearly 73 thousand genomic sequences have been processed (about 1% of the cumulative number of laboratory-positive cases in Mexico).[2]

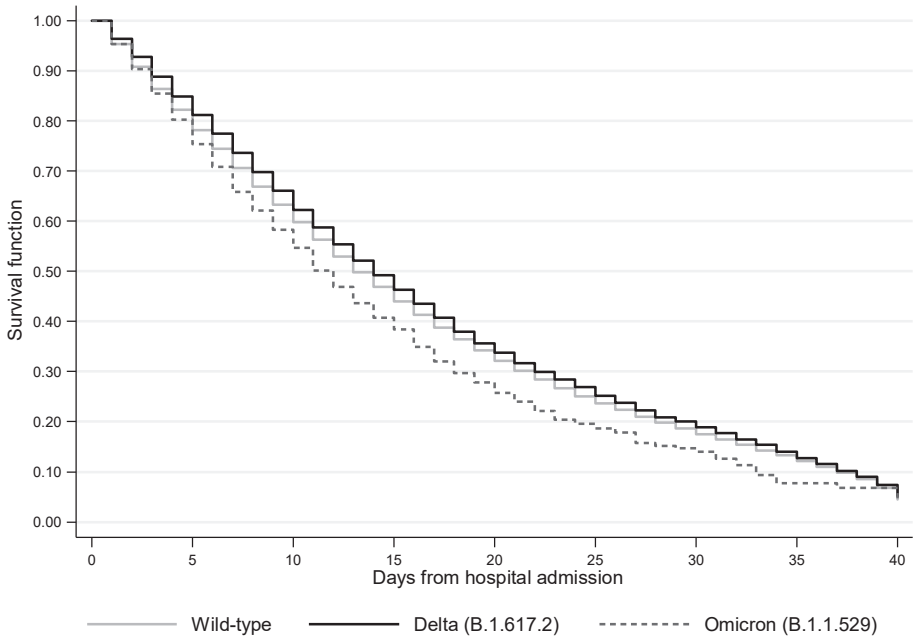

Fig. 1. Survival in adult inpatients with laboratory-confirmed COVID-19 ($n = 229{,}311$) according to the dominant SARS-COV-2 variant at symptoms onset, Mexico 2020–2022. Log-rank test: $P < 0.001$.

Conclusions

We compared the survival experience of 229 thousand adult inpatients with laboratory-positive COVID-19 according to the dominant variant at illness onset. We found variant-related differences in the risk of a fatal in-hospital outcome and the lowest rates were documented during the Omicron emergence. If later replicated, the results from our study would contribute to the knowledge of the development of the pandemic.

Author statements

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Ethical approval

This study was reviewed and approved by the Committee of Ethics in Health Research (601) of the IMSS (approval R-2020-601-022).

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Competing interests

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.10.014.

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Commentary

Ensuring oversight and protection of life, health and well-being of all detained by the Russian Federation and in Russian controlled territories of Ukraine

Marie Claire Van Hout*

Public Health Institute, Liverpool John Moore's University, United Kingdom

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ABSTRACT

Objectives: Military action by Russian forces against Ukraine commenced on 24 February 2022. The Office of the United Nations High Commissioner for Human Rights has observed serious human rights violations in the context of the Ukraine war. A range of people are detained, not limited to those meeting the definition of prisoners of war, or prisoners, but including Russian soldiers who refuse to fight and the enforced disappearance of Ukrainian civilians.
Study design: This is a Commentary article.
Methods: This Commentary concerns the detainee's right to humane conditions of detention and right to life, health and well-being (including access to medical care) when in detention in Russian-controlled territories of Ukraine and when transported into and detained in the Russian Federation itself.
Results: There is evidence of violations of the rules of war and of fundamental human rights. Prohibition of torture and other ill treatment of people deprived of their liberty is shared across international human rights and humanitarian law frameworks.
Conclusions: Russia will leave the European Court of Human Rights on 16 September 2022. The United Nations Human Rights Council must swiftly respond and create new mechanisms to monitor Russian detention standards and uphold fundamental human rights to protect the lives, health and well-being of those detained, regardless of their status as prisoner, prisoner of war or other.

Military action by Russian forces against Ukraine commenced on 24 February 2022, following parliamentary recognition of the independence of the self-proclaimed Donetsk and Luhansk People's Republics. The regional focus understandably has been on the military response to the invasion and the humanitarian response and evacuation of civilians.

On 30 March 2022, Cocco et al. highlighted the lack of attention directed towards the health and well-being of people living in Ukrainian prisons during the invasion by Russia.[1] There are however people detained by Russian military forces in Russian-controlled territories of Ukraine (number of detention settings unknown) and transferred to detention settings in the Russian Federation (hereafter *"Russia"*) itself (872 facilities[2]). These detainees are not limited to those meeting the definition of prisoners of war (POW), or indeed prisoners, but include Russian soldiers who refuse to fight and the enforced disappearance of Ukrainian civilians to unknown locations in Russia.

The United Nations High Commissioner for Human Rights has observed serious human rights violations by Russia relating to the human and health rights of those deprived of their liberty during the Ukraine conflict. The United Nations High Commissioner for Human Rights, Human Rights Watch and the World Organisation Against Torture have issued substantive reports on the torture and inhumane treatment of POW and other detainees (torture, beatings, gang rape, forced standing for long periods, prolonged interrogation, use of electroshocks, solitary confinement, deprivation of water and food, denial of medical treatment) in Russian-controlled territories, including in the 21 filtration sites used to process Ukrainian POW and civilians before forcible transfer to Russia and

* Correspondling author. LLM Professor of International Public Health Policy and Practice Public Health Institute Faculty of Health Liverpool John Moore's University 3rd Floor, Exchange Station Tithebarn Street Liverpool L2 2QP United Kingdom. Tel.: +151 231 4542; fax: +151 231 4552.
E-mail address: m.c.vanhout@ljmu.ac.uk.

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during illegal transfer of individuals including humanitarian workers to Russian penal institutions in the Kursk and Bryansk regions and other unknown locations.[3–7]

Further of note is the longstanding history of imprisonment in harsh environmental conditions of detention and associated threat to health and life of those deprived of their liberty in Russia itself.[8,9] Concerns centre on the denial of access by inspecting commissions and detention conditions characterised by congestion, extreme cold, systematic violence and abuse, inadequate food provisions, poor sanitation and ventilation, inadequate health monitoring, denial of medical responses to torture, the denial of access to medical care as punitive measure, poor disease mitigation measures resulting in disease transmission (HIV, tuberculosis, COVID-19 and other diseases in circulation) and unexplained deaths of detainees.

Blatant disregard for the lives, dignity and health of detainees during the invasion of Ukraine has also occurred in other ways. The European Court of Human Rights (ECtHR) has issued interim measures to Russia to not carry out the death penalty against two Britons and a Moroccan national accused of '*mercenary activities*' by the Donetsk Supreme Court and to ensure adequate conditions of detention with provision of sufficient medical care.[10] There are however reports that prison conditions were expressly deteriorated by the authorities across 20 regions of Russia (including St. Petersburg, Tver, Ryazan, Smolensk and Rostov) to facilitate military recruitment of prisoners (particularly those with combat experience) for operations in the Donbass.[11] Detention of Russian soldiers in eastern Ukraine for '*refusing to take part in the war*' has been documented.[12] Prisons also became military targets. On 29 July 2022, the Olenivka prison in Donetsk Oblast was attacked killing and wounding Ukrainian POW.[13]

Russian expulsion from the Council of Europe (CoE) on 16 March 2022 and the ECtHR (16 September 2022) leaves a concerning gap in access to justice by those detained by criminal justice authorities in Russia and by its armed forces in Russian-controlled territories and in the oversight and protection of the right to health of those living in Russian prisons and POW detention settings. Russia will only implement ECtHR judgements issued before 15 March 2022.[14] The majority of pending cases will be frozen in the system.

The ECtHR has been instrumental in improving the health of prison populations in Europe.[15] There are a host of ECtHR judgements against Russia regarding its treatment of people deprived of their liberty, especially concerning the violation of human and health rights under Article 3 of the European Convention on Human Rights ('*prohibition of torture*'), many of which remain unimplemented by Russia.[16] Judgements are primarily concerned with systemic inhuman and degrading treatment in detention (including in pretrial) in Russia regarding severe cell overcrowding and poor environmental health standards of detention (inadequate water, heating and ventilation, lack of separation between the sanitary and living areas, access to natural light, exposure to disease and vermin), threats to health and life in the form of exposure to violence, torture and inadequate medical care leading to chronic ill health and death (examples include *Kalashnikov v. Russia, Buntov v. Russia, Magnitsky v. Russia*, Nogin v. Russia, Khloyev v. Russia and *Ananyev and others v Russia*).[16] The ECtHR has also dealt with the context of POW detention following the Russia military conflict in Georgia (*Georgia v. Russia*) and underscored the right of Georgian civilians and POW by the Russian and/or South Ossetian forces (whose actions were attributable to the Russian authorities) to be treated humanely and detained in adequate conditions.[16] On 1 July 2022 the ECtHR issued an interim measure seeking immediate action by Russia to protect the rights of detained Ukrainian POW and to provide them with appropriate medical assistance.[17] This has been ignored.

Prohibition of torture and other ill treatment of people deprived of their liberty is shared in international human rights and humanitarian law (Common Article 3 Geneva Conventions), which provide that all detainees be treated in a humane manner. Notwithstanding these obligations during the conflict, Russia has ratified several relevant international human rights treaties (International Covenant on Civil and Political Rights (ICCPR), Convention Against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment (CAT), International Covenant on Economic, Social and Cultural Rights (ICESCR)) upholding the rights of people in detention, including the right to health and life. Whilst it accepts individual complaints against the State under ICCPR and CAT and the inquiry procedures of the CAT, it has not extended a standing invitation to United Nations (UN) Special Procedures. Nor has it ratified OP-CAT (oversight/national preventive mechanisms) or the Second Optional Protocol to the ICCPR (abolition of the death penalty). This year it has failed twice in a row to appear at its review by the UN Human Rights Committee (March and July 2022).[14]

Whilst Russian authorities have allowed the CoE's Committee for the Prevention of Torture to visit the country's prisons and released some reports on conditions, there will be no more missions by this Committee, a glaring gap that requires immediate redress. This has substantial implications for ensuring the health of those detained, including their right to access appropriate medical care and the right to be protected from disease. Little is known about the access of UN agencies and independent monitors into detention sites on Russian-held territories and Russia itself and the ability to support timely and effective investigations into alleged breaches of both international human rights and humanitarian law. On 14 June 2022, Russia's oldest antitorture human rights organisation (CAT Russia) was designated as a foreign agent and subsequently liquidated.[18]

Inadequate detention conditions, exposure to torture and violence, and medical neglect without legal, public or UN agency oversight and with threat of indiscriminate attacks on detention sites constitute a substantial risk to life, health and well-being for all detained during the Ukraine war. Lack of independent facility inspections and inhibited access to justice and access to healthcare (including medical responses to victims of torture) have enormous ramifications in terms of breaching their basic human and health rights. The routine denial of chronic illness and indeed palliative care of those detained poses a grave concern. There are potential public health ramifications, which could affect Russia, Ukraine and indeed Europe in terms of lack of oversight of disease mitigation and surveillance.

We must not ignore them or allow them to be left behind in the face of the Russian-Ukraine conflict and Russia's expulsion from the CoE. Notwithstanding the lack of accountability and potential for arbitrary detention, torture, cruel and inhuman treatment, further rule of law backsliding could result in restoration of the death penalty by Russia. It is imperative that the UN Human Rights Council acts swiftly to respond and create new mechanisms to monitor all Russian detention standards wherever they are located, in times of peace and war, and regardless of detainee status as prisoner, POW or other.

Inter arma enim silent leges.

Author statement

Conflict of interest

I declare no competing interests. There is no funding to declare, the work is self funded.

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Original Research

Factors influencing utilisation of assistive devices by the elderly in China: a community-based cross-sectional study

S. Yu [b], D. Luo [b], Y. Zhu [c], L. Yang [c], H. Li [b], J. Luo [b], K. Gu [d], D. Wu [e], Q. Zhao [b], D. Bai [c], M. Xiao [a, b, *]

[a] Department of Urology, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Road, Yuanjianggang, Yuzhong Dis, Chongqing, 400042, China
[b] Department of Nursing, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Road, Yuanjianggang, Yuzhong Dis, Chongqing, 400042, China
[c] Department of Rehabilitation Medicine, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Road, Yuanjianggang, Yuzhong Dis, Chongqing, 400042, China
[d] Service Center of Rehabilitation Assistive Technology of Sichuan Province, No.26 Longjiang Road, Chengdu, Sichuan, 610021, China
[e] Inner Mongolia Autonomous Region Rehabilitation Assistive Device Center, No.80 Airport Auxiliary Road, Saihan Dis, Inner Mongolia, 0100700471, China

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ABSTRACT

Objectives: The study aimed to gain an insight into the utilisation, self-perceived needs, and attitudes towards and influencing factors of assistive device (AD) usage among community-dwelling older adults in China.
Study design: This is a cross-sectional study.
Methods: A total of 5790 elderly people from eight communities within three provinces in China were recruited by convenience sampling. Utilisation, needs and attitudes towards ADs were assessed by a questionnaire designed by the authors. Barthel activities of daily living scale was used to determine disability, whereas cognitive function was assessed with the Mini-Mental State Examination. The impact of participant characteristics, enabling factors and demand factors on the utilisation of ADs were assessed by univariate and multifactor analyses.
Results: The prevalence of AD ownership among participants was 10.9% (n = 634), whereas the self-perceived need for ADs was 46.1% (n = 2670). Most participants had negative attitudes towards ADs, with only 37.6% (n = 2175) of participants believing that ADs were of significant help. Factors influencing the usage of ADs included participant characteristics (age, occupation, living area, education), enabling factors (economic situation, number of children) and demand factors (activities of daily living score, attitudes, self-perceived needs).
Conclusions: Although ADs for the elderly in China have become more affordable and accessible after a series of reforms, there remains a gap in AD services resulting in low AD utilisation, high self-perceived needs and misconceptions of ADs. Certain factors influencing the use of ADs are more significant than others. The findings from this study will be informative for healthcare providers and decision-makers when designing strategies to achieve universal elderly AD usage.

Introduction

The growth in the number of older adults has a multitude of implications for public health and social policy worldwide.[1] In China, the number of people aged >60 years was 264.02 million in 2020, accounting for 18.70% of the total population.[2] Ageing contributes to a higher prevalence of physical impairments and functional limitations, especially in later life.[3] More importantly, the

* Corresponding author. Department of Urology, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Road, Yuanjianggang, Yuzhong Dis, Chongqing, 400042, China. Tel.: +86 13608399433.
E-mail address: 201606@hospital.cqmu.edu.cn (M. Xiao).

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ageing process profoundly impacts medical care loads,[4] including higher demands of supportive services[5] and long-term care.[6] Elderly care must be prioritised to ensure long-term care practices and successful ageing.

Assistive devices (ADs) are defined as tools that assist individuals to maintain or improve their functioning and independence, which may not be maintained otherwise.[7] Elderly ADs are commonly used to help older people overcome obstacles, such as limitations in mobility, hearing and vision; thus, enabling these individuals to maintain independence for a longer period, including seeking medical treatment, caring for families and participating in social events.[8] Wheelchairs, walkers and hearing aids are examples of basic elderly ADs. It has been shown that more than half of the elderly population can improve their health status with the help of ADs.[9] For example, mobility devices have been associated with improved activities of daily living (ADLs), independence, quality of life, social benefits and self-esteem.[10,11] Individuals with disabilities were targeted consumers of AD services,[12] with coverage and adaptation rates reaching to 80%;[13] however, the AD needs of the elderly have not yet been met.[14] In China, the number of older adults who use and need ADs has increased with the growing elderly population.[15] In addition, the recognition that ADs play a role in supporting successful ageing is also increasing. In recent years, China has pledged to provide affordable and equitable access to quality AD services for the elderly. The government provides proportional or differentiated subsidies for ADs, whereas AD rental subsidies have gradually been included in insurance plans.[16] For example, in Shanghai, welfare services claimed that the elderly aged 60–74 years with a minimum living allowance and low income and the elderly aged ≥75 years receive a subsidy of 50% of the AD rental price.

Assessing the prevalence of ADs among the elderly is a critical first step in determining the current use of ADs.[17] Moreover, determining the proportion of the elderly who need appropriate ADs but cannot access or use them is necessary to understand the unmet demand for elderly ADs. Most previous studies on ADs have focused on specific AD usage or disability groups. For example, Ishigami et al.[18] reported that 14.7% of females and 15.2% of males in Canada between the ages of 45 and 85 years reported currently using at least one AD for hearing, vision or mobility. A living demand survey of individuals with physical and mental health problems indicated that 38.77% used various types of ADs.[19] However, these studies were unable to obtain a complete picture of AD usage in the elderly.

This study aimed to investigate the current situation and influencing factors of AD usage among the elderly population in China. The objectives of this study were to (1) describe the use, self-perceived needs and attitudes towards ADs in the elderly population; and (2) investigate the factors influencing AD usage among community-dwelling elderly adults in China. The results from this study will provide research and development centres with a basis for programme development and help relevant government authorities with future strategies and policies.

Methods

Data collection

Data were collected from a cross-sectional survey of community-dwelling older residents from July 2020 to May 2021. Eight communities were selected from three provinces in China (Sichuan, Chongqing, Inner Mogolia et al.) by convenience sampling, which were areas undergoing rapid ageing of the population and represented different administrative regions in China. Respondents were randomly selected within each community. Eligibility criteria were as follows: (1) aged ≥60 years; (2) able to communicate independently or communicate with the help of the investigators (elderly individuals with cognitive impairment, severe hearing loss, other communication disorders were excluded); and (3) willing to take part in the survey. The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China (2020-622).

Initial contact was made by the researchers with the elderly individuals or their caregivers to explain the purpose of the study and the concept of ADs. Questionnaires were personally distributed by the researchers. Individuals who were willing to participate were asked to read a consent form (or have it read to them) and then sign or mark it with a thumbprint. For participants who had difficulties completing the questionnaire, researchers assisted using an interview-style approach. In total, 5850 questionnaires were distributed, and 5790 valid responses were received (20 were not returned and 40 were not completed correctly).

Instruments

The authors designed and developed the 'Use, Self-perceived need and Attitudes towards Assistive Devices in Older Adults survey' questionnaire, which included the following sections: (1) demographic information: gender, marital status, education level, number of children, causes of physical disability, etc; (2) AD use: "whether you are using any ADs currently" (Yes or No); and (3) AD needs and attitudes: the needs item included the question "I need ADs at present" (Yes or No) and the attitudes item had four possible responses ("ADs are of significant help to the safety and health of the elderly," "ADs are only helpful to the disabled and disabled elderly people," "ADs have limited effects," "ADs have no effects"). To establish content and face validity, five senior therapists who provide AD-related services examined the questionnaire. Most comments about content validity were related to the wording of the questionnaire and items in the participant characteristic section. Inter-rater reliability was not formally tested. As this is a closed-ended questionnaire that collected quantitative data by using low inference descriptors that are readily quantified, it can be concluded that there was good internal reliability of the questionnaire.

Barthel ADL scale, with an α-coefficient of 0.782,[20] was used to evaluate the daily activity or self-care abilities of the participants. The scale consisted of 10 items, including eating, grooming, bathing, toileting and dressing. Total scores could range from 0 to 100, with 100 indicating normal abilities, 61–99 being categorised as mild difficulties, 41–60 as moderate difficulties, 21–40 as severe difficulties and <20 as profound difficulties.

To assess cognitive function, the Mini-Mental State Examination (MMSE), designed by Folstein et al. in 1975,[21] was used. The MMSE is divided into 11 items, with a possible total score of 30 points. A score of 27–30 points represented normal cognitive function, and scores <27 points were considered to have varying degrees of cognitive impairment.

Various factors that may impact the use of ADs by the elderly were considered as independent variables in this study. The model classified the factors influencing the utilisation of ADs into three categories: participant characteristics, enabling factors and demand factors.[22] Participant characteristics included gender, age, marital status and social structure (occupation, residence, education, daily travel mode). Enabling factors represented the ability of individuals to obtain health services, including financial resources (economic status, source of income, revenue and expenditure) and care resources (number of children, main caregivers). Demand factors described the demand for medical and health services due to individual physical health or functional status, which includes

Table 1
Univariate analysis results of usage of ADs.

Characteristics		n	%	Usage %	χ^2	*P*
Gender					0.062	0.803
	Male	2585	45	11		
	Female	3205	55	11		
Education level					17.78	<0.001
	Illiterate	524	9	15		
	Primary school	1943	34	12		
	Middle school	1764	30	9		
	High school or above	1559	27	11		
Age group (years)					68.383	<0.001
	60–69	2607	45	8		
	70–79	1978	34	13		
	≥80	1205	21	15		
Occupation					135.73	<0.001
	Farmer	1601	28	15		
	Worker	2953	51	11		
	Cadre	5421	9	5		
	Business person	85	2	2		
	Others	730	13	10		
Marital status					41.1	<0.001
	Married	4715	82	10		
	Divorced	159	3	8		
	Widowed	836	14	17		
	Unmarried	79	1	6		
Number of children					73.41	<0.001
	0	162	3	6		
	1	2338	40	7		
	≥2	3290	57	14		
Financial income (yuan per month)					112.6	<0.001
	≤1000	1079	19	17		
	1001–3000	2922	50	12		
	3001–6000	1651	29	5		
	≥6000	138	2	3		
Income source					4.52	0.477
	Pension	4429	76	11		
	Children subsidies	909	16	12		
	Relatives support	19	0	5		
	Salary	125	2	15		
	Others	307	5	9		
Income and expenditure condition					116	<0.001
	Income far exceed expenditure	199	3	12		
	Income slightly exceed expenditure	808	14	9		
	Income equals expenditure	3065	53	8		
	Income slightly lower than expenditure	1124	19	19		
	Income far lower than expenditure	593	10	15		
Main residence					44.45	<0.001
	City	4984	86	10		
	Town	497	9	18		
	Village	302	5	17		
	Special area	7	0.1	43		
Daily travel mode					7.95	0.047
	Elevator	820	14	12		
	Stairs	4526	78	10		
	Cement pavement	386	7	14		
	Mud pavement	58	1	16		
Primary caregiver					9.62	0.022
	Solitude	527	9	10		
	Spouse	3038	52	12		
	Family	2186	38	10		
	Domestic workers	40	1	23		
Cause of disability					105.34	<0.001
	None	5360	93	10		
	Disease	380	7	27		
	Congenital	50	1	10		
ADL					814.06	<0.001
	Normal	5216	90	7		
	Mild	398	7	41		
	Moderate	84	1	46		
	Severe	58	1	66		
	Profound	34	1	53		

Table 1 (*continued*)

Characteristics	n	%	Usage %	χ^2	*P*
MMSE				3.3	0.191
Normal	1890	33	10		
Cognitive impairment	3900	67	11		
Self-perceived needs				399.1	<0.001
Attitudes				14.05	0.003

AD, assistive device; ADL, activities of daily living; MMSE, Mini-Mental State Examination.

Table 2
Use, self-perceived needs and attitudes towards ADs.

Use, attitude and self-perceived needs	n	%
Use of ADs		
Use	634	10.9
Non-use	5156	89.1
Self-perceived needs		
"I need ADs at present"	2670	46.1
"I do not need ADs"	3120	53.9
Attitude towards ADs		
"ADs are of significant help to the safety and health of the elderly"	2175	37.6
"ADs are only helpful to the disabled and disabled elderly people"	1972	34.1
"ADs have limited effects"	1102	19.0
"ADs have no effects"	541	9.3

AD, assistive device.

health status and perception of self-care status (social activities, ADL, MMSE, causes of physical disability, attitudes, self-perceived needs).

Statistical analyses

SPSS 24.0 was used to analyse the data. Data are described as mean ± standard deviation or frequency and percentage. The Pearson Chi-squared test was used to compare the categorical variables between groups and binary logistic regression analysed the factors influencing ADs use behaviour. A *P*-value <0.05 was defined as statistically significant difference.

Results

Demographic characteristics

Among participants, 3205 (55.4%) were female and 2585 (44.6%) were male. In terms of age groups, 2607 (44.9%) were aged 60–69 years, 1978 (34.2%) were aged 70–79 years and 1205 (20.8%) were aged ≥80 years. In total, 34% (n = 1943) were primary school graduates and 51% (n = 2953) were workers. Most subjects were married (n = 4715, 82%), lived in the city (n = 4984, 86%), had two or more children (n = 3290, 57%) and had a spouse as the primary caregiver (n = 3038, 52%). For 78% (n = 4526) of participants, stairs were the daily travel mode. Regarding financial status, 50% (n = 2922) of participants had a monthly income of 1001–3000 yuan, 76% (n = 4429) reported pension as the income source and 53% (n = 3065) responded that their income equalled their expenditure. Most participants did not have a disability (n = 5360, 93%). Based on ADL and MMSE scores, respectively, 90% (n = 5216) of participants had normal independence/self-care abilities and 67% (n = 3900) had cognitive impairment. Table 1 provides more details.

Utilisation, self-perceived needs and attitudes towards ADs

Table 2 shows the use, self-perceived needs and attitudes towards ADs. The prevalence of AD use was 10.9% (n = 634) of study participants. Of participants, 46.1% (n = 2670) reported a self-perceived need for ADs and 53.9% (n = 3120) reported no need of ADs. In total, 37.6% (n = 2175) of participants agreed that "ADs are of significant help to the safety and health of the elderly," 34.1% (n = 1972) selected "ADs are only helpful to the disabled and disabled elderly adults," 19% (n = 1102) thought "ADs have limited effects," and 9.3% (n = 541) believed that "ADs have no effects."

Univariate analysis of factors influencing the use of ADs by the elderly

The variance inflation factor of the model was less than 10, which indicated no multi-collinearity between the variables. For educational level, age, occupation, marital status, number of children, economic status, income and expenditure, main residence, daily travel mode, main caregivers, causes of physical disability, social activities, needs, attitudes and ADL, the differences were statistically significant ($P < 0.05$). No significant difference was seen with gender, income source or MMSE ($P > 0.05$, see Table 1).

Multifactor analysis of factors influencing the use of ADs by the elderly

The dependent , and the independent variables were those that showed statistical differences in the univariate analysis. Binary logistic regression analysis was carried out, and the Hausman test of the model indicated that the model was a good fit ($\chi^2 = 1127.673$, $P < 0.001$). The results showed that educational level, age, occupation, number of children, financial situation, main residence, attitudes toward ADs, self-perceived needs and ADL were the factors influencing the use of ADs by the elderly ($P < 0.05$, see Table 3).

Discussion

This is the first study to investigate the use of ADs among older adults in China. The present study identified that ADs for the elderly are currently underutilised (10.9%),[23,24] and there are high self-perceived needs (46.1%) and negative attitudes towards ADs (with only 37.6% believing that ADs are of significant help) in China. Underutilisation generally arises as a result of insufficient availability of ADs or lack of willingness to use ADs;[25] thus, collecting comprehensive information about the supply and demand

Table 3
Binary logistic analysis results for usage of ADs.

Variables (Reference)		*P*	Exp(B)	95% CI
Education level (high school or above)				
	Illiterate	0.001	0.491	0.32, 0.751
	Primary school	0.001	0.602	0.449, 0.809
	Middle school	0.063	0.768	0.582, 1.015
Age group (≥80)				
	60–69	0.005	0.65	0.482, 0.875
	70–79	0.155	0.822	0.628, 1.077
Occupation (others)				
	Farmer	0.002	2.565	1.406, 4.679
	Worker	0.003	2.277	1.329, 3.902
	Cadre	0.047	2.04	1.009, 4.124
	Business person	0.001	11.649	2.889, 46.974
Marital status (unmarried)				
	Married	0.42	0.555	0.133, 2.324
	Divorced	0.558	0.637	0.141, 2.882
	Widowed	0.857	0.877	0.21, 3.661
Number of children (≥2)				
	0	0.049	0.385	0.149, 0.998
	1	<0.001	0.612	0.479, 0.782
Financial condition (≥6000)				
	≤1000	0.042	3.333	1.045, 10.635
	1001–3000	0.003	5.405	1.772, 16.49
	3001–6000	0.08	2.678	0.888, 8.069
Income and expenditure condition (income far lower than expenditure)				
	Income far exceed expenditure	0.357	1.339	90.72, 2.49
	Income slightly exceed expenditure	0.436	0.835	0.531, 1.314
	Income equals expenditure	0.28	0.822	0.576, 1.173
	Income slightly lower than expenditure	0.077	1.373	0.966, 1.951
Main residence (special area)				
	City	0.041	0.157	0.026, 0.93
	Town	0.043	0.155	0.025, 0.939
	Village	0.054	0.166	0.027, 1.031
Daily travel mode (mud pavement)				
	Elevator	0.74	1.169	0.465, 2.937
	Stairs	0.952	1.028	0.42, 2.515
	Cement pavement	0.996	1.002	0.406, 2.477
Primary caregiver (domestic workers)				
	Solitude	0.618	0.757	0.253, 2.263
	Spouse	0.734	1.203	0.415, 3.49
	Family	0.745	0.84	0.293, 2.406
Cause of disability (congenital)				
Disease		0.517	1.471	0.458, 4.723
Self-perceived need (no need)				
	In demand	<0.001	0.233	0.191, 0.284
	May need it later	.	0.136	0.136, 1.43
Attitude (no effects)				
	Of significant help to the elderly	0.048	1.524	1.003, 2.315
	Only helpful for the disabled and disabled elderly	0.011	1.729	1.136, 2.632
	Have limited effects	0.083	1.472	0.951, 2.28
ADL (profound disability)				
	Normal	0.004	0.31	0.139, 0.692
	Mild disability	0.2	1.698	0.756, 3.813
	Moderate disability	0.418	1.458	0.586, 3.63
	Severe disability	<0.001	25.351	7.69, 83.575

AD, assistive device; ADL, activities of daily living; CI, confidence interval.

of ADs is necessary. Moreover, to improve elderly ADs services, factors predicting ADs usage must be considered.

Demographic characteristics

This study showed that age, occupation, education and residential area impacted ADs usage.

First, age had an impact on AD utilisation, as ageing results in substantial and sustained declines in physical function.[27] The impact of age on AD usage is a familiar concept in society.[26] Zhang Wenjuan et al.[24] showed that the proportion of the elderly population using ADs to compensate for reduced function increased with age.

Second, individuals whose occupation was as a worker were more likely to use ADs, possibly because higher rates of employed workers experienced work-related injuries, which may have resulted in disabilities, financial burdens from treatment and mental health problems.[26]

Third, the observation that the elderly with lower educational attainment used ADs at higher rates than those with higher education is consistent with a previous study.[28] Previous findings suggest that education may be a protective factor; thus, when activity restrictions develop, those with higher education may not begin using ADs as soon as those with lower education because they may have the knowledge and resources to compensate in other ways, such as by hiring help.[18,27]

In line with a previous study,[29] elderly urban residents showed higher use rates of AD use than rural residents. This has been attributed to the fact that most AD centres and allocation

institutions are in urban areas, therefore increasing AD accessibility in these areas.[30] In other words, geographical boundaries impacted AD distribution, indicating that face-to-face services are not ideal for screening potential elderly users and adapting ADs in remote areas. An online AD adapter platform is necessary.[31]

Enabling factors

The present study showed that financial situation and the number of children were significant enabling factors for AD usage in the elderly.

The observation that the prevalence of ADs was highest among those with a low monthly income was somewhat surprising. As has been previously reported, cost is a major barrier to not using ADs,[32] and more favourable economic conditions are important predictors of accessibility to health services.[33] In this study, one plausible interpretation is that when physical function decreases, the elderly in the lower-income group may seek help from inexpensive aids instead of medical resources.

A higher number of children also predicted higher AD use. Family bonds show a remarkable increase with age,[34] suggesting that the elderly are more likely to assist the family, for example, undertaking the double burden of taking care of their grandchildren and doing housework.[35] Such physical demands make them dependent on aids for independent living. In addition, the role of family members in relation to AD use deserves further investigation. Family caregivers have been shown to be instrumental in determining the AD needs and sourcing ADs for elderly relatives;[36] however, the elderly with more children are also more likely to have additional family caregivers, resulting in less dependency on ADs.

Demand factors

In terms of demand factors, the present study showed that the use of ADs by the elderly is mainly driven by ADL, attitudes towards ADs and self-perceived needs. It is not surprising that ownership of ADs was influenced by ADL impairments, revealing that using ADs is the most common coping mechanism for the elderly with disabilities. On the basis of disablement process models, ADs were included as a modifying factor to improve the disabling process.[37] Other studies have shown that homebound elderly individuals equipped with ADs reduced their self-reported difficulty and time required to perform ADLs.[38] Intriguingly, the present study indicated that those with profound disabilities reported less AD usage, which may illustrate the inability of ADs to compensate for the most severe degrees of disability. In addition, several problems with the quality of ADs have been reported among the elderly, such as difficulty of assembly, rough appearance, unsuitable size and lack of structural strength.[39] Moreover, it is assumed that elderly individuals with profound disabilities are more likely to be long-term bedridden and require home nursing instead of equipment aids. Further investigation is needed to explore the usage experiences and demands of this population group.

Accurate information is necessary to establish positive beliefs towards seeking healthy behaviours.[40] As shown in the present study, the elderly population who believed in the effectiveness of ADs showed higher rates of AD usage; however, most of the elderly showed mistrust of ADs. Therefore, it is essential to strengthen education programmes aimed at the elderly, caregivers and healthcare professionals.[41]

Older adults who perceived that they had no need for ADs showed the highest AD ownership, whereas those who believed they needed ADs had the lowest usage rate. Owning ADs may be a result of an individual's current health status, regardless of their self-perceived need. This study showed that possession of ADs was much lower than self-perceived needs, which is a problem that needs addressing. Primary health care should be used to prescribe ADs to achieve better coverage of ADs to the elderly.[42]

Strengths and limitations

This is the first study to investigate the status of AD use by the elderly in China. The study findings provide guidance for improving AD services and policies for the elderly. However, this study also has some limitations. This study was conducted on a sample population from three representative cities in China. Despite the large sample size, the results may still raise concerns over the generalisability of the findings. Moreover, this study only explores the prevalence of AD use. To gain a better understanding of the issue, future studies should investigate the types of ADs that the elderly need and use, the reason they need and use them, and their usage experience. Moreover, further studies could use longitudinal data to investigate the causal relationship among variables over time to more accurately reflect actual AD usage and adopt both quantitative and qualitative approaches to explore in-depth views and/or opinions of the issues.

Conclusions

Although ADs for the elderly in China have become more affordable and accessible after a series of reforms, there remains a gap in AD services, resulting in low AD utilisation, high self-perceived needs and misconceptions of ADs. Certain factors influencing the use of ADs are more significant than others. The findings from this study will be informative for healthcare providers and decision-makers when designing strategies to achieve universal elderly AD usage, which should include effective AD service delivery, education programmes and online AD adapter platforms.

Author statements

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Ethical approval

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China (2020-622).

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Competing interests

None declared.

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Review Paper

Features of human papillomavirus vaccination education strategies in low- and middle-income countries: a scoping review

E.A. Marfo [a, *], K.D. King [a], C.A. Adjei [b], S.E. MacDonald [a]

[a] Faculty of Nursing, University of Alberta, Edmonton, Alberta, Canada
[b] School of Nursing and Midwifery, University of Ghana, Legon, Accra, Ghana

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ABSTRACT

Objective: We aimed to describe studies on human papillomavirus (HPV) vaccination education strategies from low- and middle-income countries in the published literature that could be applicable in Sub-Sahara Africa.
Study design: This scoping review was guided by Arksey and O'Malley's methodological framework advanced by Levac et al.
Methods: We searched four electronic health sciences databases for relevant reports published between January 2006 and January 2021. Two reviewers screened for inclusion and extracted data for analysis and synthesis. Descriptive statistics and narrative descriptions were used to summarize the findings.
Results: The database search retrieved 1757 reports, of which 48 were from low- and middle-income countries and met the inclusion criteria. Of these, there were 39 interventional studies (81.3%). Less than one-fifth of the studies ($n = 9$) reported a theoretical basis for their strategies. Most strategies sought to improve knowledge and awareness about HPV (75%, $n = 36$), whereas outcomes for the remaining studies were related to increasing HPV vaccine acceptability. HPV education strategies (1) primarily targeted females, (2) were mostly provided by health professionals, and (3) used various modalities of learning, including in-person sessions, text-based materials, media, theater, and online delivery.
Conclusions: HPV educational strategies are underresearched in most LMICs, suggesting the need for more primary observational, interventional, and experimental research, as well as program evaluations, focused on HPV educational strategies and theoretically informed. Once additional studies are added to the body of evidence, it will be valuable to review and synthesize diverse sources of evidence to determine what educational strategies are most useful and have the greatest impact on HPV vaccination in these settings, particularly Sub-Saharan Africa.

Introduction

Cervical cancer affects a disproportionate number of people in Sub-Sahara Africa (SSA).[1] Of the 20 countries with the highest burden of cervical cancer worldwide, 19 of them are from this region.[2] Annually, approximately 117,316 cases of cervical cancer and 76,745 deaths are reported in SSA.[3] Vaccines are safe and effective against human papillomavirus (HPV)-related cancers;[4,5] however, uptake remains low.[6,7]

Effective HPV educational strategies will be crucial in preparing stakeholders for national HPV vaccination programs when they are implemented in many SSA countries.[8] However, a preliminary search of two health science databases (Cumulative Index of Nursing and Allied Health Literature [CINAHL] and MEDLINE) to identify reviews that examined HPV vaccine education strategies in SSA found no systematic or scoping reviews on this topic.

According to the World Bank, the countries in SSA are classified as low or middle income.[9] Although low- and middle-income countries (LMICs) have significant contextual differences, disparities in sexual and reproductive health, including HPV vaccination in SSA, are generally reflective of vaccination landscapes across LMICs.[10] The knowledge of the characteristics of HPV educational

* Corresponding author.
E-mail address: marfo@ualberta.ca (E.A. Marfo).

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strategies in LMICs may inform HPV vaccine education planning in SSA. Thus, conducting a scoping review to identify the depth, breadth, and gaps in current knowledge on this topic was necessary.

Scoping the literature will help map and identify education strategies for HPV vaccine awareness in LMICs, albeit only those that have been researched and published. This will generate insights into what strategies have been studied and, in turn, provide direction for future research on HPV education strategies in SSA. Therefore, this review sought to answer the following questions: (1) What features of HPV vaccination education strategies exist in the published literature? (2) What are the educational strategies identified and reported in the published literature? and (3) Is there sufficient evidence to warrant a systematic review of the topic?

Study design

Arksey and O'Malley's[11] methodological guidance for scoping reviews, advanced by Levac et al., underpinned this study.[12] This framework constitutes (1) identifying a research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) collating, summarizing, and reporting the results. We incorporated the optional step proposed by Arksey and O'Malley, namely, expert consultation, by consulting with the fourth author (S.E.M.), an expert in childhood vaccination.

Methods

Study inclusion/exclusion criteria

Studies eligible for inclusion were determined using the Population, Concept, Context criteria.[13] There were no limiters on populations included in the studies so long as the studies were focused on the concept of interest. The concepts were HPV vaccine education strategies in the context of LMICs.[9] We included original research of quantitative, qualitative, and mixed-method designs. Only studies published between January 2006 to January 2021 were included, as HPV vaccines became available in 2006.[6] We excluded non-primary research reports (editorials, commentaries, opinions) and studies not published in English. Conference abstracts were also excluded because it is common for there to be inconsistencies between an abstract and the full report.[14]

Search strategy

Studies on HPV education and communication strategies in LMICs were identified by searching electronic databases (MEDLINE, CINAHL, Global Health, and Embase) on January 15, 2021. The search sought articles that focused on human papillomavirus, HPV; education strategies or campaigns; communication strategies; and LMICs. The search terms were developed and applied with the help of a research librarian (see Supplementary Material I Comprehensive Search Strategy). Articles whose full-text reports could not be found were requested from authors via email communication.

Study selection

Two authors (E.A.M. and K.D.K.) independently conducted level 1 (title/abstract) and level 2 (full text) screening based on the established inclusion criteria using Covidence software for systematic reviews. Conflicts were resolved through consensus, and further disagreements were resolved through consultations with the fourth author (S.E.M.) for expert guidance and validation of selected reports.

Data extraction

The data extraction tool (available on request) was developed, piloted, and modified by E.A.M. and K.D.K. in a Microsoft Excel spreadsheet. Data were extracted from the articles retained after screening by one author (E.A.M. or K.D.K.) and then validated by the another author (E.A.M. or K.D.K.). The information extracted included title, authors, year of publication, country, income classification of country, methodological elements (study design, theoretical framework, population, sample size, and intervention), findings, implications, and recommendations (see Supplemental Material II- Data Extraction Table). Quality appraisal was not conducted, as the focus of this research was to identify and describe the nature of studies on HPV research in this area, not to assess their quality.

Data analysis and synthesis

Descriptive statistics using pivot tables were conducted to report the frequencies and percentages of the characteristics of studies and their findings. We used narrative descriptions to summarize features of studies, and figures and tables were used to report these findings.

Results

We retrieved 1757 reports from database searching. A total of 48 reports from LMICs met the inclusion criteria after the removal of duplicates as reported in the Preferred Reporting Items for Systematic Reviews and Meta-analysis for Scoping Reviews (PRISMA-ScR) flow chart (see Fig. 1). Thirty-seven LMICs were represented in the reports, representing 27% ($n = 37$) of 137 LMICs listed by the World Bank.[9]

Study characteristics

Most of the reports (79.2%, $n = 38$) included in this review were quantitative designs, with few qualitative studies (12.5%, $n = 6$) and fewer mixed methods designs (8.3%, $n = 4$). The sample size of included studies ranged from eight to 87,580 participants. A total of 10 (20.8%) studies had a sample size <100, whereas 22 (45.8%) had a sample size between 100 and 500. Fourteen studies (29.2%) had a sample size >500, and two studies did not report the sample size. Participants for most studies were female (54.2%, $n = 26$), followed by studies without sex limitations on participants (43.8, $n = 21$). One (2.1%) study focused only on male participants. Reported educational strategies described a range of target groups (i.e., professions or social roles) and age categories (i.e., adolescents, adults), but this was not consistently reported.

Countries of origin and income levels of included studies

Most of the studies (87.5%, $n = 42$) originated from middle-income countries. Three studies (6.3%) came from low-income countries, and the other reports (6.3%, $n = 3$) were multinational studies comprising both LMICs. The three countries with the most research on the topic were India (12.5%, $n = 6$), Nigeria (10.4%, $n = 5$), and China (8.3%, $n = 4$). Studies from low-income countries originated from Mali, Mozambique, and Uganda (Table 1).

Theoretical frameworks

Most studies (81.3%, $n = 39$) did not report a theoretical framework. Among those studies that reported a theoretical framework, the Health Belief Model was mostly used (6.25%, $n = 3$),

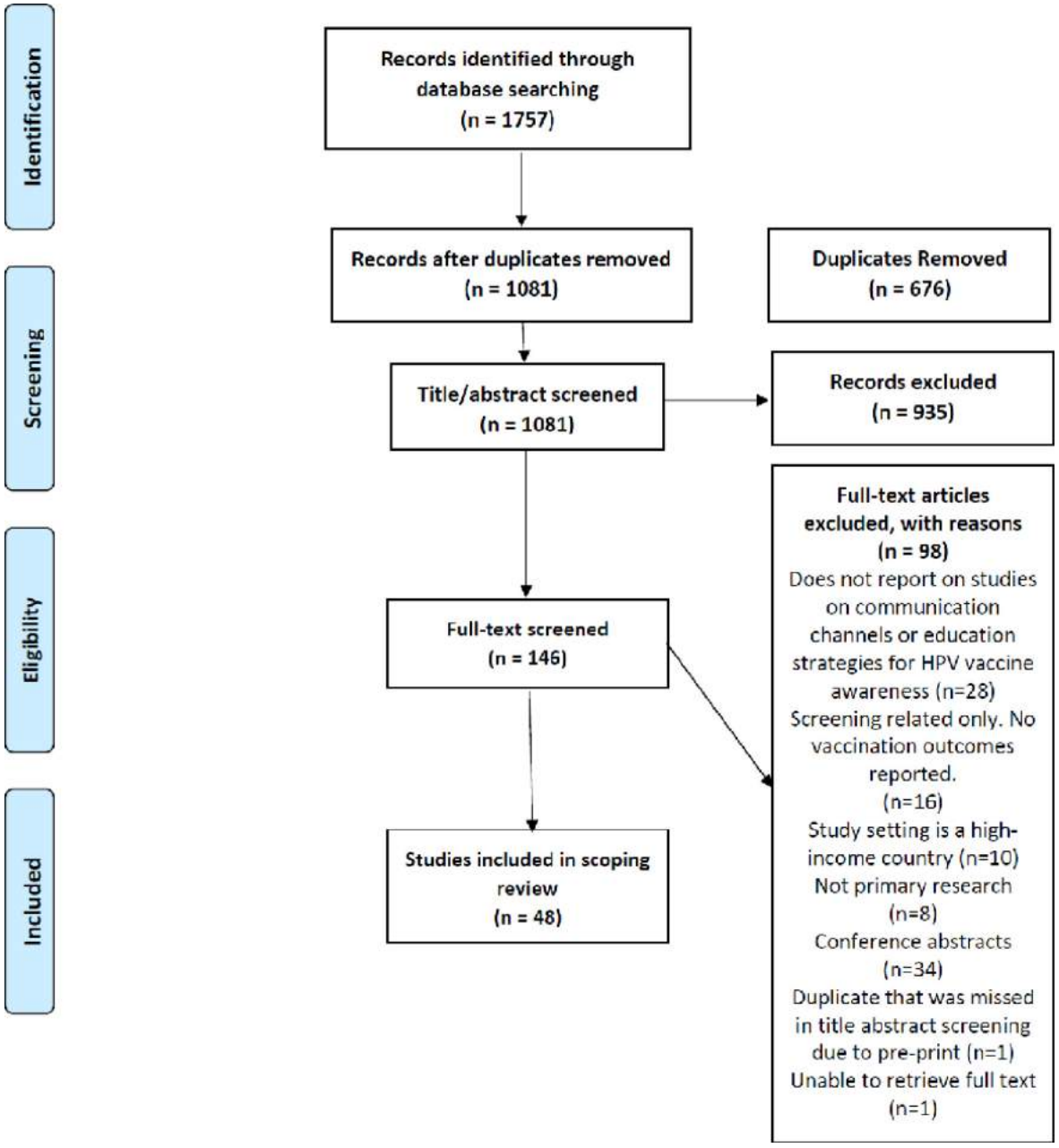

Fig. 1. PRISMA diagram. Adapted from Moher et al.[34]

followed by the PRECEDE/PROCEED (4.16%, $n = 2$). Social Constructionism (2.08%, $n = 1$), Consolidated Framework for Implementation Research (2.08%, $n = 1$), Pender Health Promotion Model (2.08%, $n = 1$), and Theory of Social Representations (2.08%, $n = 1$) underpinned one study each.

Features of studies

Publication year of included studies. None of the studies included in this review was published between 2006 and 2010. Less than half (45.8%, $n = 22$) of studies were published from 2011 through 2017. Most studies (54%, $n = 26$) were published between 2018 and 2020 (see Fig. 2).

Types of studies (intervention/non-intervention). A total of 39 (81.3%) reports included in this review were interventional studies. The remaining were non-interventional studies (18.8%, $n = 9$). However, they all described some elements of education that occurred before or during their research.

Of the interventional studies included, 32 (82.1%) were individual or group-level interventions, targeting specific populations (i.e. adolescent girls, parents, etc.). A total of 6 (15.4%) studies were multilevel interventions, targeting multiple population groups (e.g. parents, teachers, and adolescents), and included community or institutional approaches (e.g. unions, schools, workplaces, etc.). One study (2.6%) was a system-level intervention, which focused on a large-scale pilot HPV vaccination program. The interventional studies evaluated in these reports included theatrical interventions, in-person educational presentations (i.e. workshops, symposiums, lectures, health talks, etc.), text-based interventions (i.e. posters, leaflets, factsheets, newsletters, letters, etc.), public media (i.e., radio television, newspapers, public announcements, etc.), and online resources (i.e., videos, web-radio; see Data Extraction Table).

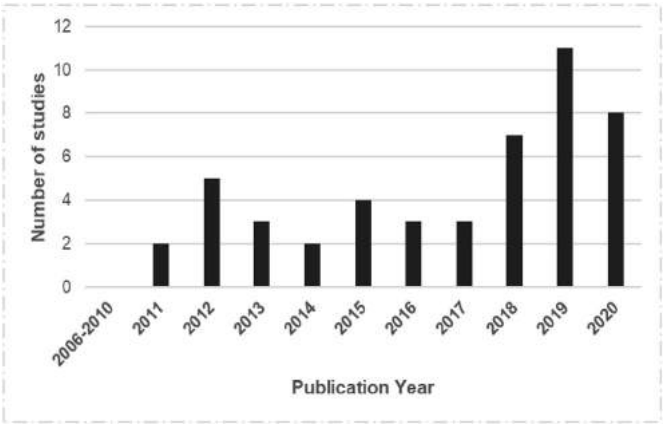

Fig. 2. Study counts by publication year.

Non-intervention studies described educational strategies in their research but did not deliver an intervention as part of their research. Of the educational or communication strategies described, four (44.4%) were individual or group strategies targeting specific populations. There were two multilevel strategies (22.2%) looking at multiple groups, and there were three (33.3%) system-level strategies, which explored broad systemic efforts to increase vaccination. These strategies involved HPV vaccination demonstration projects, pilot projects, vaccination campaigns, and HPV or cervical cancer screening programs, in which the educational outcomes were not the research objective.

Providers of educational/communication strategies. The providers of educational strategies included a broad range of stakeholders and agencies. In most of the reports, only health professionals (29.2%, $n = 14$; i.e., nurses, physicians, etc.) provided HPV educational strategies. In eight of the studies (16.7%), a team of diverse providers was involved (i.e. teachers, health professionals, and community members). In the remaining reports, the strategies were provided by researchers, diverse groups of students (i.e. medical students, secondary school students), community health workers, or different institutional providers (i.e. non-governmental organizations, government departments, unions; see Fig. 3). Fourteen studies (29.2%, $n = 14$) did not report on the providers.

Outcomes of educational strategies. The expected outcomes of the educational strategies varied across reports. Most strategies sought to improve knowledge and awareness about HPV (75%, $n = 36$), whereas others included outcomes related to increasing HPV vaccine acceptability (intention to vaccinate or actual vaccine uptake). Most strategies (81.3%, $n = 39$) achieved their expected outcomes. A total of six strategies (12.5%) reported both positive and negative outcomes. Only three strategies (6.3%) did not achieve their outcomes (Table 2).

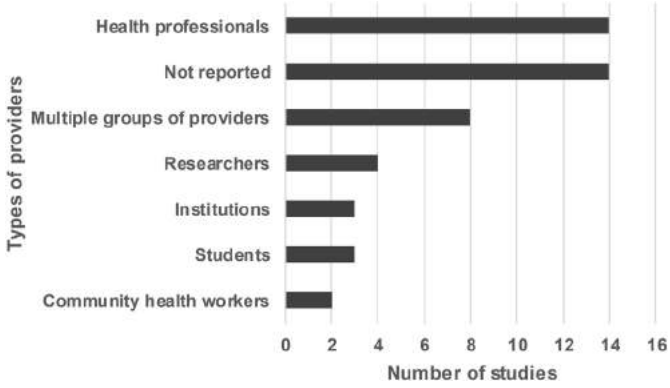

Fig. 3. Counts of studies by types of providers of strategies.

Discussion

This scoping review aimed to identify and describe the features of HPV educational strategies from LMICs and determine whether there is sufficient evidence for a systematic review. The findings are discussed below.

Types of HPV educational strategies from LMICs

Research on most HPV educational strategies in LMICs used quantitative designs with a few mixed methods and qualitative methods. A review on strategies to increase HPV vaccine uptake reported that most studies used quantitative designs such as randomized controlled trials.[15] Although quantitative methods are useful in directly measuring outcomes such as vaccine uptake or change in knowledge, awareness, or vaccine acceptability, these designs have their limitations, in that they are rarely contextually situated. An expanded qualitative exploration of HPV educational strategies can offer a contextual understanding of what works and what does not work in each unique context within LMICs. There are opportunities for increased mixed methods studies that capture quantitative outcome data to measure impact and the valuable contextual knowledge generated in qualitative methods.

Most strategies targeted females, whereas only one study targeted males. Until recently, HPV vaccination programs in most countries prioritized females,[16] potentially resulting in gender-inequitable HPV vaccination education strategies as is evident from our results. Evidence suggests that males and some gender-diverse populations have significant risks of acquiring HPV infections and potential HPV-related cancers.[17] Hence, HPV educational strategies should be sensitive to sexual and gender differences. HPV vaccination educational strategies targeted at diverse populations inclusive of additional intersections of sex, gender, and sexuality are critical, given the diverse needs of the different communities in LMICs, especially in SSA. The complex and nuanced sexual and reproductive health, including HPV vaccination needs in SSA, reflect the complexity that exists across LMICs; therefore, educational strategies identified in this review can be adapted to meet the local needs of SSA. Sexual and reproductive health disparities require country-specific, culturally sensitive, and multisectoral approaches; therefore, it would be beneficial to adapt successful interventions from other LMICs to SSA, keeping those principles in mind.[18]

The extent of research on HPV educational strategies in LMICs

The 48 reports included in this review originated from 37 countries, representing less than one-third of the 137 LIMCs.[9] Only three countries were in the low-income category, representing less than 15% of low-income countries.[9] Only nine studies originated from SSA, representing less than a quarter of the 48 countries in that region.[9] These findings suggest the limited nature of research on this topic in LMICs and SSA. This may be due to inadequate funding for research, planning, and implementing HPV education strategies in these contexts.[19] Existing epidemics (i.e. HIV, malaria, and tuberculosis) and inadequate epidemiological data on HPV-related cancer may render HPV educational strategies a lower priority in LIMCs.

Theoretical basis of HPV educational studies from LIMCs

Our review showed that most HPV education strategies are not guided by theoretical frameworks. This is not surprising, as the public health discipline has historically been driven mainly by positivist philosophical orientations that favor causality and atheoretical approaches to research.[20] Evidence suggests that theory-guided interventions allow for systematic and effective approaches to planning, implementing, monitoring, evaluating, sustaining, and scaling up social interventions.[21,22]

Given the broad range of complex individual and structural factors that impact HPV vaccination, the intersectionality theoretical framework, which helps examine how different social identities intersect to create multiple levels of privileges and marginalization[23] might assist in understanding the HPV educational needs of the diverse target populations. There is evidence from higher income settings that interactions between sex and race impact HPV vaccination initiation,[24] as well as characteristics such as age, parental socio-economic status, HIV status, urban/rural status, insurance coverage, and sexual orientation.[25,26] Previous research[27] that has examined factors influencing LMICs vaccine adoption (including HPV vaccination) has identified that recommendations from World Health Organization, available epidemiological data, and cost-effectiveness and affordability are primary drivers for vaccine implementation. Given that much of the research around HPV vaccination acceptability and access has occurred in non-LMICs,[28] and the authors have not found any intersectionality-informed research in this area, it appears that this is an area of opportunity for a more complex analysis of the barriers and facilitators of HPV vaccination in this setting.

Table 1
Frequency of origin of included studies ($N = 48$).

Country/region	Number of articles	Percentage of articles
Africa		
Cameroon	2	4.2
Ghana	1	2.1
Kenya	3	6.3
Mali	1	2.1
Mozambique	1	2.1
Nigeria	5	10.4
Tanzania	1	2.1
Uganda	1	2.1
Zambia	1	2.1
Asia		
Cambodia	2	4.2
China	4	8.3
India	6	12.5
Indonesia	1	2.1
Malaysia	1	2.1
Pakistan	1	2.1
Saudi Arabia	1	2.1
Turkey	1	2.1
Vietnam	2	4.2
Central America		
Grenada	1	2.1
Honduras	1	2.1
Europe		
Romania	1	2.1
Oceania		
Fiji	1	2.1
Papua New Guinea	1	2.1
South America		
Brazil	3	6.3
Colombia	1	2.1
Peru	1	2.1
Multinational/multiregional		
Bhutan, Bolivia, Cambodia, Cameroon, Haiti, Lesotho, and Nepal	1	2.1
Bhutan, Bolivia, Cambodia, Cameroon, Georgia, Ghana, Guyana, Haiti, Honduras, Kenya, Kiribati, Lesotho, Mali, Moldova, Nepal, Tanzania, and Uganda	1	2.1
Uganda and Vietnam	1	2.1

Features of HPV educational studies from LIMCs

Most of the reports included in this review were published within the past 3 years. This finding highlights the increasing research focus on understanding the perceptions and attitudes toward HPV vaccination to strategies that enhance HPV vaccination uptake in LIMCs. This is evident as more than 80% of the reports included in this review were intervention studies, although "intervention" was not included in our search strategy. Again, in some non-interventional, researchers provided educational information in the form of short presentations and fact sheets.

About one-third of the HPV educational strategies were provided by health professionals. Experts suggested involving health professionals in HPV vaccination programs, as they are trusted by the public.[29] In about 30% of the studies, the researchers did not report on providers of educational strategies. This may be due to restricted reporting standards by certain journals. This is problematic as the lack of a detailed description of HPV educational strategies, including the providers, hinders the replication of studies with positive outcomes in SSA.

Finally, we found that most of the strategies were effective, with some studies reporting both positive and negative outcomes. Only a few strategies were found to be ineffective. This may be due to publication bias resulting from journal editors and reviewers rejecting studies with insignificant findings.[30,31] Future studies may replicate successful HPV strategies in other SSA countries to determine their impact on vaccine knowledge and uptake in those contexts. Also, inasmuch as it is important to disseminate effective HPV education strategies, it is equally salient to publish studies with unsuccessful outcomes, as they could inform HPV education planning programs on measures to avoid achieving negative outcomes in future projects.

Implications

There is limited research on HPV educational strategies in most LMICs, especially in low-income countries, which presents a knowledge gap on this topic between this socio-economic category of countries and high-income countries.[28,32] Research funding agencies should prioritize proposals on HPV educational strategies from LIMCs to bridge this knowledge gap. More primary HPV educational research using observational, interventional, and experimental designs, as well as surveys and program evaluations, are warranted in LMICs and SSA in particular. Future research may also use an integrative review approach,[33] allowing for the synthesis of evidence from diverse sources, including reports, gray

Table 2
Counts of studies by expected outcomes.

Expected outcomes of studies	Number of studies, *n* (%)
HPV knowledge and awareness	36 (75)
HPV vaccine acceptability	12 (25)
Intention to vaccinate	9 (19)
HPV vaccine uptake	15 (31)
Combined outcomes (i.e. vaccine intention, acceptability, uptake, or knowledge and awareness)	17 (35.4)

* Note that total does not equal 100% due to the many studies having multiple outcomes.

literature, and policy documents from the websites of ministries of health. This may inform practice, given the limited primary studies for detailed systematic reviews currently. Future HPV educational strategies should use intersectional theoretical frameworks to analyze these complex individual and social factors that influence access to inclusive HPV information and HPV education strategies. Importantly, future research should study education strategies attentive to intersecting factors (i.e. eligibility, age, gender, income, parental education status, vaccine type and dose [single dose or series], etc.) that influence HPV vaccination to determine what education strategies are appropriate in a specific SSA and LMIC context. Finally, qualitative and mixed methods research designs could offer a context-specific understanding of factors to consider when planning HPV education strategies in LMICs.

Strengths and limitations

This review was limited to only published studies; therefore, publication bias is a possible limitation. There may be educational strategies that exist but were not researched in LMICs, meaning that potentially valuable strategies were not captured in our review. Given that some LIMCs use languages other than English for research, it is possible that our review may not capture studies published in other languages. However, our review included studies from all global regions except North America, thereby capturing diverse educational strategies. We did not extract data on specific age groups of the target populations; however, our review included strategies for diverse age groups.

Conclusion

We found limited research on HPV educational strategies in LMICs and SSA, suggesting a need for more primary observational, interventional, and experimental research, as well as program evaluations, focused on HPV educational strategies. Once additional primary studies are completed, it will be valuable to systematically review and synthesize the evidence. Synthesizing diverse sources of evidence will be critical to determining what educational strategies are most useful and have the greatest impact on HPV vaccination in LMICs, particularly SSA.

Author statements

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Ethical approval

None sought as this project includes no human participants.

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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.2022.09.013.

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Commentary

Health impacts of the rising cost of living: reframing the UK narrative

L. Marshall [a], J. Bibby [a], R. Suckling [b], B. Holden [c, *]

[a] The Health Foundation, London EC4Y 8BB, UK
[b] Doncaster Council, Doncaster DN1 3BU, UK
[c] School of Health and Related Research, The University of Sheffield, Sheffield S10 2TN, UK

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The full extent of the impact of the rising cost of living on people's health in the United Kingdom will not be known for many years. What is certain is that the economic and health impacts will not be felt equally across society.

The literature is replete with evidence of what to do and where to act to mitigate the effects of financial insecurity on health. But galvanising political attention and action requires an understanding of the determinants and drivers of health. Work in the United Kingdom by the Health Foundation has shown that the wider determinants of health are poorly understood amongst the public – and many decision-makers. Working with the FrameWorks Institute, the Health Foundation has developed techniques to reframe our communications about health and build greater awareness and understanding of the wider determinants of health.[1] Applying these insights will be critical to building recognition of the cost of living crisis as a health crisis and creating support for action.

The cost of living crisis is a health crisis

Poverty and health are closely interlinked, and living in poverty is bad for health.[2]

On average, men in the most deprived tenth of areas in England in 2018–2020 were living nearly 10 fewer years than those in the least deprived tenth of areas; for females, the gap was nearly 8 years.[3] Recent Health Foundation analysis has shown the uneven diagnosis and progression of disease with, on average, a 60-year-old woman in the poorest tenth of local areas of England having diagnosed illness equivalent to that of a 76-year-old woman in the wealthiest tenth of areas.[4]

Living in poverty makes it difficult to afford the building blocks of good health, including good quality, warm homes and healthy food. Constant worry about making ends meet can lead to chronic stress, anxiety and depression.[5]

The Institute for Fiscal Studies estimated the annual inflation rate in April to be 10.9% for the poorest tenth of households, compared with 7.9% in the richest tenth. And Resolution Foundation analysis of the September 2022 fiscal statement finds that while the richest 5% in the United Kingdom will see their disposable incomes grow by 2% in 2023–2024, the rest of the population will get poorer, with the poorest 5% seeing the greatest falls of 9% in their household disposable income.[6] This is in the context of more than a decade of austerity in the United Kingdom and the resulting stalled life expectancy trends.[7] The poorest households have experienced – and still face – the greatest economic shocks and the greatest health risks.[8]

The United Kingdom entered the cost of living crisis with high levels of poverty. In 2019/2020, more than one in five of the UK population were living in poverty.[9] The rates of poverty are higher in children than in any other age group, with one in three (4.3 million) UK children living in poverty in 2019/2020. The immediate and longer term impacts of experiencing poverty at an early age will be profound. Financial insecurity can directly affect children's outcomes through constraints on parents' ability to afford the basics such as food and housing.

Financial insecurity takes away or limits household's choices and may mean they have to prioritise the urgent over the longer term. Consuming a healthy diet in the United Kingdom is more expensive than a less healthy one, and there are socio-economic inequalities in the healthiness of diets.[10] It is not unsurprising then that there are stark inequalities throughout the life course in the incidence and death rates of diet-related diseases, including

* Corresponding author.
E-mail address: b.holden@sheffield.ac.uk (B. Holden).

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dental decay in childhood, obesity at all ages, and longer term outcomes including preventable cancers and cardiovascular disease.[11] A Food Foundation report in April estimated that 2.6 million children aged <18 years live in households that do not have access to a healthy and affordable diet, putting them at risk of suffering from these and other diet-related diseases.[12]

The financial strain caused by not being able to make ends meet can also create parental stress and depression, as well as conflict between parents. This can in turn affect children, compounding mental health problems that have arisen from the pandemic.[13]

The recent Marmot review – *Fuel poverty, cold homes and health inequalities in the UK* – highlights the lifelong health risks to children living in cold homes. With estimates that more than half of all UK households will be in fuel poverty this winter, there is no doubt that there will be significant short- and long-term harms to health that will widen inequalities.[14] Households with children, especially lone parent households, are the most likely to be in fuel poverty. For children and young people, living in cold homes is associated with multiple health harms. These include impacts on development in the very early years, reduced resistance to respiratory infections, increased risk of asthma and acute asthma attacks, as well as multiple mental health risks. These health impacts, as well as the fact that it is harder to study and do homework in a cold home, can significantly affect a child's education.

Reframing the narrative

Work by the Health Foundation and FrameWorks has found a mismatch between public understanding in the United Kingdom of what influences health (namely, individuals' behaviours and their access to care) and the evidence base on the contribution of the wider determinants.[15] When talking about solutions to health inequalities, attention too readily turns to the National Health Service (NHS) and to individuals' willpower and discipline.

Developed using rigorous ethnographic and communications research methodologies, the Health Foundation's recently published toolkit sets out recommendations for framing public health communications to tell a more powerful story about health that inspires action and change.

1. **Show why it matters:** Lives are being cut short. We need to open communications with inequalities in how long people can expect to live in the United Kingdom and the fact that too many lives are being cut short.
2. **Harness the power of explanation:** Most people do not understand how the world around us shapes our health. We can increase understanding by taking a 'deep-dive' explanation into one of the wider determinants (jobs or housing work well) and by using a 'building blocks' metaphor to talk about the wider determinants.
3. **Show change is possible:** People can feel fatalistic about the possibility of change when it comes to health. We need to show change is possible by building solutions into our communications early and being explicit that we can make a difference.
4. **Use certain arguments with caution:** Part of telling a powerful story is knowing what not to say. The wrong message can decrease support for change, and the toolkit provides guidance on talking about the economic cost of the wider determinants, the NHS and the COVID-19 pandemic.
5. **Use data to strengthen your story, not tell it:** Naked numbers can reinforce unhelpful ways of thinking because people interpret them through their own existing beliefs. Help people make sense of facts and figures by putting them in context.

Galvanising action

Drawing on this approach, Local Authority Public Health leaders are already working in their places to focus attention and action to mitigate the effects of rising cost of living and support those in the greatest need.

Public Health leaders are also coming together to collaboratively address the crisis. In the north of England, the Yorkshire and Humber Association of Directors of Public Health Network[16] is working on a joint approach to the rising cost of living in the region, seeking to align their planned work with that of Local Authority leaders and Chief Executives. This work recognises actions that could be taken at a regional level that would make a difference and add value to ongoing local work.

The initial joint action plan covers objectives such as government and industry lobbying, sharing good practice, partnering with Yorkshire Universities[17] to research long-term structural solutions and supporting community-led approaches and maintaining infrastructure.

This work attempts to balance short-, medium- and long-term approaches. Short-term activity focuses on income maximisation, making it easier to get help and a compassionate approach to debt and financial resilience training. Other short-term activities include support to local food networks, the faith sector and the voluntary, community and social enterprise sectors.

Examples of medium-term objectives include improving employment opportunities and providing affordable housing. For England, the Local Government Association Cost of Living Hub provides a repository of best practice by councils and local partners.[18]

Long-term approaches encourage a sustainable and inclusive approach to growth and economic development in local places, which is underpinned by improvements in health and well-being. These approaches may have the added benefit of addressing multiple challenges facing the United Kingdom. For example, work to retrofit housing and reform transport systems that aims to address climate change can have added benefits to local economies, health and the rising cost of living.

A specific UK example of this is the 10-year Doncaster Borough Strategy "*Doncaster Delivering Together*." This proposes new ways of working that respond to local needs and opportunities and seeks to reduce inequalities and improve population well-being. Structured around six well-being goals, Doncaster's partnership strategy builds on the Borough's recent successes and has taken on board the views of residents, businesses, voluntary and community organisations, schools, healthcare providers, visitors and developers.[19] Short-term activities include developing proposals for the UK Shared Prosperity Fund[20] and longer term activities include establishing a Fairness and Wellbeing Commission to take further steps to leave no-one behind.

In summary

The cost of living crisis in the United Kingdom is a health crisis that will hit the most vulnerable in our society the hardest: including people living in poverty and, perhaps especially, children. However, there are solutions. As public health professionals, we need to communicate in ways that help people understand the impact of the crisis and support the action urgently needed.

Author statements

Ethical approval

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Original Research

Historical trends in mortality from "older" vaccine-preventable diseases, Colombia: implications for elimination and control

C. Arango-Úsuga*, J. Ochoa, A. León, D. Hincapié-Palacio

Universidad de Antioquia, Facultad Nacional de Salud Pública, Medellín, Colombia

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ABSTRACT

Objective: This study aimed to describe the trends in mortality from eight vaccine-preventable diseases in Colombia in the last 40 years and their relationship with vaccination coverage.
Study design: It is a population-based descriptive study.
Methods: The frequencies of deaths by decade, disease, sex, and the specific mortality rates by age group were calculated. Using a negative binomial regression model, the 10-year changes in mortality and their relationship with vaccination coverage were determined.
Results: The number of deaths and the adjusted rates decreased since 1989 in all diseases (incidence rate ratio <1 when compared with the 1979–1988 decade). Vaccination coverage below 90% is associated with an increase in mortality from diphtheria, measles, mumps, neonatal tetanus, and pertussis.
Conclusion: Historical changes in mortality support the benefits of vaccination, but new efforts are required to sustain the elimination of diseases.

Introduction

Vaccination has made an important contribution to the improvement of human and animal health. Its benefits are traditionally verified in decreased morbidity and mortality resulting from serious diseases that particularly affect children.[1] Mortality attributable to vaccine-preventable diseases is one of the most important indicators of population development and reflects the impact of national vaccination programs[2] when comparing their historical evolution since the introduction of each vaccine.[3]

Studies on mortality from vaccine-preventable diseases are scarce. In 2007, Roush analyzed historical mortality trends for 13 vaccine-preventable diseases and verified the "surprising" decrease in this indicator in the United States.[2] In 2016, Van Wijhe M et al. used historical data (cohorts born between 1903 and 1992) to point out the association between increased vaccination coverage and decreased (nearly zero) mortality from vaccine-preventable diseases in the Netherlands.[3] Simonsen reiterated the importance of epidemiological studies that use historical data to verify temporal transitions and relationships between mortality and vaccination.[4]

In Colombia, one of the Latin American and Caribbean countries with the most complete vaccination program, the study of vaccine-preventable disease mortality is limited, with scattered studies located in periodic epidemiological surveillance reports of each disease.

In Colombia, the Expanded Program of Immunizations (PAI, Programa Ampliado de Inmunizaciones in Spanish) was regulated between 1974 and 1977 in accordance with the World Health Organization (WHO) guidelines. The WHO recommended the strengthening and promotion of the expansion of vaccination programs in the countries of the poor world at the 29th World Health Assembly in 1976. This recommendation was based on the high mortality from measles, diphtheria, pertussis, tetanus, poliomyelitis, and childhood tuberculosis.[5] The national vaccination programs were gradually consolidated (with variations between countries) in the Region of the Americas after this guideline. In 1952, the national vaccination card was regulated14 as a requirement for school enrollment in Colombia. The "mandatory vaccines" protected against smallpox, diphtheria-pertussis, and tuberculosis.[6] Later, polio and measles vaccines were included. The national vaccination coverages achieved in the first stage of the program (1982) were polio 64.6%, diphtheria-pertussis-tetanus 47.2%, and measles 22.4%.[6]

This work systematized the evolution of mortality of eight vaccine-preventable diseases (diphtheria, pertussis, neonatal and other tetanus, measles, mumps, congenital rubella, and polio) and

* Corresponding author. Calle 62 Número 52-59, Facultad Nacional de Salud Pública, Universidad de Antioquia, Medellín, Colombia.
E-mail address: carlos.arangou@udea.edu.co (C. Arango-Úsuga).

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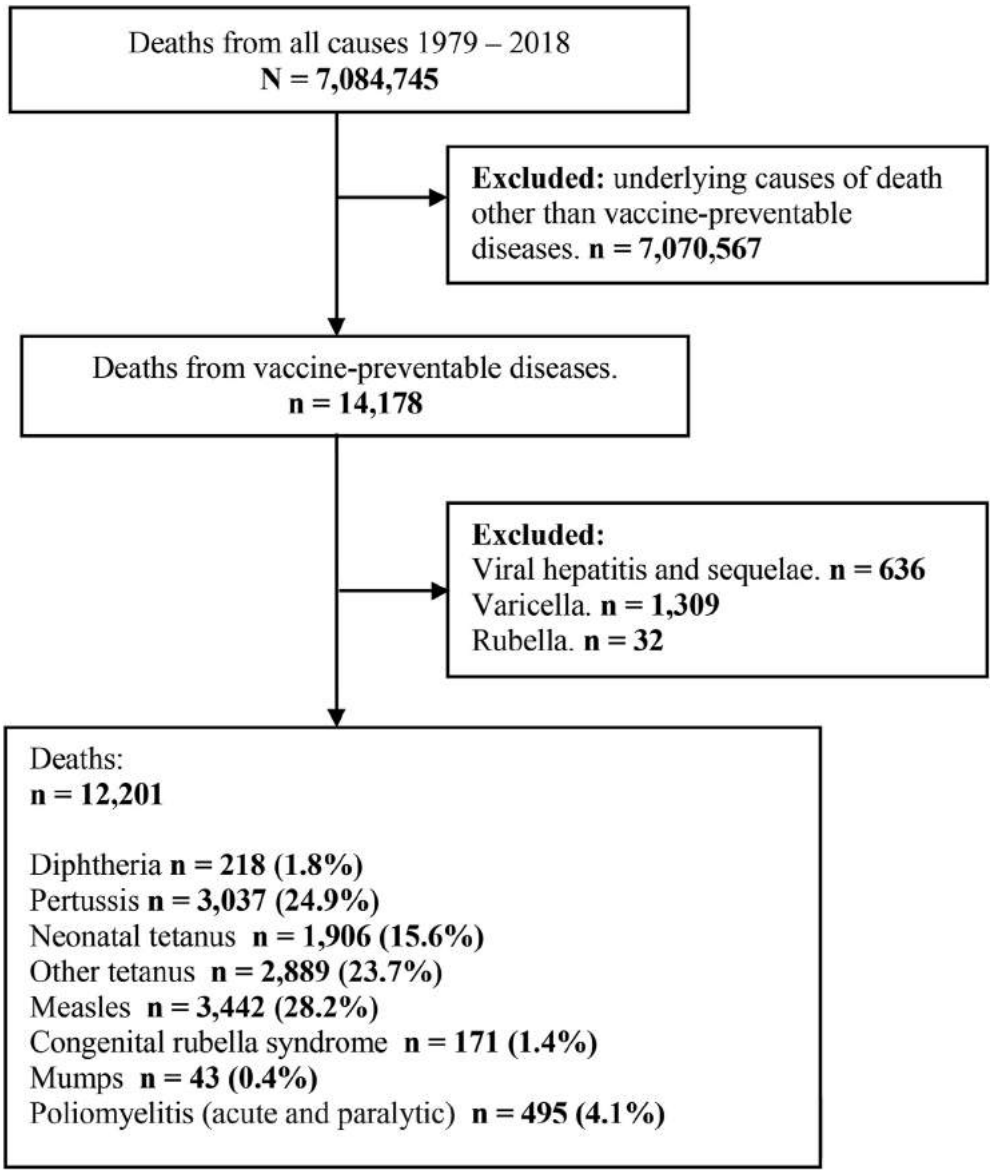

Fig. 1. Flow diagram. Mortality from vaccine-preventable diseases, Colombia, 1979–2018.

its relationship with vaccination coverage in Colombia over 40 years from the perspective of historical data.

Methods

Data on mortality were obtained from official death records consolidated by the National Administrative Department of Statistics of Colombia (DANE, Departamento Administrativo Nacional de Estadística de Colombia in Spanish)[7] for eight vaccine-preventable diseases encoded in the *International Classification of Diseases, Ninth Revision*, between 1985 and 1996, and the *International Classification of Diseases, Tenth Revision,* between 1986 and 2018 (Appendix A. Supplementary data). Mortality from paralytic and/or acute poliomyelitis and from congenital rubella syndrome was included in the analysis. Mortality from sequelae of poliomyelitis, viral hepatitis, chickenpox, and unspecified rubella was excluded.[2] The denominators (population of Colombia) were obtained from the DANE census projections.[8] Birth estimates (used to calculate neonatal tetanus rates) were obtained from World Bank (1979–1997)[9] and DANE publications (1998–2018).[7] Vaccination coverage was obtained from the Pan American Health Organization[10] and the PAI of Colombia.[11]

The information was divided by decade since 1979. The frequencies of deaths by decade, disease, sex, and the specific mortality rates by age group were calculated. The rates per decade were adjusted for age (direct method) using the standard population calculated by Stata version 13 (StataCorp, College Station, TX, USA).

A negative binomial regression model, used by previous studies on mortality, was built.[12] The dependent variable was the mortality rate (its logarithm) constructed with the number of deaths per year, and the exposure was the annual population of Colombia. The covariates were the decade and vaccination coverage. Incidence rate ratios (IRRs) and percentage change per decade (1 − IRR) were constructed by comparing the period 1979–1988 (the first stage of PAI development) with subsequent decades. Data processing and analysis were conducted in Power BI (Microsoft), Excel (Microsoft), and Stata version 14 (StataCorp, College Station, TX, USA).

This study was approved by the Bioethics Committee of the National School of Public Health of the University of Antioquia (session 204 of February 1, 2019, Code 021-2019).

Results

During 40 years (1979–2018), 12,201 deaths from vaccine-preventable diseases in Colombia were included in this study: 92.4% of deaths were attributable to measles (28.2%), pertussis (24.9%), and neonatal (15.6%) and other tetanus (23.7%; Fig. 1).

The number of deaths and the adjusted mortality rates have decreased since 1989 in all selected diseases. Specific mortality rates were higher in the under 15 years old age group (Table B1. Appendix B. Supplementary data). Vaccination coverage has increased since 1982, with annual fluctuations since that year (Fig. 2).

A decrease in mortality was observed (IRR <1) when compared with the 1979–1988 decade. The decrease was close to 100% in measles (1999–2008 IRR: 0.0000; and 2009–2018 IRR: 0.0002). For polio, the decrease in mortality was 100% in the decade 1999–2008 (IRR: 0.00) and 2009–2018 (IRR: 0.00). In neonatal tetanus, a 99% decrease was achieved (IRR: 0.01, 95% confidence interval [CI] 0.005–0.03), and in diphtheria, a decrease of 97% was achieved during 2009–2018 (IRR: 0.03, 95% CI 0.01–0.13). The IRR had less reduction in the last decade analyzed in congenital rubella, mumps, other tetanus, and pertussis. Mortality increased with diphtheria-tetanus-pertussis (DTP) vaccination coverage below 90%, with 194% in diphtheria (IRR: 2.94, 95% CI: 1.10–7.84), 120% in measles (IRR: 2.20, 95% CI: 0.48–10.02), 116% in mumps (IRR: 2.16, 95% CI: 0.25–18.89), 79% in neonatal tetanus (IRR: 1.79, 95% CI: 1.05–3.04), and 74% in pertussis (IRR: 1.74, 95% CI: 0.94–3.23; Table 1).

Table 1
IRRs for the eight underlying causes of death by decade, percentage of vaccination coverage, and 10-year percentage changes, Colombia, 1979–2018.

Underlying cause of death	Period (decade) vaccination coverage	IRR (95% CI)	Percentage change in mortality (95% CI)
Diphtheria	1979–1988	Reference	
	1989–1998	**0.22 (0.12–0.41)**	−78 (−88 to −59)
	1999–2008	**0.07 (0.03–0.17)**	−93 (−97 to −83)
	2009–2018	**0.03 (0.01–0.13)**	−97 (−99 to −87)
	DTP coverage ≥90%	Reference	
	DTP coverage <90%	**2.94 (1.10–7.84)**	194 (10–684)
Pertussis	1979–1988	Reference	
	1989–1998	**0.12 (0.07–0.20)**	−88 (−93 to −80)
	1999–2008	**0.07 (0.04–0.13)**	−93 (−96 to −87)
	2009–2018	**0.07 (0.03–0.16)**	−93 (−97 to −84)
	DTP coverage ≥90%	Reference	
	DTP coverage <90%	1.74 (0.94–3.23)	74 (−6 to 223)
Neonatal tetanus	1979–1988	Reference	
	1989–1998	**0.18 (0.12–0.26)**	−82 (−88 to −74)
	1999–2008	**0.04 (0.02–0.07)**	−96 (−98 to −93)
	2009–2018	**0.01 (0.005–0.03)**	−99 (−99.5 to −97)
	DTP coverage ≥90%	Reference	
	DTP coverage <90%	**1.79 (1.05–3.04)**	79 (5–204)
Other tetanus	1979–1988	Reference	
	1989–1998	**0.24 (0.18–0.33)**	−76 (−82 to −67)
	1999–2008	**0.15 (0.10–0.21)**	−85 (−90 to −79)
	2009–2018	**0.07 (0.05–0.11)**	−93 (−95 to −89)
	DTP coverage ≥90%	Reference	
	DTP coverage <90%	1.26 (0.92–1.72)	26 (−8 to 72)
Measles	1979–1988	Reference	
	1989–1998	**0.11 (0.04–0.31)**	−89 (−96 to −69)
	1999–2008[a]	0.00	−100
	2009–2018	**0.0002 (0.00002–0.002)**	−99.98 (−99.998 to −99.8)
	MMR coverage ≥90%	Reference	
	MMR coverage <90%	2.20 (0.48–10.02)	120 (−52 to 902)
Congenital rubella	1979–1988	Reference	
	1989–1998	1.09 (0.70–1.72)	9 (−30 to 72)
	1999–2008	**0.19 (0.10–0.36)**	−81 (−90 to −64)
	2009–2018	**0.14 (0.07–0.26)**	−86 (−93 to −74)
	MMR coverage ≥90%	Reference	
	MMR coverage <90%	0.88 (0.53–1.48)	−12 (−47 to 48)
Mumps	1979–1988	Reference	
	1989–1998	**0.10 (0.03–0.36)**	−90 (−97 to −64)
	1999–2008	**0.09 (0.02–0.31)**	−91 (−98 to −69)
	2009–2018	**0.11 (0.04–0.29)**	−89 (−96 to −71)
	MMR coverage ≥90%	Reference	
	MMR coverage <90%	2.16 (0.25–18.89)	116 (−75 to 1.789)
Poliomyelitis	1979–1988	Reference	
	1989–1998	**0.01 (0.0002–0.14)**	−99 (−99.98 to −86)
	1999–2008[a]	0.00	−100
	2009–2018[a]	0.00	−100
	Polio coverage ≥90%	Reference	
	Polio coverage <90%	1.4 (0.001–1.11)	−96 (−99.9 to 11)

CI, confidence interval; DTP, diphtheria-tetanus-pertussis vaccine; IRR, incident rate ratio; MMR, measles-mumps-rubella vaccine.
Significant 95% CIs in bold.
[a] CI is not calculated.

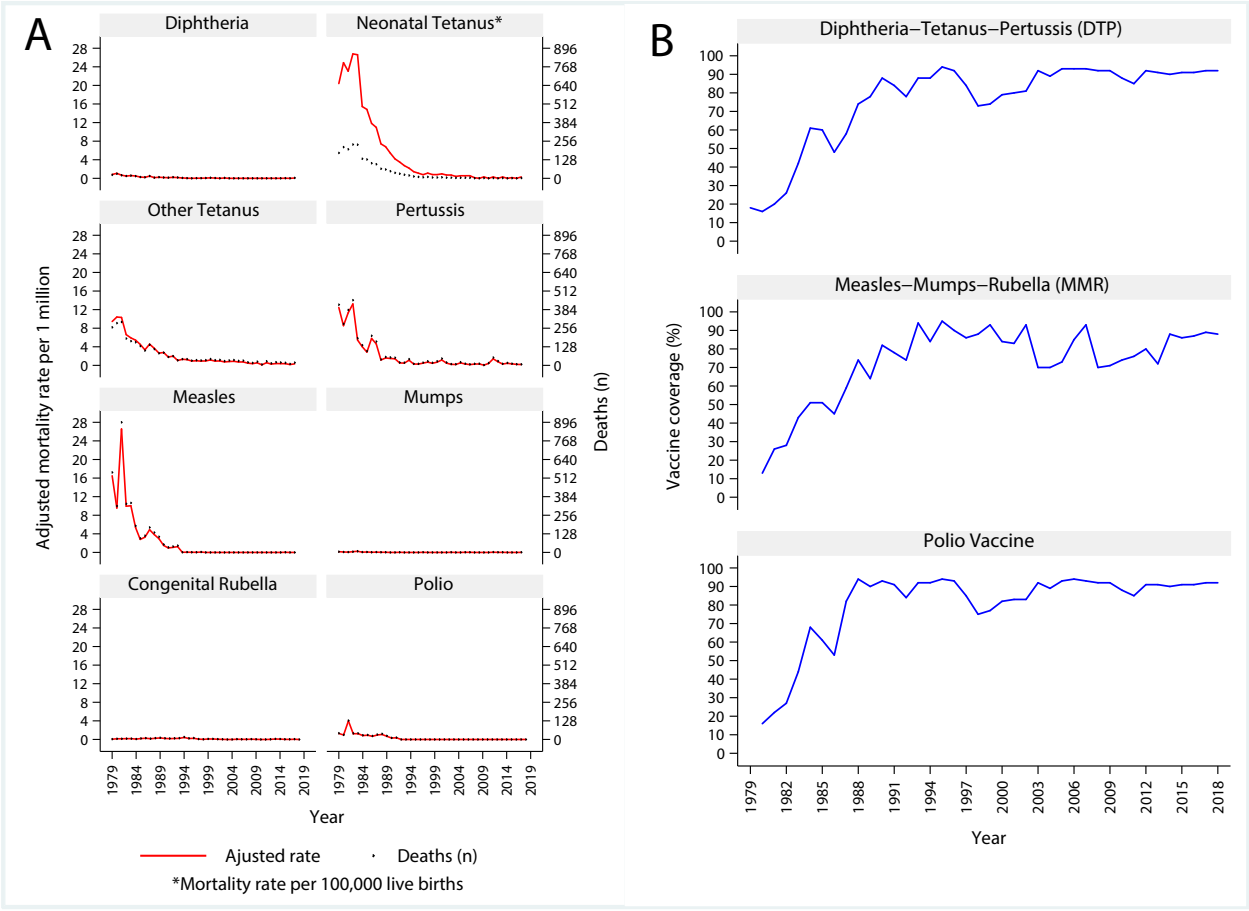

Fig. 2. (A) Number of deaths and age-adjusted rates per 1,000,000 inhabitants. (B) Percentage vaccination coverage with diphtheria-tetanus-pertussis (DTP), measles-mumps-rubella (MMR) and polio vaccine, Colombia, 1979–2018.

Discussion

This work presents the evolution of the mortality of eight vaccine-preventable diseases according to the available historical data that support the development of the Expanded Program of Immunizations (PAI, Programa Ampliado de Inmunizaciones in Spanish) in Colombia. The benefits of vaccination and, probably, the changes in medical care for these diseases are highlighted, where necessary, to consider the inequalities (of both interventions) between urban and rural areas of the country. Narváez pointed out in 2017[13] that vaccination coverage in Colombia is heterogeneous, with uneven distribution within the country that is related to poverty, access to health services, and ethnic inequalities. McGovern stated in 2015[14] that there is a relationship between vaccination coverage and infant mortality. This work quantified an increase in mortality from diphtheria and neonatal tetanus when vaccination coverage (DTP) was less than 90%.

Neonatal tetanus is considered a tracer disease for mortality monitoring by public health authorities and the Colombian EPI. It agrees with the WHO in that incidence and, particularly, mortality from this disease constitute a "triple failure" of the health system: failure of the routine vaccination program, prenatal control, and "clean" delivery and umbilical cord care practices.[15]

Pertussis is a disease that requires monitoring of mortality in urban and rural areas of Colombia. Liu estimated the number of deaths in children (aged 1 year and 59 months) between 2000 and 2015 in Colombia and found a decrease in neonatal tetanus and measles cases and an increase in deaths from pertussis since 2012.[16] Carrasquilla[17] found a decrease in mortality in children under 1 year of age after the introduction of maternal vaccination for tetanus, diphtheria, and pertussis in Bogotá (Colombia) in 2014. It is considered necessary to verify the frequency of hospitalization and mortality due to pertussis in children under 2 months of age to complement the measurement of the impact of maternal vaccination with tetanus, diphtheria, and pertussis.

Robertson[18] explored the indirect effects of the COVID-19 pandemic through its interruption of neonatal care activities and vaccination in the population of poor countries. For Colombia, this author modeled a hypothetical reduction in umbilical cord care and in DTP and measles vaccination coverage, which is an alert for possible increased incidence and mortality from neonatal tetanus, measles, and pertussis due to the pandemic. Salazar[19] recently described "the rapid increase in violence, poverty and inequity" and threats to ecosystems (forests and badlands) in Colombia. The deterioration of social conditions, environmental conditions, the peace process, and the COVID-19 pandemic are conditions that may increase vaccine-preventable mortality (described in this work).

The main strength of this work is in the systematization of vaccine-preventable disease mortality (over 40 years), an otherwise scattered chapter in Colombian health information.

The increase in mortality with vaccination coverage below 90% was not observed in polio and congenital rubella. This finding, apparently paradoxical, is related to the low frequency of deaths recorded in Colombia for these two diseases in the last 19 years. The global polio eradication initiative[20] has had an impact primarily on reducing the endemic transmission of wild poliovirus cases, with reducing mortality being an indirect effect of vaccination, although this requires

further studies.[21] Particularly in Colombia, since 1992, there have been no deaths from acute and paralytic polio in the country, possibly related to the intensive use of different immunization and epidemiological surveillance strategies since 1980 and the certification that indigenous circulation of the wild poliovirus was interrupted in 1994 in the Region of the Americas, including Colombia.[22] This historical circumstance guided our work with this disease. In this sense, we only included the *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, Tenth Revision,* codes (acute and paralytic polio) and excluded the sequelae of poliomyelitis. This proposed analysis coincides with the work of Roush.[2]

This work also has important limitations, and its results need to be expanded. The quality of data on the underlying cause of death (medical certification) from diseases in the process of elimination may not be accurate.[12] It is prudent to expand and present the results from a local or regional perspective, including municipal vaccination coverage and the potential relationship between socioeconomic variables and mortality from these diseases in Colombian populations (urban and rural).

In Colombia, it is necessary to promote the integration of the experience of elimination of polio, measles, and rubella to reduce mortality from mumps and congenital rubella syndrome.[23] This integration could also include the diseases prevented with the DTP vaccine, with the experience of the elimination of neonatal tetanus to support the prevention of illness and death from tetanus and pertussis in adults.

Conclusions

Mortality attributable to the selected vaccine-preventable diseases has decreased in Colombia in the last 40 years. This reduction is evidence of the benefits of the country's PAI. Monitoring mortality and its relationship with vaccination coverage allow disease elimination and control monitoring. Additional efforts are necessary to increase and sustain vaccination coverage, avoid the loss of achievements in the elimination of the diseases studied, and must be done while meeting the expectation of having zero deaths from vaccine-preventable diseases.

Author statements

Ethical approval

This study was approved by the Bioethics Committee of the National School of Public Health of the University of Antioquia (session 204 of February 1, 2019, Code 021-2019).

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Competing interests

The authors have no conflicts of interest related to this article.

Authors' contributions

C.A. and J.O. designed the study and obtained the data. C.A. and A.L. carried out all calculations with the supervision of J.O. and D.H. All authors drafted the article, provided methodological input, interpreted the results, critically revised the article, and have approved the final version for publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.09.020.

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Review Paper

Impacts of COVID-19 pandemic on preterm birth: a systematic review and meta-analysis

X.D. Yao [a, c], L.J. Zhu [a, c], J. Yin [b, **], J. Wen [a, *]

[a] Nanjing Maternity and Child Health Care Institute, Women's Hospital of Nanjing Medical University, Nanjing Maternity and Child Health Care Hospital, Nanjing, China
[b] Department of Neonatology, Women's Hospital of Nanjing Medical University, Nanjing Maternity and Child Health Care Hospital, Nanjing, China

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ABSTRACT

Objectives: The COVID-19 pandemic has significantly affected healthcare systems and daily well-being. However, the reports of the indirect impacts of the pandemic on preterm birth remain conflicting. We performed a meta-analysis to examine whether the pandemic altered the risk of preterm birth.
Study design: This was a systematic review and meta-analysis of the previous literature.
Methods: We searched MEDLINE and Embase databases until March 2022 using appropriate keywords and extracted 63 eligible studies that compared preterm between the COVID-19 pandemic period and the prepandemic period. A random effects model was used to obtain the pooled odds of each outcome. The study protocol was registered with PROSPERO (No. CRD42022326717).
Results: The search identified 3827 studies, of which 63 reports were included. A total of 3,220,370 pregnancies during the COVID-19 pandemic period and 6,122,615 pregnancies during the prepandemic period were studied. Compared with the prepandemic period, we identified a significant decreased odds of preterm birth (PTB; <37 weeks' gestation; pooled odds ratio [OR; 95% confidence interval (CI)] = 0.96 [0.94, 0.98]; $I^2 = 78.7\%$; 62 studies) and extremely PTB (<28 weeks' gestation; pooled OR [95% CI] = 0.92 [0.87, 0.97]; $I^2 = 26.4\%$; 25 studies) during the pandemic, whereas there was only a borderline significant reduction in the odds of very PTB (<32 weeks' gestation; pooled OR [95% CI] = 0.93 [0.86, 1.01]; $I^2 = 90.1\%$; 33 studies) between the two periods. There was significant publication bias for PTB.
Conclusion: Pooled results suggested the COVID-19 pandemic was associated with preterm birth, although there was only a borderline significant reduction for very PTB during the pandemic compared with the prepandemic period. Large studies showed conflicting results, and further research on whether the change is related to pandemic mitigation measures was warranted.

Introduction

The COVID-19 pandemic has resulted in substantial morbidity and mortality and also created a profound impact on healthcare systems, social functioning, and daily well-being.[1,2] To restrict the spread of the disease, countries imposed national or regional lockdowns, which consisted of multiple restrictions measures, including stay-at-home orders, working at home, healthcare disruption, and school or shop closure except for emergency services.[3,4] The widespread lockdown is unprecedented, and the impact on human physical and mental health is not fully understood.[5]

Previous studies have found that the COVID-19 pandemic may have influenced obstetric interventions and birth outcomes due to the disruption of maternal and neonatal health services and massive stress from psychosocial and economic consequences of the pandemic.[6,7] Most attention has been paid to the impact of the pandemic on preterm birth (PTB), but with inconsistent results and insufficient analysis. Reductions in PTB rates during the COVID-19 pandemic compared with before the pandemic have been reported in many countries, such as Australia,[8] the United States,[9–12] Israel,[13,14] England,[15] Denmark, and Ireland,[16,17] whereas studies in China, the Netherlands, and Spain have not found such changes.[18–20] Vaccaro et al.[21] reported no difference in the risk of PTB (<37 weeks' gestation) during the pandemic compared with

* Corresponding author.
** Corresponding author.
E-mail addresses: yinjing826@126.com (J. Yin), wenj2010@139.com (J. Wen).
[c] These authors contributed equally to this work.

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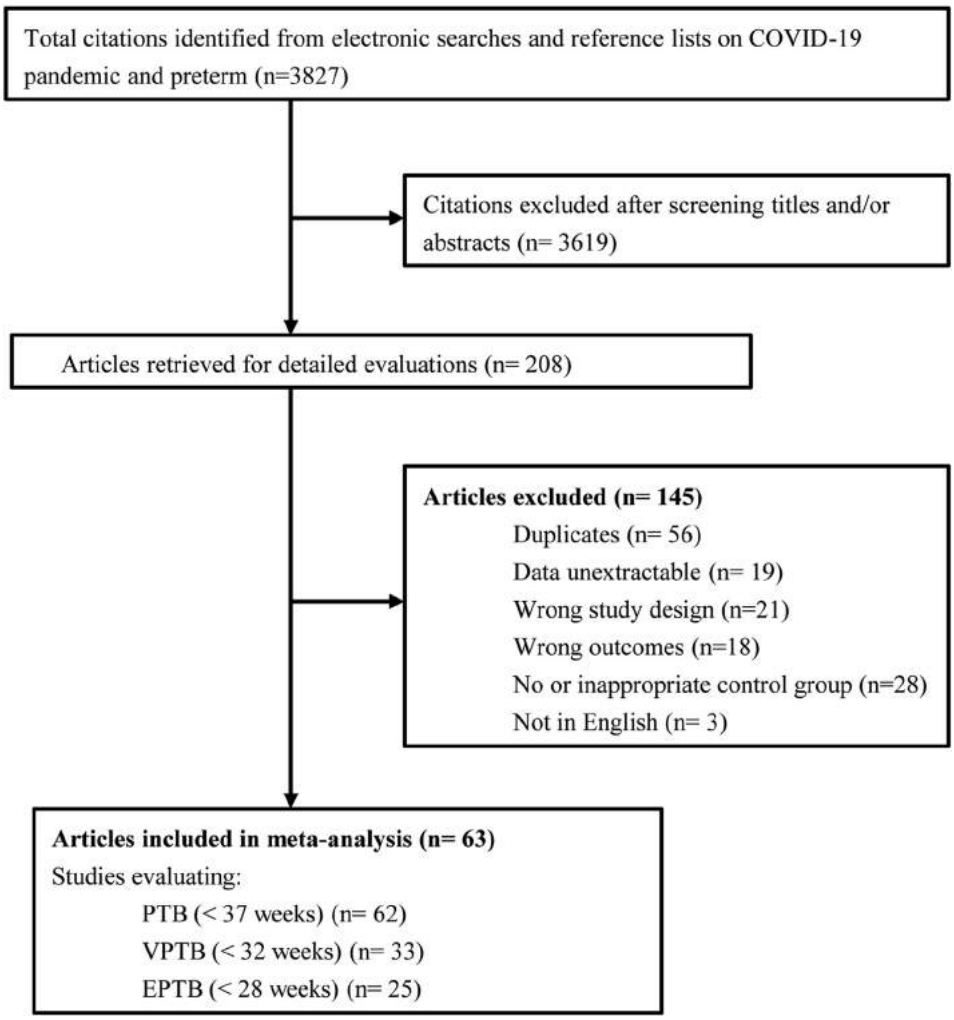

Fig. 1. Flowchart of study selection.

the prepandemic period based on a rapid review of 13 studies. In other studies, preterm was not significantly changed overall but was decreased in high-income countries,[22] and Yang et al.[23] only found a significantly reduced risk in the data from unadjusted estimates and single-center studies. However, the indirect effect of the COVID-19 pandemic on PTB may be affected by more confounding factors, such as sample size, countries, study population, comparative period (seasonality), and study quality. A comprehensive and thorough study with further subgroup analysis for these factors is needed to assess the association between the pandemic and preterm.

Given the inconsistent conclusions from previous studies, the meta-analysis of these articles was conducted to estimate the impact of the global COVID-19 pandemic on PTB and further assess the confounding factors' effects by subgroup analysis.

Methods

We conducted a meta-analysis of previous studies to determine the effects of the COVID-19 pandemic on preterm delivery. This review was performed according to the Preferred Reporting Items in Systematic Reviews and Meta-analyses (PRISMA) guidelines.[24] The study protocol was registered with PROSPERO (No. CRD42022326717).

Sources: Search strategy and selection criteria

We electronically retrieved MEDLINE and Embase databases up to March 2022 for relevant articles. The following terms were used in the search: "preterm" or "premature" or "PTB" in combination with "2019-nCoV" or "COVID-19" or "SARS-COV-2". Studies were included if (1) PTB was compared between the pandemic period vs the prepandemic period; (2) effect size (odds ratios [ORs] or risk ratios [RRs]) with 95% confidence interval (CI) was provided or could be calculated; (3) published in English. We excluded studies that were case reports or not published as full reports; studies with wrong study design (women with SARS-COV-2 infection were not excluded or the outcomes were not compared in general populations) or without control subjects (only reports on the rate of preterm during the pandemic) or with inappropriate comparison groups; studies of only SARS-COV-2 infected women.

Quality assessment

Sixty-three eligible studies included in this study were scored according to the Newcastle–Ottawa Scale.[25] Quality assessment of these studies was based on three categories: selection, comparability, and outcomes. The studies with scores ranged from 0 to 9; those with a score of 0–3 were considered to have a high risk of

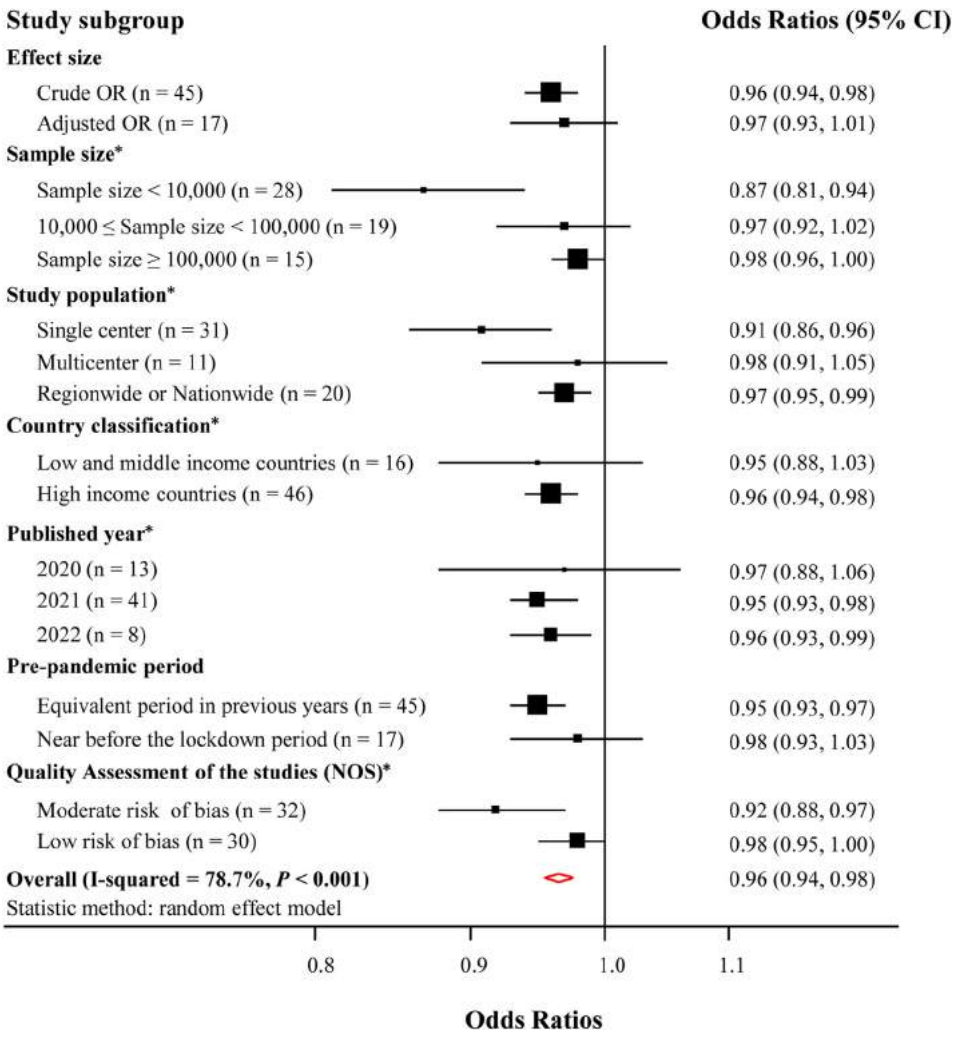

Fig. 2. Forest plot for odds of preterm birth <37 weeks' gestation (*Test for heterogeneity between subgroups [$P < 0.1$]).

bias, 4–6 had a moderate risk of bias, and 7–9 had a low risk of bias, respectively.

Statistical analyses

The following data were extracted: authors, publication date, study design, sample size, study population, pandemic period definition, prepandemic period definition, effect size, and other related information. For studies adopting multivariate logistic regression for adjustment of confounders, we extracted adjusted OR and 95% CI. Otherwise, we calculated OR and 95% CI based on the extracted data for unadjusted studies. The outcome of interest in this review was preterm. Furthermore, we calculated preterm birth (<37 weeks of gestation), very PTB (VPTB; <32 weeks of gestation), and extremely PTB (EPTB; <28 weeks of gestation) based on the clinician's best estimate of gestational age. A random effects model was used to obtain the pooled odds of each outcome. Statistical heterogeneity among studies was evaluated using the Chi-squared test, I^2 statistics, and *P* values. The small study effects were assessed by funnel plots, and asymmetry was assessed with Egger's test.[26]

We conducted a subgroup analysis for factors that could potentially affect the association between the pandemic and PTB: effect size (adjusted OR or crude OR), sample size (<10,000; 10,000–100,000; or ≥100,000), study population (single center, multicenter, or regionwide/nationwide), country classification (low-/middle-income or high-income country according to World Bank classifications), published year (2020, 2021, or 2022), prepandemic period definition (equivalent period in previous years or near before the lockdown period), and quality assessment of included studies (moderate or low risk of bias). In addition, we performed sensitivity analysis by omitting each study individually and recalculating the pooled effect size estimates for the remaining studies to assess the effect of individual studies on the pooled results. All statistical analyses were two sided and performed using STATA software (Version 11.0; Stata Corp; College Station; USA).

Results

Initially, 3827 studies were retrieved, and 63 previously published articles were eligible for inclusion with further screening.[1,3–5,7–20,27–71] There were 62 reports provided data on the odds of PTB during the pandemic compared with the prepandemic period, 33 reports included the odds of VPTB, and 25 studies included the data of EPTB (Fig. 1). Table S1 in the supplementary material shows the characteristics of included studies in the quantitative synthesis. All the studies used a historical cohort design. A total of 3,220,370 pregnancies during the COVID-19 pandemic period and 6,122,615 pregnancies during the prepandemic period were studied. Twenty-nine countries were

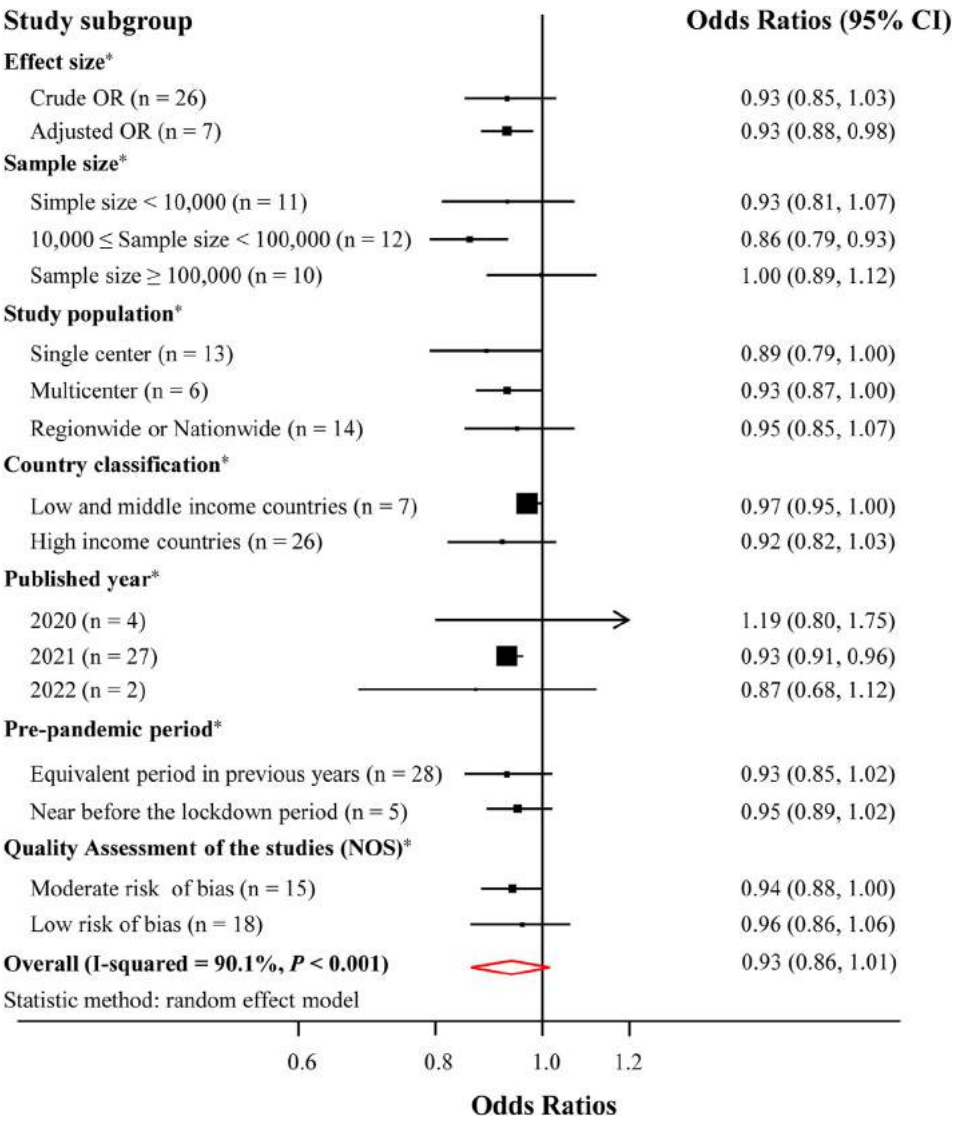

Fig. 3. Forest plot for odds of very preterm birth <32 weeks' gestation (*Test for heterogeneity between subgroups [$P < 0.1$]).

represented, with substantial variation in pandemic mitigation measures among countries. There were 31 reports from single-center studies, 12 multicenter studies, and 14 national registries, and the remaining six were regional reports. The duration of the "pandemic period" studied varied from 1 month to 15 months, and the duration of the "prepandemic period" studied varied from 2 months to 15 years. And the sample sizes varied from 81 to 2,219,914 pregnancies. The scores of quality assessments of the studies ranged from 5 to 9 (Table S2). There were 33 articles with moderate risk of bias and 30 articles with low risk of bias.

PTB (<37 weeks of gestation) was reported in 62 studies. There was a significant reduction in the rate of PTB during the pandemic period compared with the prepandemic period (pooled OR [95% CI] = 0.96 [0.94, 0.98], I^2 = 78.7%, 62 studies; Fig. 2). Test for heterogeneity among subgroups revealed significant differences besides effect size and prepandemic period ($P < 0.1$). VPTB (<32 weeks of gestation) was reported in 33 studies with varying gestational weeks thresholds and conflicting findings. There was a reduction in the odds of VPTB with a borderline significance (pooled OR [95% CI] = 0.93 [0.86, 1.01], I^2 = 90.1%, 33 studies; Fig. 3). Further heterogeneity test showed significant difference among subgroups ($P < 0.1$). Twenty-five studies reported EPTB (<28 weeks of gestation), which showed a significant decrease in EPTB (pooled OR [95% CI] = 0.92 [0.87, 0.97], I^2 = 26.4%, 25 studies; Fig. 4). Then subgroups analyses suggested that there was no heterogeneity ($P > 0.1$). Moreover, we found evidence of a small study effect for PTB (Egger's $P = 0.018$) but not for VPTB (Egger's $P = 0.235$) and EPTB (Egger's $P = 0.441$; Fig. 5).

In the sensitivity analysis, the pooled estimates of PTB and EPTB were not significantly changed when a study was omitted, suggesting that no one study had a large effect on the pooled estimate. However, for VPTB, when study conducted by Main et al. was omitted,[10] the pooled result became significant, and the heterogeneity became non-significant (pooled OR [95% CI] = 0.93 [0.90, 0.97], I^2 = 27.2%).

Discussion

The present meta-analysis aimed to investigate and systematically analyze the relationship between the COVID-19 pandemic and PTB. We specifically excluded articles that only reported outcomes of the pregnant population infected with COVID-19. The indirect impact of the COVID-19 lockdown on preterm was more noticed. The results showed the significant reduction in PTB and EPTB but

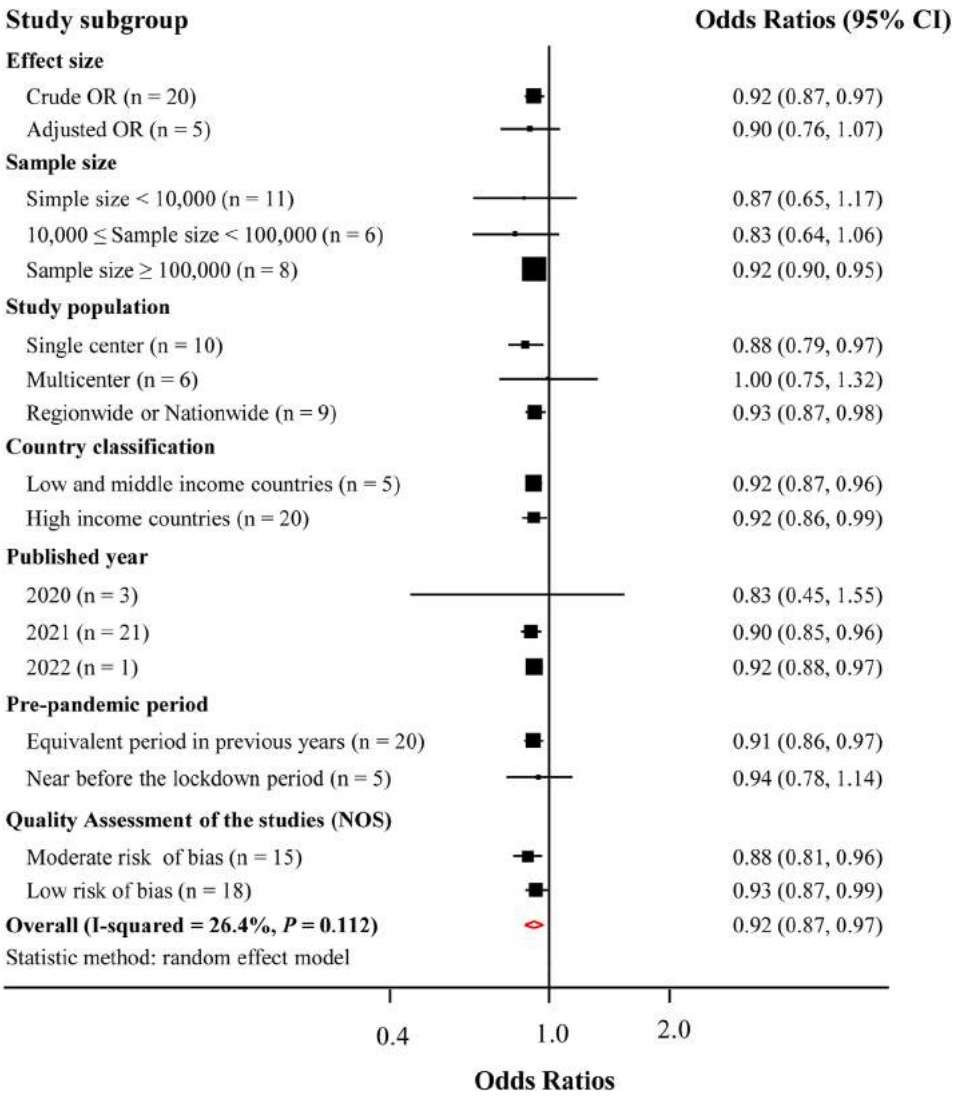

Fig. 4. Forest plot for odds of extremely preterm birth <28 weeks' gestation.

no difference in VPTB during the pandemic compared with before the pandemic.

In this meta-analysis, PTB was significantly decreased overall, but the previous meta-analysis reported by Chmielewska et al.,[22] Vaccaro et al.,[21] and Yang et al.[23] suggested no differences in pooled ORs. Further subgroups analysis, Chmielewska et al.[22] found PTB was decreased in high-income countries, and Yang et al.[23] found the reduction of PTB was only noted in unadjusted estimates and single-center studies. Moreover, they reported no reduction in unadjusted odds of PTB <34 weeks', <32 weeks', and <28 weeks' gestation. Inconsistency among conclusions from different studies and a lack of detailed evidence to inform the effects of the COVID-19 pandemic on VPTB and EPTB prompted us to conduct a more specifically quantitative synthesis.

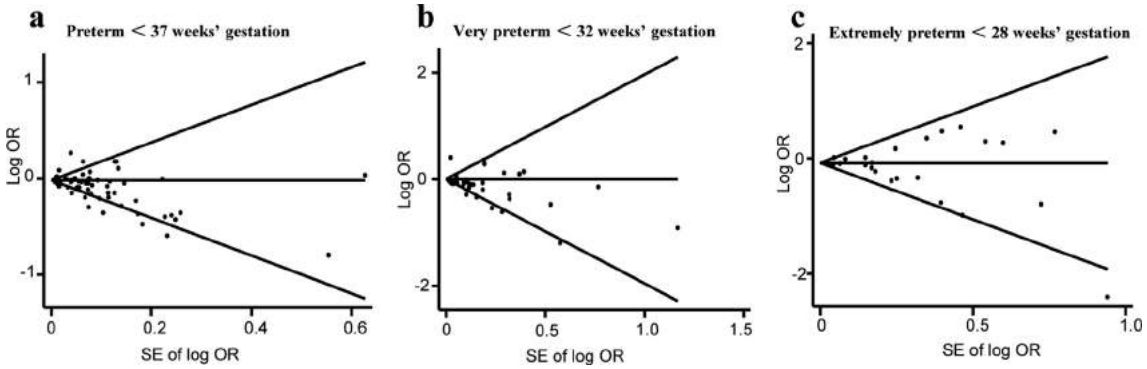

Fig. 5. Funnel plots for studies reporting on preterm birth.

We identified an overall reduction in the odds of PTB during the pandemic compared with before the pandemic. However, the further subgroup analysis showed there was no difference in PTB in specific subgroups, such as the data from adjusted odds, the studies from multicenter or low- and middle-income countries, and the prepandemic period defined as near before the lockdown. There could be several reasons for this conflict, such as the heterogeneity of the study populations, variation in sample sizes, lengths or definition of the pandemic and prepandemic periods, and the quality of studies. In addition, the significant statistical heterogeneity was also partly explained by the methodological heterogeneity of the studies and the variation in lockdown measures among countries based on the results of subgroup analysis.

The researchers have proposed that COVID-19–related lockdown may cause socioenvironmental and behavioral modifications, including maternal workload reduction, improved air quality, reduced maternal non-COVID-19–related infections, reductions in physical activity, and better nutritional support, thus playing a role in pregnancy prolongation and exert a beneficial impact on PTB.[3,5,30,40] On the other hand, several recent studies have shown that COVID-19 pandemic–related stressors and quarantine measures have exacerbated perinatal anxiety and depression.[72,73] Stress, worries, and anxieties during pregnancy are often associated with PTB.[74] Moreover, COVID-19 lockdown may result in a reduction in antenatal care and fetal surveillance. Therefore, the impact of the pandemic on PTB is a double-edged sword. And for the risk of VPTB, there was no overall difference during the pandemic, but analyses of adjusted odds and 10,000 $\leq$ sample size $\leq$ 100,000 studies only suggested VPTB might be reduced. Furthermore, we found the high heterogeneity disappeared for VPTB, and the risk of VPTB became significant reduction when the study of Main et al.[10] was omitted. The study reported the preterm change in the peak period of the COVID-19 outbreak in California compared with before the pandemic, which was conducted from April 2020 to July 2020 without any response measures or even masks in the period. Specific local political and epidemic circumstances may have contributed to the heterogeneity of the study. Although the previous meta-analysis showed there was no difference in PTB before 32 gestational weeks,[23] we conducted a larger number of subjects included in pooled analyses and found a significant change in EPTB.

The advantages of this review included the comprehensive search and synthesis of a broad range of articles for PTB. In addition, our meta-analysis included large populations from 29 countries, mainly arising from national or state or provincial data. We summarized the available global data on the impact of the COVID-19 pandemic on PTB. Nevertheless, this study had some limitations. There was the heterogeneity in methodology, study populations, and the definitions of the groups, leading to the limiting of the comparability of results. Also, we only included the impact of the pandemic on PTB for improving the precision of pooled estimates; more birth outcomes should be assessed.

PTB is a major determinant of neonatal mortality and morbidity with long-term adverse consequences during childhood and adulthood.[75,76] Further research needs more attention on whether changes in PTB are related to changes in health-related behaviors during the pandemic. There is also a need to assess the availability of maternal and newborn health services. Research in these areas will allow us to draw up plans and allocate resources effectively for immediate care after the pandemic and for future health system crises.

Conclusion

Our study suggested that the pandemic period was marked by an overall substantial decrease in PTB and EPTB. However, there was heterogeneity between the subgroups and publication bias in PTB. VPTB was not significantly changed overall but was decreased in studies with adjusted odds and 10,000 $\leq$ sample size $\leq$ 100,000. The results show the considerable disparity between countries. Further research was warranted to investigate if the change is related to pandemic mitigation measures.

Author statements

Ethical approval

None sought.

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Competing interests

None declared.

Authors' contributions

J.W. initiated, conceived, and supervised the study. X.Y., L.Z., and J.Y. did data collection and performed the data analysis. All authors approved the final format of the submitted article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.10.015.

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Original Research

Longitudinal perspective on cryptocurrency trading and increased gambling problems: a 3 wave national survey study

A. Oksanen*, H. Hagfors, I. Vuorinen, I. Savolainen

Faculty of Social Sciences, Tampere University, Finland

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ABSTRACT

Objectives: Cryptocurrency trading has gained popularity over the last few years. Trading is facilitated by online platforms that enable 24/7 trading. Cryptocurrency trading is potentially attractive to gamblers, and it may increase their gambling problems. Furthermore, cryptocurrency trading might be a particularly harmful activity for those gambling offshore. We investigated whether cryptocurrency trading predicts excessive gambling over time. We also analyzed how cryptocurrency trading combined with offshore gambling is associated with excessive gambling.

Study design: This was a population-based longitudinal survey study.

Methods: We surveyed a sample of Finnish people aged 18–75 years (N = 1022, 51.27% male) at three time points in 6-month intervals: April 2021 (T1), October to November 2021 (T2), and April to May 2022 (T3). Of the original T1 respondents, 66.80% took part in T2 and T3. Outcome measure was excessive gambling using the Problem Gambling Severity Index, and the predictor was cryptocurrency trading. We adjusted models for onshore and offshore gambling online, excessive gaming (Internet Gaming Disorder Test), excessive internet use (Compulsive Internet Use Scale), excessive alcohol use (Alcohol Use Disorders Identification Test), and sociodemographic background factors. We used multilevel regression models to investigate within-person and between-person effects.

Results: Cryptocurrency trading has increased in popularity over time. Within-person changes in cryptocurrency trading predicted increased excessive gambling. Excessive gambling was also generally more common among cryptocurrency traders. The full model that was adjusted for the number of confounding factors showed that cryptocurrency trading had a within-person effect on excessive gambling. Of the confounding factors, offshore online gambling, excessive gaming, and excessive internet use had within-person effects on excessive gambling. Offshore and onshore online gamblers and excessive gamers showed more excessive gambling than others. Those participants who were both cryptocurrency traders and offshore gamblers showed significantly higher rate of excessive gambling than others.

Conclusions: Cryptocurrency trading is a risky activity and associated with a higher rate of excessive gambling over time. Such activity is especially risky among offshore online gamblers, who could view cryptocurrency trading as another form of gambling or as a way to make money for gambling. Policymakers and counselors should be aware of the risks of cryptocurrency trading.

Introduction

Cryptocurrency trading has received increasing attention over the past few years. Various global companies have created platforms that make cryptocurrency trading easily accessible and convenient. These services and platforms are currently widely marketed not only online but also at major sporting events.[1] For example, crypto.com became an official partner of Formula 1 in 2022. At the same time, 2022 has shown the volatility of cryptocurrency trading with the complete collapse of stablecoin TerraUSD in May.

Cryptocurrency trading is based on blockchain technology,[2] a distributed ledger that allows for real-time peer-to-peer operations, through which people can buy and sell virtual currencies any time of the day.[3] Bitcoin is the most well-known cryptocurrency, but thousands of cryptocurrencies are currently on the market.[4] Cryptocurrency trading has caused concerns among policymakers because of its risks, including high volatility, cybersecurity, and lack of regulation, which may be attractive to, for example, criminal groups.[5]

* Corresponding author. Faculty of Social Sciences, 33014, Tampere University, Tampere, Finland.
E-mail address: atte.oksanen@tuni.fi (A. Oksanen).

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The cryptocurrency market's high volatility, fast-paced environment, focus on short-term gains, and high risks are among factors that have led cryptocurrency trading to be considered an online gambling-like activity in academic literature.[3,6] Whereas previous research has shown that excessive day trading and stock market trading is related to problem gambling,[7–9] researchers have analyzed the associations and similarities of cryptotrading and gambling in fewer recent studies. Mills and Nower found that trading cryptocurrencies was strongly associated with excessive gambling.[6] Oksanen et al. found that cryptocurrency trading was associated with excessive gambling (i.e. gambling problems), excessive gaming, and excessive internet use.[9] Cryptocurrency traders are likely motivated by novelty and risk-seeking behavior and influenced by prior investing patterns.[10,11] However, longitudinal research is necessary to analyze cryptocurrency trading's potentially growing impact on gambling problems.

Previous studies have suggested that people found trading platforms while at home at the beginning of the COVID-19 pandemic in 2020.[12,13] At the same time, regular gambling activities were lacking due to lockdowns and the resultant lack of sporting events.[14] Gamblers might have moved to speculative trading markets at this point. According to a cross-national study, investing during COVID-19 increased the most in countries that produced more gambling opportunities.[15] It is equally likely that due to the COVID-19 pandemic, many gamblers moved to online gambling sites that did not suffer from lockdowns. It is therefore very important to analyze cryptocurrency trading in the context of online gambling in general.

The rapid rise of online gambling has made offshore gambling sites available to anyone interested.[16,17] Offshore gambling refers to operators who do not hold valid licenses in given jurisdictional areas but provide gambling services to customers in that area against the local restrictions, thus providing gamblers a way to circumvent these restrictions and conceal their gambling. In previous studies, offshore gambling has been associated with more severe gambling problems than gambling on licensed onshore sites.[16,17] Offshore gambling sites can be tempting for many, as they are often heavily advertised with high payout rates, benefits and bonuses, and the ability to use local currency.[17] At the same time, they pose a risk of excessive gambling with their almost unlimited selection of potentially high-risk gambling options with little regulation. Given the similarities between online gambling and cryptocurrency trading, cryptocurrency trading can serve as an attractive expansion of monetary activities for those engaged in offshore gambling. Moreover, cryptocurrency traders and offshore gamblers share similar demographic characteristics, such as being male and young.[3,6,9,18,19]

We investigated whether cryptocurrency trading predicts gambling problems over time. We were mostly interested in the changes over time within individuals (i.e. within-person change). This is the first longitudinal study to investigate the role of cryptocurrency trading in excessive gambling. Our research questions were the following:

1) Does cryptocurrency trading predict excessive gambling over time?
2) How is cryptocurrency trading combined with offshore gambling associated with excessive gambling?

Methods

Participants and procedure

This study is based on longitudinal *Gambling in the Digital Age* survey. We surveyed a sample of Finnish speakers in mainland Finland. They were aged 18–75 years ($N = 1022$; 51.27% male, 48.43% female, and 0.03% other gender). We collected the data at three points in 6-month intervals: April 2021 (T1), October–November 2021 (T2), and April–May 2022 (T3). Of the original T1 respondents, 66.80% took part in T2 and T3. The participants represented all areas of mainland Finland, and 36.30% were from the Helsinki-Uusimaa region, 20.25% from Southern Finland, 24.27% from Western Finland, and 19.18% from Northern and Eastern Finland.

Non-response analysis between those who responded at all three points ($N = 1022$) and the original T1 respondents ($N = 1530$) showed that the respondents in the final sample were, on average, older (49.50 years vs 46.67 years). No major dropout occurred based on gender, geographical area, income, education, marital status, or occupational status, but the mean rate of excessive gambling based on the Problem Gambling Severity Index (PGSI) was lower in the final sample than in T1 (1.15 vs 1.31). Considering that our sample in T1 included more gamblers than some estimations in the general population,[20] our final sample is closer to these estimations. The final data do not include any major biases, compared with the general population, based on population census figures by Statistics Finland.[21]

After each phase of data collection, we reviewed the data in accordance with the data quality protocol of the project that was stored on the Open Science Framework website before data collection. Integrity and quality checks on the data included attention checks, patterned-response checks, rapid-response checks, and nonsensical-response checks.[22,23] We also checked the open-ended comments that some of the participants gave after the survey to evaluate potentially biased motives to respond or other potential problems with the survey.

The Academic Ethics Committee of the Tampere region approved the study in March 2021. Participation was voluntary, and we informed the participants about the aims of the study. The study also complies with the European Code of Conduct for Research Integrity, the General Data Protection Regulation of European Union, and fundamental ethics principles, including those reflected in the Charter of Fundamental Rights of the European Union.

Measures

As the dependent variable for our study, we used the PGSI, which is a widely used general population screener for excessive gambling.[24–26] We asked respondents about their gambling problems during the previous 6 months (e.g. “Have you felt guilty about the way you gamble or what happens when you gamble?”). The response choices were 0 (*never*), 1 (*sometimes*), 2 (*most of the time*), and 3 (*almost always*). Higher PGSI scores indicate more severe excessive gambling. The scale had excellent internal consistency at all points, as measured with McDonald's omega (T1: $\omega = 0.94$, T2: $\omega = 0.93$, T3: $\omega = 0.94$).

Cryptocurrency trading was the main independent variable. We asked about cryptocurrency trading in a pattern of questions on activities taken place during the past 6 months. The question was, “How often have you traded in crypto markets (e.g., Binance, BitPanda)?” We created a dummy variable for those who had traded in crypto markets within the previous 6 months (0 = no, 1 = yes).

We measured onshore and offshore online gambling in a larger pattern about activities during the past 6 months. The question on onshore online gambling concerned the gambling monopoly Veikkaus site. Regarding offshore online gambling sites, we asked about “gambling in offshore online gambling sites (other than Veikkaus or Paf).” For both measures, we created dummy variables indicating those gambling in onshore and offshore online sites during the past 6 months (0 = no, 1 = yes).

As a measure for excessive gaming, we used the 10-item Internet Gaming Disorder Test,[27] which contains statements about excessive behaviors in gaming (e.g. “How often have you felt

restless, irritable, anxious and/or sad when you were unable to play or played less than usual?"). We were interested in the previous 6 months. Answer choices were 0 (*never*), 1 (*sometimes*), and 2 (*often*). Higher Internet Gaming Disorder Test scores indicated more severe excessive gaming. The scale had good internal consistency, ranging from good to excellent (T1: $\omega = 0.88$, T2: $\omega = 0.90$, T3: $\omega = 0.88$).

We used the Compulsive Internet Use Scale (CIUS) to measure excessive internet use.[28] The CIUS includes 14 items and has been widely used in studies on excessive, problematic, or addictive internet use.[29,30] Similar to other screeners of excessive behavior, it measures withdrawal, loss of control, continued use despite negative consequences, guilt, and negative comments from close ones (e.g. "do others (e.g., friends, parents, partner) say you should use the internet less?"). The participants responded on a scale from 0 (*never*) to 4 (*very often*). Higher CIUS scores indicate more severe excessive internet use. The scale had excellent internal consistency at all points (T1: $\omega = 0.95$, T2: $\omega = 0.95$, T3: $\omega = 0.95$).

To measure excessive alcohol use, we used the Alcohol Use Disorders Identification Test, which is a widely used three-item screener for excessive drinking.[31,32] The three items measure frequency of drinking, heavy drinking, and units per drinking occasion, and response options range from 0 to 4. Higher Alcohol Use Disorders Identification Test scores indicate a higher risk for excessive drinking. The scale showed good internal consistency at all points (T1: $\omega = 0.82$, T2: $\omega = 0.83$, T3: $\omega = 0.84$).

To measure psychological distress, we used the 5-item Mental Health Inventory, which is a short version of the original long inventory, and it includes items on mood, such as positive affect, emotional control, depression, and anxiety (e.g. "How much of the time, during the last month, have you felt downhearted and blue?").[33] The 5-item Mental Health Inventory is considered a valid screener of mood disorders in the general population.[34–36] Response options range from 1 (*none of the time*) to 6 (*all of the time*), and we reverse coded two of the items on positive affect. The measure had good internal consistency at all points (T1: $\omega = 0.89$, T2: $\omega = 0.88$, T3: $\omega = 0.87$).

Background information included sociodemographic variables that we treated as controls. We created a dummy variable for age, indicating 40 years or older (69.37%). For male gender, we created a dummy variable (51.27% of the participants). We grouped participants who chose "other" gender ($n = 3$) together with those who chose "female." We categorized education on the basis of having at least a science university degree (i.e. typically master's degree, 21.72%) and high income on the basis of at least 4000 euros income per month (17.03%). We also created a dummy variable for those married or in a registered relationship (59.78%) and for those who were working as employed, self-employed, or with scholarship (51.57%).

Statistical analyses

We conducted statistical analyses using Stata 17 software. We report short descriptive findings followed by the main analyses, focusing on the relationship between cryptocurrency trading and excessive gambling. The linear multilevel hybrid models had excessive gambling as a dependent variable, and we were mainly interested in cryptocurrency trading's effects on excessive gambling over time. Hybrid models allow for the estimation of within-person effects and between-person effects simultaneously in the same model, and they thus combined the strengths of random-effect and fixed-effect approaches and solved their shortcomings.[37,38] We ran these models with xthybrid command in Stata.[38] Within-person effects indicate how changes in time-variant independent variables are associated with changes in the time-variant dependent variable. Between-person variables show group differences between individuals.

The models also included several within-person and between-person control variables. For example, our model controlled for onshore and offshore online gambling and accounted for excessive drinking, gaming, and internet use and psychological distress. Adjustments of these factors gave us better grounds to claim that the main independent variable of interest has an effect on the dependent variable. As this is a longitudinal study, our main point of interest was only the within-person effect of cryptocurrency trading on excessive gambling. We report regression coefficients (B) and their standard errors, 95% confidence intervals (95% CIs), Z values, and *P*-values for statistical significance.

Our additional analyses focused on the interaction between cryptocurrency trading and onshore and offshore online gambling. We conducted these analyses using multilevel linear mixed-effects regression in Stata. This model had robust Huber-White standard errors and an unstructured covariance structure for random intercepts and slopes. We adjusted the model for the same control and sociodemographic variables as in the main hybrid models. We present plotted predictive margins in figure.

Results

In T1, 5.28% of the participants were trading cryptocurrencies. Cryptocurrency trading had increased in popularity over time, as in T2, 6.26% of participants were trading cryptocurrencies and 7.34% in T3 (see Table 1). The fixed-effects change of cryptocurrency trading over time was statistically significant between T1 and T3 ($P = 0.004$). Onshore and offshore online gambling did not increase from T1 to T3, and none of the changes over time were statistically significant.

We ran the first hybrid models including cryptocurrency trading as an independent variable and age and male gender as controls. The results show that cryptocurrency trading had a within-person effect (B = 1.22, 95% CI = 0.47, 1.97, Z = 3.17, $P = 0.002$) and a between-person effect (B = 3.32, 95% CI = 1.69, 4.94, Z = 3.99, $P < 0.001$) on excessive gambling. These results show that increases in cryptocurrency trading are associated with increases in PGSI scores for excessive gambling (within-person effect). Furthermore, cryptocurrency traders had higher average PGSI scores than those not trading cryptocurrencies (between-person effect).

Table 2 presents our full models. They show that after we adjusted a number of confounding factors, cryptocurrency trading's within-person effect on excessive gambling was statistically significant (B = 0.94, 95% CI = 0.35, 1.52, Z = 3.13, $P = 0.002$). Cryptocurrency trading's between-person effect was no longer statistically significant. This is explained by number of stronger between-person predictors. Regarding control variables, offshore online gambling and excessive gaming had within-person and between-person effects on excessive gambling. Excessive internet use had a within-person effect and onshore online gambling a between-person effect on excessive gambling.

The last part of our analysis focused on the potential role of offshore online gambling. We found out that among offshore gamblers, many traded cryptocurrencies, and the proportion increased over time. In T1, 19.08% of offshore gamblers traded cryptocurrencies; in T2, 24.49%; and in T3, 28.06%. Relatively few onshore gamblers traded cryptocurrencies: 7.09% in T1, 8.20% in T2, and 9.95% in T3. Our multilevel linear mixed-effect model focused on interactions of onshore and offshore online gambling with cryptocurrency trading. We found that offshore online gambling and cryptocurrency trading interacted, indicating that excessive gambling is particularly strong among cryptocurrency traders who gamble offshore (see Fig. 1).

Table 1
Descriptive statistics of main study variables.

Continuous variables	Range	T1, M (SD)	T2, M (SD)	T3, M (SD)	Zero order correlations at T1						
					1	2	3	4	5	6	7
1. Excessive gambling	0–25	1.15 (3.02)	1.12 (2.98)	1.11 (3.04)	1						
2. Excessive gaming	0–16	1.12 (2.36)	1.24 (2.52)	1.10 (2.28)	0.53***	1					
3. Excessive internet use	0–52	7.95 (9.06)	8.20 (9.65)	7.85 (9.31)	0.32***	0.49***	1				
4. Excessive drinking	0–12	3.54 (2.71)	3.46 (2.73)	3.42 (2.72)	0.17***	0.08*	0.03	1			
5. Distress	5–30	12.24 (4.67)	12.20 (4.58)	12.28 (4.43)	0.24***	0.31***	0.43***	0.07*	1		
Categorical variables	Coding	T1, % yes	T2, % yes	T3, % yes							
6. Cryptocurrency trading	0/1	5.28%	6.26%	7.34%	0.22***	0.21***	0.17***	0.0499	0.12***	1	
7. Onshore online gambling	0/1	63.50%	62.04%	61.94%	0.23***	0.11***	0.02	0.16***	0.03	0.11***	1
8. Offshore online gambling	0/1	14.87%	14.38%	13.60%	0.47***	0.26***	0.11***	0.21***	0.13***	0.26***	0.27***

Note. ***$P < 0.001$, *$P < 0.05$.

Discussion

We investigated whether cryptocurrency trading predicts excessive gambling over time. We also analyzed how cryptocurrency trading combined with offshore gambling is associated with excessive gambling. We found that cryptocurrency trading had increased its popularity a bit over time in our sample. Cryptocurrency trading had a robust within-person effect on excessive gambling in all our models. Considering that we adjusted our model for the number of confounding factors, cryptocurrency trading is likely increasing excessive gambling.

Previous studies have not included longitudinal data, but our results are in line with general notions produced by the previous research.[6,9] Cryptocurrency trading is a highly speculative activity, and major winnings promised by the sites are potentially attractive to users. Given the potential fast and large gains, high-risk cryptocurrency traders may make fast-paced transactions that do not nurture a growing investment over time but are instead similar to action-oriented gambling and characterized by chasing and feelings of rush.[6] It is also conceivable that options to use high leverage for trading are very attractive to those who already have existing gambling problems. Our results show that an increase over time in cryptocurrency trading is associated with increases in excessive gambling.

Our results also showed that offshore online gambling had strong within-person and between-person effects on excessive gambling, which shows that not only those who gamble offshore report stronger excessive gambling but the increase in offshore gambling over time is associated with an increase in excessive gambling. The potential harms of offshore gambling are currently widely discussed.[15,16] Our results provide new longitudinal evidence of the phenomenon and demonstrate that offshore online gambling is a more significant risk factor in excessive gambling than regulated onshore online gambling.

The combination of offshore gambling and cryptocurrency trading was clearly associated with more severe gambling problems in our results. We believe this result is important as cryptocurrency traders are likely attracted to offshore online gambling sites and offshore online gamblers to cryptocurrency trading activities. Some online operators even take bets on cryptocurrencies, which may encourage gamblers to explore new forms of cryptocurrency trading. These types of expanded gambling and trading opportunities highlight the shortcomings of online gambling operators to provide a certain level of safety for their users and ways

Table 2
Hybrid models showing within-person and between-person effects on excessive gambling.

	Full model				
	B	SE (B)	95% CI	Z	*P*
Within-person effects					
Cryptocurrency trading	0.94	0.30	0.35 to 1.52	3.13	0.002
Onshore online gambling	0.04	0.08	−0.12 to 0.20	0.49	0.625
Offshore online gambling	0.65	0.20	0.26 to 1.05	3.24	0.001
Excessive gaming	0.27	0.05	0.17 to 0.37	5.36	<0.001
Excessive internet use	0.05	0.01	0.03 to 0.07	4.49	<0.001
Excessive drinking	0.08	0.04	−0.01 to 0.16	1.83	0.067
Distress	0.00	0.01	−0.02 to 0.02	0.05	0.961
Between-person effects					
Cryptocurrency trading	0.32	0.50	−0.67 to 1.30	0.64	0.525
Onshore gambling online	0.51	0.11	0.30 to 0.72	4.80	<0.001
Offshore gambling online	3.49	0.44	2.62 to 4.36	7.84	<0.001
Excessive gaming	0.51	0.08	0.35 to 0.67	6.35	<0.001
Excessive internet use	0.02	0.01	−0.01 to 0.05	1.37	0.170
Excessive drinking	0.05	0.03	−0.01 to 0.11	1.65	0.100
Distress	0.02	0.02	−0.01 to 0.06	1.26	0.208
Controls					
Age ≥40 years	0.53	0.18	0.18 to 0.88	2.97	0.003
Male	−0.26	0.14	−0.53 to 0.02	−1.83	0.067
University degree	−0.15	0.13	−0.40 to 0.11	−1.12	0.261
High income	−0.09	0.19	−0.46 to 0.27	−0.49	0.626
In official relationship	−0.10	0.14	−0.38 to 0.18	−0.69	0.491
Working	−0.05	0.13	−0.31 to 0.20	−0.40	0.690

CI, confidence interval.

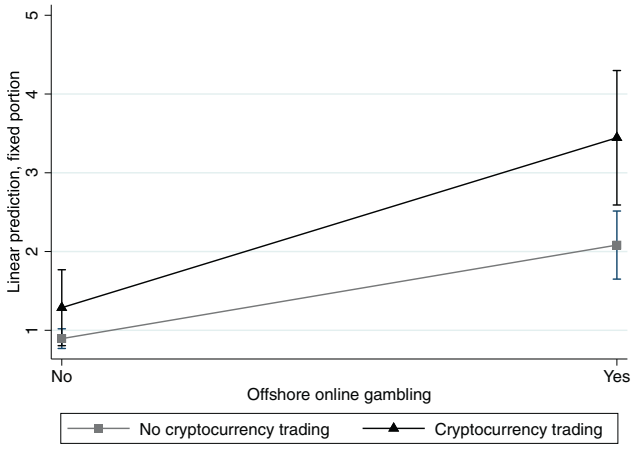

Fig. 1. Excessive gambling among those who trade cryptocurrencies and gamble offshore.

to moderate their gambling, and call for safer gambling and consumer protection practices.[39] There are also indications that as the marketing of traditional gambling has been banned in professional sports, the advertising of cryptocurrency trading and financial trading apps has increased.[1] As the online environment makes it easier to become involved in various types of risky behaviors and conceal them from others, it is possible that the occurrence of more severe gambling and other problems also increases. These trends involving offshore online gambling and cryptocurrency trading should be researched and monitored closely in future as they represent a fast-changing area and, as such, a challenge for legislators and policymakers to keep up with.

Limitations and strengths

We limited this study to participants from Finland, so future researchers could investigate the observed associations in cross-cultural contexts. Our study is also limited by self-reported measures, as the results were based on the participants' perceptions and evaluation of themselves. Similarly, as participation was voluntary, it may have been influenced by participants' personal interest in the topic. The study's strengths include longitudinal sample and low dropout rate. This is also the first longitudinal study to investigate cryptocurrency trading's effect on excessive gambling.

Conclusion

The results of this three-wave longitudinal study show that cryptocurrency trading predicts excessive gambling. Cryptocurrency trading combined with offshore online gambling was associated with more severe excessive gambling. Our results imply that cryptocurrency trading should be considered a very risky activity for online gamblers. Cryptocurrency trading itself is highly speculative activity, but it is marketed aggressively to consumers despite the risks. Existing problems with gambling are likely to increase with cryptocurrency trading. Policymakers and councilors should be aware of the risks of cryptocurrency trading.

Author statements

Ethical approval

The local academic ethics committee approved the study in March 2021. Participation was voluntary, and we informed the participants about the aims of the study. The study also complies with the European Code of Conduct for Research Integrity, the General Data Protection Regulation of European Union, and fundamental ethics principles, including those reflected in the Charter of Fundamental Rights of the European Union.

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Competing interests

None of the authors have a conflict of interest to declare.

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Original Research

National long COVID impact and risk factors

J. Baruch [a, b, *, c], C. Zahra [a, c], T. Cardona [a], T. Melillo [a]

[a] Infectious Disease Prevention & Control Unit, Ministry for Health, Pieta, Malta
[b] European Programme for Intervention Epidemiology Training, European Centre for Disease Prevention and Control, Solna, Sweden

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ABSTRACT

Objective: Our objective was to estimate the prevalence and risk factors for long COVID symptoms among polymerase chain reaction–confirmed COVID-19 patients (hospitalised and community) in Malta.
Study design: This was a national cross-sectional survey among COVID-19 patients in Malta during 2020.
Methods: Patients were sent a questionnaire 3–6 months after testing positive. Data were analysed descriptively to estimate symptom prevalence, and multivariable logistic regressions were used to determine the risk factors for long COVID symptoms. Age, sex, initial symptoms, hospitalisation, and healthcare worker status were used as risk factors and symptoms (cough, shortness of breath, fatigue, anxiety, sadness, and memory loss) 2.5 months or more after COVID-19 onset were used as outcomes.
Results: Of 8446 eligible participants, 2665 (31.55%) responded with a median age of 37 years. Initial symptoms were reported in 82% of responders, and 7.73% were hospitalised. Among the long COVID symptoms, fatigue persisted among most non-hospitalised responders, whereas anxiety, shortness of breath, and sadness were the most common symptoms. Female sex, hospitalisation, and initial symptoms were associated with higher odds of fatigue, shortness of breath, cough, anxiety, sadness, and memory loss as long COVID symptoms.
Conclusions: Our study is the first to highlight long COVID symptoms and risk factors in Malta, showing that long COVID is common among hospitalised and non-hospitalised patients. These data should increase awareness of long COVID and facilitate support to those affected nationally.

Introduction

Long COVID has been defined in several ways. Recently, the World Health Organization used the Delphi method to agree on a definition.[1] Observations from various studies have indicated a significant variation in reported symptoms ranging from fatigue, dyspnoea, joint pains, chest pain, headaches, hair loss and changes in hearing with or without tinnitus to psychological disorders such as memory loss, anxiety, depression, disorders of sleep and concentration and attention disorders.[2]

However, the extent of the impact of long COVID in Malta is still unknown, and a better understanding of these long-term effects could aid in policymaking and resource allocation. Our objective was to estimate the prevalence and risk factors for long COVID symptoms and complications among polymerase chain reaction (PCR)-confirmed COVID-19 patients in Malta.

Methods

Study design

A cross-sectional survey was carried out using an online self-administered questionnaire via a Google form. Demographics, COVID-19-episode information (e.g. symptoms experienced, hospitalisation) and long COVID symptoms persisting for more than 2.5 months after the COVID-19 episode (Supplementary Table 1).

Participants

Participants were eligible if they had tested PCR positive for SARS-CoV-2 in Malta during 2020, had COVID-19 only once, had a registered working email address and were not asylum seekers/refugees or deceased. The questionnaire was sent to 8446 eligible participants 3–6 months after their positive PCR test result. A second email was sent after 2.5 weeks. In addition, based on the government definition (personal communication), two waves were defined in our study: wave 1, from 6 March 2020 to 17 July 2020; and wave 2, from 18 July to 31 December 2020.

* Corresponding author. Infectious Disease Prevention & Control Unit, Ministry for Health, Pieta, Malta.
E-mail address: joaquin.baruch@gov.mt (J. Baruch).
[c] Authors contributed equally.

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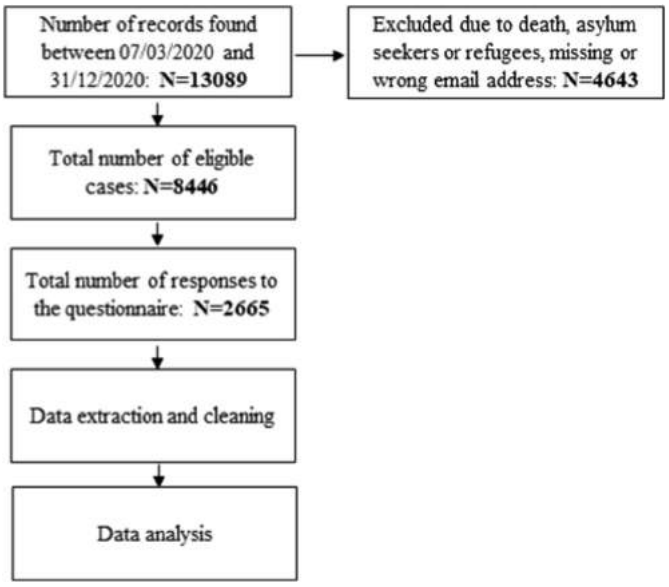

Fig. 1. Flowchart of inclusion and exclusion criteria of a national survey of long COVID in Malta.

Data analysis

Data were analysed descriptively to estimate symptom prevalence. Although no preselection strategy was used to adjust for response bias, the respondents' age, gender and hospitalisation during the first and second waves were compared among all cases testing positive in Malta, those eligible to participate and the study responders. Specifically, the proportion of patients in each demographic group was compared descriptively to the sampling frame to assess potential data gaps or overrepresentation. Logistic regression was used to determine the risk factors for long COVID symptoms. Age, sex, wave number, healthcare worker status, initial symptoms, and hospitalisation due to COVID-19 were used as covariates. Symptoms persisting for more than 2.5 months from the COVID-19 episode were modelled as a dichotomous outcome on each model. Six models were fitted using the following outcomes: fatigue, shortness of breath, cough, anxiety, sadness and memory loss. All analyses were performed using R studio (R version: R 4.1.2)[11].

Results

Response rate

There were 13,089 COVID-19 cases recorded during 2020 in Malta. Of these, 4643 records were excluded, and 2665 replies were received (response rate = 31.55%; Fig. 1).

Description of the data

The median age was 37 years (interquartile range = 21 years), 56% were female, and 7.73% of the responders had been hospitalised during their initial COVID-19 episode. Supplementary Table 1 compares the characteristics (age, gender, wave, and hospitalisation) of all cases in 2020, the eligible participants, and those who responded to our questionnaire. Most characteristics were observed to be similarly represented in the three groups, signifying minimal selection and response bias.

Symptoms reported after isolation discharge from public health

The most common long COVID symptoms affecting more than 10% of respondents were anxiety, fatigue, and feeling of sadness (Supplementary Table 2). One in four patients (25.4%) persisted with at least one long COVID symptom, whereas 28.7% and 14.0% reported at least three or more and five or more long COVID symptoms, respectively. These numbers were higher among patients initially hospitalised: 44.2% reported at least one symptom a month after discharge, and 33.0% and 18.4% of patients presented three or more and five or more long COVID symptoms, respectively.

Risk factors for long COVID symptoms

Wavenumber was not associated with our discharge symptoms, and there was no significant interaction between age and hospitalisation. Female patients, initial hospital admission, and initial symptoms were associated with higher odds of fatigue, shortness of breath, cough, anxiety, sadness, and memory loss (Table 1). Participants in the 30–59 years age group were associated with higher odds of fatigue, cough, and memory loss than those in the less than 30 years age categories. However, there was no association between age and shortness of breath (Table 1). Conversely, patients aged 60 years were associated with lower odds of sadness and anxiety than those younger than 30 years (Table 1). Finally, healthcare workers were associated with lower odds of sadness than non-healthcare workers (Table 1).

Discussion

We evaluated the distribution of long COVID symptoms and their risk factors among COVID-19 patients diagnosed during the first year of the pandemic in Malta. We found that a large proportion of hospitalised and non-hospitalised COVID-19 patients presented with long COVID symptoms, and that as disease severity increased, patients had higher odds of presenting with long COVID.

Our study's prevalence of long COVID symptoms was similar to other studies. For example, a study in Germany with a similarly low hospitalisation rate and follow-up time found that 9.7% and 8.6% of patients presented with fatigue and shortness of breath, respectively.[3] In our study, female patients presented higher odds of long COVID symptoms than males (fatigue, shortness of breath, cough, anxiety, sadness and memory loss). Although patients in other reported studies were all hospitalised, they also observed female sex as a risk factor for myalgia, fatigue and anxiety.[4] One possible explanation is that because of cultural reasons, in Malta, females were impacted by restriction measurements in higher proportions than males, given that they are the usual carers of their children and elderly relatives, which might explain the higher odds of anxiety and sadness observed in the data when compared with other studies.[4]

Younger age categories were associated with higher odds of anxiety and depression when compared with the older age categories. This was consistent with other studies carried out elsewhere.[5,6] One study linked these observations to increased use of social media by younger age groups, which could lead to more exposure to news about COVID-19.[5] Another possible explanation accounting for the differences between age groups could be the different presentation of sadness and anxiety in older persons, leading to misdiagnose by clinicians and lack of awareness by the sufferers themselves.[7]

Conversely, people in the 30–59 years age category had higher odds of developing fatigue, cough, and memory loss than those younger than 30 years. This is not surprising, given that those in the 30–59 years age category tend to have more severe symptoms than

Table 1
Multivariable analysis (odds ratio [95% confidence interval]) of risk factors for fatigue, shortness of breath, cough, memory loss, anxiety, and sadness as long COVID symptoms from a national survey in Malta (N = 2665).

Risk factor		Fatigue		Shortness of breath		Cough	
Prevalence	N (%)	258 (9.7%)		378 (14.2%)		141 (5.3%)	
		OR	*P-value*	OR	*P-value*	OR	*P-value*
Hospitalisation (no)	2459 (92.3%)	Ref	<0.01	Ref	<0.01	Ref	<0.01
Yes	206 (7.7%)	2.99 (2.04–4.31)		3.36 (2.37–4.71)		3.18 (1.89–5.15)	
Sex (female)	1493 (56.0%)	Ref	<0.01	Ref	<0.01	Ref	<0.01
Male	1172 (44.0%)	0.4 (0.3–0.54)		0.41 (0.31–0.53)		0.45 (0.29–0.68)	
Initial symptoms (no)	475 (17.8%)	Ref	<0.01	Ref	<0.01	Ref	0.12
Yes	2190 (82.2%)	2.08 (1.38–3.27)		2.61 (1.75–4.05)		1.6 (0.92–3.04)	
Age (<30)	771 (28.9%)	Ref		Ref		Ref	
30–59	1615 (60.6%)	1.86 (1.36–2.6)	<0.01	1.25 (0.96–1.65)	0.11	1.66 (1.06–2.68)	0.03
>59	279 (10.5%)	1.35 (0.79–2.27)	0.26	0.82 (0.49–1.31)	0.41	0.92 (0.38–2.01)	0.84
Risk factor		**Memory loss**		**Anxiety**		**Sadness**	
Prevalence	N (%)	147 (5.5%)		293 (11.0%)		287 (10.8%)	
		OR	*P-value*	OR	*P-value*	OR	*P-value*
Hospitalisation (no)	2459 (92.3%)	Ref	<0.01	Ref	<0.01	Ref	<0.01
Yes	206 (7.7%)	2.00 (1.17–3.25)		3.34 (2.31–4.77)		3.3 (2.28–4.72)	
Sex (female)	1493 (56.0%)	Ref	<0.01	Ref	<0.01	Ref	<0.01
Male	1172 (44.0%)	0.41 (0.28–0.6)		0.35 (0.26–0.47)		0.41 (0.31–0.54)	
Initial symptoms (no)	475 (17.8%)	Ref	<0.01	Ref	<0.01	Ref	<0.01
Yes	2190 (82.2%)	2.49 (1.42–4.8)		3.15 (2–5.27)		2.74 (1.77–4.47)	
Age (<30)	771 (28.9%)	Ref	<0.01	Ref		Ref	
30–59	1615 (60.6%)	2.35 (1.54–3.71)	<0.01	1.2 (0.91–1.6)	0.20	1.26 (0.95–1.68)	0.11
>59	279 (10.5%)	1 (0.41–2.16)	1.00	0.51 (0.27–0.89)	0.02	0.48 (0.25–0.85)	0.02
Healthcare worker (no)	2401 (90.1%)	Ref	NA	Ref	0.12	Ref	0.03
Yes	264 (9.9%)	NA	NA	0.7 (0.43–1.08)		0.58 (0.34–0.91)	

OR, odds ratio.

those in the younger category. Studies reviewed in the literature indicated that older patients had a higher risk of developing long COVID-19 symptoms;[8] however, our study did not show similar results. Although lack of association does not prove independence, a two-fold reason could account for this. First, older patients were more likely to die from COVID-19, thus leading to survivor bias. Second, younger patients were more likely to be reached by email, therefore causing selection bias.

It is well known that frontline workers are at higher risk of infection than the general population when a new unknown disease emerges. Therefore, it is surprising that although higher odds of mental health problems were identified during previous health emergencies, being a healthcare worker was associated with lower odds of sadness. A potential explanation could be that most studies compare the risk of mental health disorders among the whole population rather than COVID-19–positive patients. Therefore, although this study does not refute the previous evidence, it is necessary to continue investing in frontline workers' mental health.

Limitations and strengths

As we conducted this study, long COVID has been defined further. Currently, the accepted definition includes symptoms 3 months from COVID-19 onset. In our study, patients were classified as having symptoms for 2.5 months or more. The small difference between the currently accepted definition and ours should not limit our interpretation, as patients were interviewed 3–6 months after their initial episode.

There were other limitations in our study. First, we did not collect information regarding comorbidities or underlying health conditions. These were not part of the initial protocol but have been demonstrated to be confounders or effect modifiers on the association of risk factors and long COVID-19 symptoms.[9] Second, treatments were not evaluated in this study, and it is known that dexamethasone and oxygen treatment could reduce some of the symptoms in hospitalised patients. However, 93% of our study participants were non-hospitalised patients and were unlikely to be under these treatments. Third, the number of factors explored in our analyses was limited. For example, future studies could also consider socio-economic factors and access to health care as potential risk factors for long COVID. And fourth, as no COVID-19 vaccinations were available at the time, our study population was limited to unvaccinated individuals.

Our study had several strengths. First, except for some large registry-based studies similar to the one by Estiri et al.,[10] most studies have a smaller sample size. Second, we presented data from a national survey, and national data can leverage policy when presented to decision-makers. Third, we used a comprehensive sampling frame that allowed us to identify differences between respondents and not respondents, which can help identify potential sources of bias.

Conclusion

It is essential to understand the characteristics and risk factors for long COVID to effectively communicate with the local population. In addition, the associations between hospitalisation and symptom severity with long COVID symptoms are important for follow-up of discharged COVID-19 patients and resource allocation. National evidence-based decisions could aid in COVID-19 case management, helping increase clinicians' awareness regarding long COVID, offering support to COVID-19 survivors to re-establish their pre-COVID-19 health.

Author statements

Ethical approval

Ethical approval for this study (HEC18/2020) was obtained from the Health Ethics Committee, Malta.

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Competing interests

None declared.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2022.09.021.

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Original Research

Nursing factors associated with length of stay and readmission rate of the elderly residents from nursing home based on LTCfocus database

Yunping Zhang [a, 1, *], Xueping Zhao [b, 1], Beibei Zhao [a], Lu Xu [a], Xiaofang Chen [c], Aichao Ruan [d]

[a] School of Nursing and Midwifery, Jiangsu College of Nursing, Huaian 223005, PR China
[b] School of Nursing, Soochow University, Suzhou 215031, PR China
[c] Suzhou Industrial Park Centers for Disease Control and Prevention, Suzhou, 215021, PR China
[d] Department of Critical Care Medicine, The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University, Huaian, 223001, PR China

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ABSTRACT

Objectives: Nursing factors have been found to be associated with a reduction in readmission rates. Nevertheless, few attentions have been given to the effect of nursing factors on nursing home (NH) residents. This study was to assess the impact of nursing factors on the hospital readmissions and length of stay (LOS) of the elderly residents from the NH.

Study design: This was a cross-sectional study.

Methods: Data were extracted from the NH of the LTCFocus.org data set between 2011 and 2018. The study included residents aged ≥55 years who were admitted to NH in the United States, following a hospitalization event. The nursing factors included facility-level data elements and medical care personnel. An unsupervised machine learning algorithm (K-means) was used to cluster NH according to readmission rate and LOS. Multivariate logistic regression analysis was performed.

Results: This study consisted of 107,000 NH-year observations. The median readmission rate was 17%, with a median LOS was 28.00 days. Three clusters were identified: cluster 1 was a high readmission rate with high LOS, cluster 2 was a low readmission rate with low LOS, and cluster 3 was a high readmission rate with low LOS. Multifacility and admission/bed were associated with a reduction in readmission rate and LOS in both cluster 1 vs cluster 2 and cluster 3 vs cluster 2. The special care unit and registered nurses' ratio were associated with decreased readmission rate and LOS in cluster 1 vs cluster 2. Total beds and Alzheimer unit decreased the readmission rate and LOS, whereas certified nursing assistant increased the readmission rate and LOS in cluster 3 vs cluster 2. NH for profit was associated with elevated readmission rate and LOS in cluster 1 vs cluster 2 and decreased readmission rate and LOS in cluster 3 vs cluster 2. Based on the subgroup analysis, the certified nursing assistant decreased readmission rate and LOS in cluster 1 vs cluster 2 and increased readmission rate and LOS in cluster 3 vs cluster 2 (all $P < 0.005$).

Conclusion: This study indicates the importance of the improvement of nurse number and level and the inputs of facility characteristics in NH.

Introduction

The nursing home (NH) is defined as handicap-friendly accessible housing designed for older people with permanent and substantial physical and/or mental disabilities who require care day and night and who cannot remain safely in their own homes.[1,2] With the accelerated aging population, NH is serving an increasing proportion of residents.[3] Approximately annually 20%–25% of NH residents are readmitted to a hospital within a month, with recent estimates ranging from 40% to 47%.[4,5] An increasing delay of discharge has been observed among patients with long-term care needs.[6] Hospital readmissions and long length of stay (LOS) pose serious challenges and burdens for individuals as well as for the economy.[7] Therefore, a clearer understanding of what factors affect the risk of hospital readmission and LOS is important to decrease readmission and nursing cost burden.

* Corresponding author. School of Nursing and Midwifery, Jiangsu College of Nursing, No.9. KeJi Avenue, Qing Jiang Pu District, Huaian 223005, PR China. Tel.: +86 13511545786.
E-mail address: hnzhyunping@outlook.com (Y. Zhang).
[1] Yunping Zhang and Xueping Zhao are co-authors of the first author.

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Previous studies have identified multiple related factors for hospital readmission and LOS. Medicaid NH reimbursement rates and bed-hold policies were related to the quality of care.[8] A higher proportion of Medicaid residents decreases the probability of community discharge. Increased Medicare census was also found to be associated with a significant decline in performance on the long-stay quality measures among non-profit facilities.[9] It is well documented that system factors such as state policies, payment incentives, market competition, and resource allocation affect the hospitalizations among NH residents.[8,10–12] In recent years, higher staffing levels have been generally found to be associated with a reduction in readmission rates.[13] Facility characteristics were also associated with the readmission rates of residents.[10] Nevertheless, few attentions have been given to the effect of nursing factors on NH residents. Whether nursing factors are associated with LOS and readmission rate in NH need to be assessed.

In this study, we seek to evaluate the association between nursing factors and LOS and the readmission rate of the elderly. This study may provide a reference for the reduction of LOS in NH residents and improvement of the quality of NH care.

Methods

Study design and participants

In this cross-sectional study, NH-level data were obtained from LTCFocUS.org (http://ltcfocus.org) over the period of 2011 and 2018. This publicly available data set from Brown University has provider characteristics of all Medicare- and Medicaid-certified NH in the United States. The study includes residents aged $\geq$55 years who were admitted to NH in the United States, following a hospitalization event. Initially, 122,641 records of NHs were identified. Hospital-based NHs (N = 6490) were excluded as their practice pattern, and resident population might differ from freestanding NH.[14] We dropped NHs with zero staffing hours (7,656). Our final sample consisted of 107,000 NHs. As the data sets included in the study were downloaded from public databases, the study did not need the approval of an ethics committee.

Data collection

We collected data including (1) facility-level data elements: total beds, Alzheimer unit (yes/no), special care unit (SCU; yes/no), multifacility (yes/no), structure (profit, yes/no), Medicaid, Medicare, chain status (yes/no), physician extender (yes/no), the proportion of residents who are physically restrained, admission/bed, registered nurse (RN) ratio; (2) medical care personnel included direct-care staff (DCS), RN hours per resident day, licensed practical nurse (LPN) hours per resident day, and certified nursing assistant (CNA) hours per resident day; (3) person-level variables: average age, gender (the percent of female), ethnicity, and admissions from acute care (percent); (4) The NH residents' health: average acuity index, bladder incontinent, bowel incontinent, hypertension, ventilator, obese, long stay with daily pain, long stay with pressure ulcers, long activities of daily living (ADL), cognitive function scale (CFS), Resource Utilization Group Nursing Case Mix Index (RUGS NCMI); (5) successful discharge, hospitalizations per resident year, readmission rate, and median LOS.

Variables and outcome

Multifacility meant whether a facility was owned or leased by a multifacility (chain) organization. Restrained residents referred to the proportion of facility residents who were restrained. The physician extender indicated whether or not the facility had a nurse practitioner or physician's assistant. Admission/bed was the number of admissions divided by the total number of beds. DCS referred to the number of RN, LPN, and CNA hours during the 2 weeks before their annual survey. RN ratio was constructed based on the number of RN full-time equivalents divided by the total number of RN and LPN full-time equivalents. The acuity index was a measure of the care needed by an NH's residents, which was calculated based on the number of residents needing various levels of ADL assistance, and the number of residents receiving special treatment. Long stay with daily pain was defined as the proportion of long-stay residents with daily pain (Minimum Data Set, MDS 3.0). Long stay with pressure ulcers referred to the proportion of high-risk long-stay residents with pressure ulcers (MDS 3.0). CFS referred to the proportion of residents present with a CFS score of 1 (low cognitive impairment). The average RUGS NCMI referred to the average RUGS NCMI (a measure of the relative intensity of care of different NH populations) for all residents admitted during the calendar year (MDS 3.0). The MDS was a federally mandated clinical assessment instrument administered to all residents in Medicare- or Medicaid-certified NH. The MDS includes over 400 data elements related to the physical, mental, and psychosocial health of the residents and is administered to all NH residents within 14 days of admission and at prescribed intervals thereafter.

Outcomes

The denominator for readmission rate was the total admissions, defined as the total number of admissions to the facility for persons 55 and older for individuals with available risk factors within 18 days of the entry date (not taken from the discharge assessment) from hospitals. The numerator was the number of these admissions who were discharged to an acute hospital within 30 days of admission.

LOS was calculated for new admissions to a nursing facility from a hospital. New admissions were defined as any admission assessment from a hospital with no assessments in the 100 days before the admission assessment. Each person's LOS was calculated based on the number of days between their admission and discharge. If they were not discharged within 120 days from admission, they are assigned a LOS of 120 days no matter how long they stayed past 120 days. When an individual had an interruption in service that was 10 days or less, their LOS related to their subsequent readmission to the skilled nursing facility (SNF) would be counted with the prior admission's LOS. When an individual has an interruption in service (e.g. is hospitalized) that was greater than 10 days, their LOS ended on the day of discharge to the hospital. Any subsequent admission to the SNF was not counted unless it met the criteria for a new admission as stated previously.

Statistical analysis

An unsupervised machine learning algorithm (K-means) clustered all NH-year observations into multiple groups. K-means is a centroid-based clustering algorithm that performs this grouping by partitioning a data set into K clusters by minimizing the sum of squared distance in each cluster.[15] K-means has the advantage of being computationally efficient and allows an intuitive visualization of the relationship of the data points to their respective clusters. LOS and readmission rates were selected as clustering variables. In the modeling process, the number of clusters (K) was first specified, and then the K-means algorithm randomly selected k objects as the initial cluster centers. Then, it assigned each observation to the closest centroid, and the cluster centroid will be updated sequentially. This process was iterated until the total within the sum of the square was minimized, and each NH-year observation was assigned to one group based on the distance to

the centers, measured by the Euclidean Distance. The number of clusters was determined by the visual examination of the reduction in the sum of squared distances by the changes in clusters.

Mean ± standard deviation was used to describe the normal distribution of measurement data, analysis of variance was used for comparison between the three groups, and *t*-test was used for comparisons between the two groups. Non-normal distribution was exhibited as [M (Q_1, Q_3)], and the Kruskal-Wallis H rank-sum test was used for comparison between groups. The enumeration data were described as the number of cases and constituent ratio n (%), and the Chi-squared test was used for comparison between groups. The missing values were filled by multiple interpolations using the "mice" package in R software. Sensitivity analysis was performed on the data before and after multiple interpolations. Multivariate logistic regression analysis was performed to explore the effect of nursing factors on the LOS and the readmission rate of the elderly. Annual percent change (APC), and corresponding *P* values of trends were determined using JointPoint software (version 4.8.0.1).

All statistical tests were conducted by two-tailed tests, and the differences tested by $\alpha = 0.05$ were statistically significant between the three groups, whereas the differences tested by $\alpha = 0.025$ were statistically significant between the two groups. K-means clustering, stone aggregation, and Calinski were completed using R V3.6.3 (https://www.R-project.org/). The remaining statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Trends in readmission rate, LOS, and each cluster between 2011 and 2018

From 2011 to 2018, 107,000 NH-year observations were selected in this study. The flowchart of data collection is shown in Fig. 1. Over the study period of 2011–2016, at the NH level, the percent of the readmission decreased from approximately 24%–17.5% and increased from 17.5% to 20% from 2016 to 2017. Readmission rate and LOS trends in NH from 2011 to 2018 are depicted in Fig. 2. And the APC trends in readmission rates and LOS between 2011 and 2018 are described in Table 1. Three NH clusters were identified by the K-means algorithm, as shown in Fig. 3. Cluster 1 was a high readmission rate and high LOS. Cluster 2 was a low readmission rate and low LOS. Cluster 3 was a high readmission rate with low LOS. The APC trends of each cluster in different years are shown in Table 2. Fig. 4 presents the trends in the number of NHs in each cluster over time. From 2011 to 2018, the number of cluster 1 decreased from 6306 to 2344. Over the period of 2011–2017, the number of cluster 2 increased from 6017 to 8174 and decreased to 4500 in 2018. From 2011 to 2018, the number of cluster 3 decreased from 2011 to 718.

Descriptive results of the NHs in 2018

Descriptive results of all NHs in 2018 are presented in Table 3. The average age was 78.96 ± 6.87 years. The average total beds were 112 (81, 137), 101 (70, 130), and 86 (55, 120) for cluster 1, cluster 2, and cluster 3, respectively. There were 229 (9.77%), 724 (16.09%), and 103 (14.35%) Alzheimer unit in cluster 1, cluster 2, and cluster 3, respectively. Cluster 1 had 266 (11.35%) SCU, cluster 2 had 802 (17.82%), and cluster 3 had 128 (17.83%). Most NH was for-profit (73.63%) and multifacility (60.43.0%). Cluster 3 had lower admission/bed (0.69 vs 1.98 and 1.55). Cluster 2 had higher RN ratio (0.35 vs 0.27 and 0.30), more DCS (3.55 vs 3.32, and 3.30), RN (0.44 vs 0.32, and 0.33), and CNA (2.27 vs 2.12, and 2.18). Cluster 1 had higher occupancy rate (79.16 ± 14.52). The median readmission rate was 0.17 (0.13, 0.21), with hospitalizations per resident year varying from 0.72 to 1.35. The median LOS was 28.00 (22.00, 40.00) days.

Nursing factors on readmission rate and LOS

Multifacility was associated with reduction of readmission rate and LOS in both cluster 1 vs cluster 2 (odds ratio [OR]: 0.87, 95% confidence interval [CI]: 0.84–0.89; $P < 0.001$) and cluster 3 vs cluster 2 (OR: 0.68, 95% CI: 0.64–0.72; $P < 0.001$). A decreased readmission rate and LOS were also observed in cluster 1 vs cluster 2 (OR: 0.89, 95% CI: 0.88–0.90; $P < 0.001$) and cluster 3 vs cluster 2 (OR: 0.12, 95% CI: 0.11–0.13; $P < 0.001$) with admission/bed. The SCU (OR: 0.88, 95% CI: 0.79–0.98; $P = 0.022$) and RN ratio (OR: 0.33, 95% CI: 0.29–0.38; $P < 0.001$) were associated with decreased readmission rate and LOS in both cluster 1 vs cluster 2. Total beds (OR: 0.99, 95% CI: 0.99–0.99; $P < 0.001$) and Alzheimer unit (OR: 0.74, 95% CI: 0.60–0.91; $P = 0.005$) decreased the readmission rate and LOS, whereas CNA (OR: 1.19, 95% CI: 1.14–1.24; $P < 0.001$) increased the readmission rate and LOS in cluster 3 vs cluster 2. NH for profit was associated with elevated readmission rate and LOS in cluster 1 vs cluster 2 (OR: 1.22, 95% CI: 1.17–1.26; $P < 0.001$) and decreased readmission rate and LOS in cluster 3 vs cluster 2 (OR: 0.73, 95% CI: 0.68–0.78; $P < 0.001$; Table 4).

Subgroup analysis of nursing factors on readmission rate and LOS

Subgroup analysis of nursing factors on readmission rate and LOS was based on ages. When age <75 years, multifacility and admission/bed were still associated decreased readmission rate and LOS in cluster 1 vs cluster 2 (OR: 0.75, 95% CI: 0.70–0.81; $P < 0.001$; and OR: 0.83, 95% CI: 0.80–0.86; $P < 0.001$) and cluster 3 vs cluster 2 (OR: 0.58, 95% CI: 0.52–0.65; $P < 0.001$). RN ratio was also associated with a reduction in readmission rate and LOS (OR: 0.48, 95% CI: 0.36–0.64; $P < 0.001$) in cluster 1 vs cluster 2. CNA was associated with decreased readmission rate and LOS in cluster 1 vs cluster 2 (OR: 0.89, 95% CI: 0.84–0.94; $P < 0.001$), however, associated with increased readmission rate and LOS in cluster 3 vs cluster 2 (OR: 1.18, 95% CI: 1.09–1.27; $P < 0.001$). Regarding age ≥75 years, total beds decreased the readmission rate and LOS in cluster 1 vs cluster 2 (OR: 1.00, 95% CI: 1.00–1.00; $P = 0.000$) and cluster 3 vs cluster 2 (OR: 0.99, 95% CI: 0.99–0.99; $P < 0.001$). SCU was associated with the reduction of readmission rate and LOS in cluster 1 vs cluster 2 (OR: 0.84, 95% CI: 0.73–0.97; $P = 0.015$). NH for profit was associated with increased readmission rate and LOS in cluster 1 vs cluster 2 (OR: 1.35, 95% CI: 1.30–1.40; $P < 0.001$) and associated with decreased readmission rate and LOS in cluster 3 vs cluster 2 (OR: 0.77, 95% CI: 0.72–0.83; $P < 0.001$). The CAN decreased readmission rate and LOS in cluster 1 vs cluster 2 (OR: 0.97, 95% CI: 0.94–0.99; $P = 0.013$) and increased readmission rate and LOS in cluster 3 vs cluster 2 (OR: 1.18, 95% CI: 1.12–1.24; $P < 0.001$; Table 5).

Discussion

The understanding of the role that the nursing factors play in the LOS and readmission rate among NH residents is limited. Thereby, this study was to evaluate the association between nursing factors and LOS and the readmission rate of the elderly. From 2011 to 2018, readmission rates and LOS experienced a decline overall but rebounded slightly in some years. In this study, the LOS and readmission rates of NH residents were influenced by facility characteristics, including total beds, Alzheimer unit, SCU, admission/bed, for-profit ownership, and multifacility. Moreover, nursing staffing number and level were associated with readmission rates and LOS, with RN ratio decreasing the readmission rate and LOS and CNA

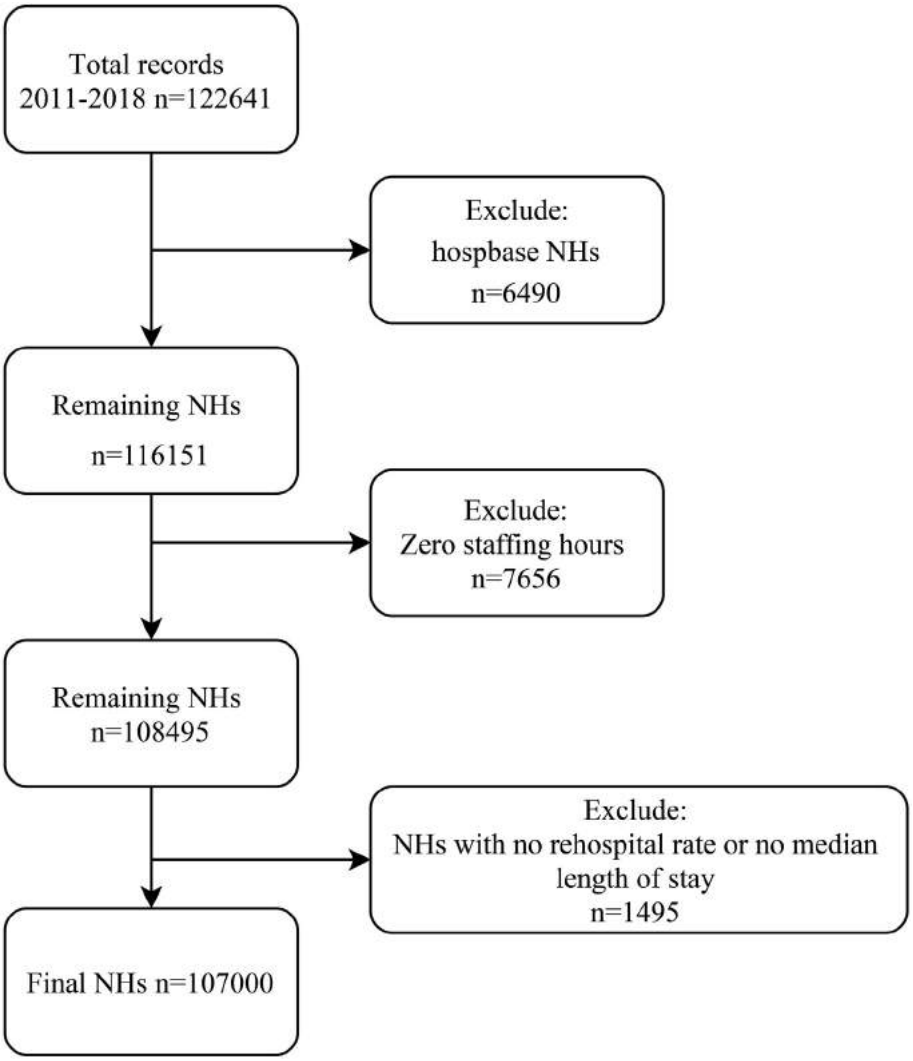

Fig. 1. The flowchart of data collection.

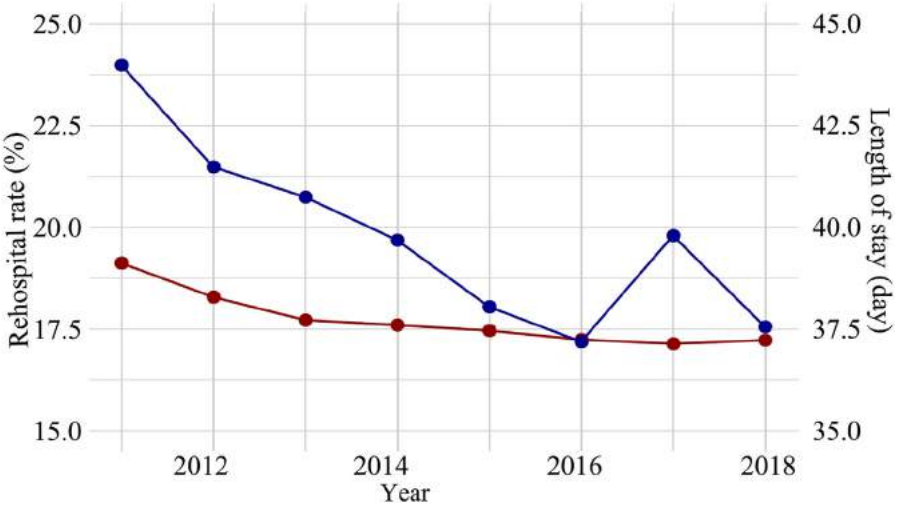

Fig. 2. Readmission rate and LOS trends in NH from 2011 to 2018. *Blue represents readmission rate, and red represents LOS. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

Table 1
APC trends in readmission rates and LOS between 2011 and 2018.

Years	Variables	APC	*P*
2011–2013	Readmission rate	−3.74	0.013
2013–2018	Readmission rate	−0.69	0.032
2011–2018	LOS	−2.02	0.009

APC, Annual percent change; LOS, length of stay.
$P < 0.05$ was considered to be statistically significant.

Table 2
APC trends of each cluster in different years.

Years	Clusters	APC	*P*
2011–2013	Cluster 1	−8.85	0.085
	Cluster 2	12.93	0.01
2013–2018	Cluster 1	−3.6	0.002
	Cluster 2	2.1	0.021
2011–2018	Cluster 3	−4.03	0.104

APC, annual percent change.
Cluster 1: high readmission rate and high length of stay (LOS); Cluster 2: low readmission rate and low LOS; Cluster 3: high readmission rate with low LOS.
$P < 0.05$ was considered to be statistically significant.

increasing the readmission rate and LOS. Based on the subgroup analysis, CNA may decrease readmission while increasing LOS.

Our study demonstrated that total beds in NHs were associated with a reduction in readmission and LOS. Gaughan et al.[16] hypothesized nursing and care home supply reduce delayed hospital discharges and found that delayed discharges in hospitals do respond to the availability of care home beds, with an increase in care home beds of 10% reducing social care delayed discharges by 6–9%. Similarly, Spiers et al.[17] reported that greater availability of care home beds was associated with fewer readmissions, delayed discharges, and reduced LOS. A reduced supply of NH beds could cause longer waiting lists for NH placement.[18] Therefore, it is necessary to ensure that there are enough beds in NHs. We also found that Alzheimer's unit and SCU were related to the decreased LOS and readmission rates. We speculate that the effects of the SCU

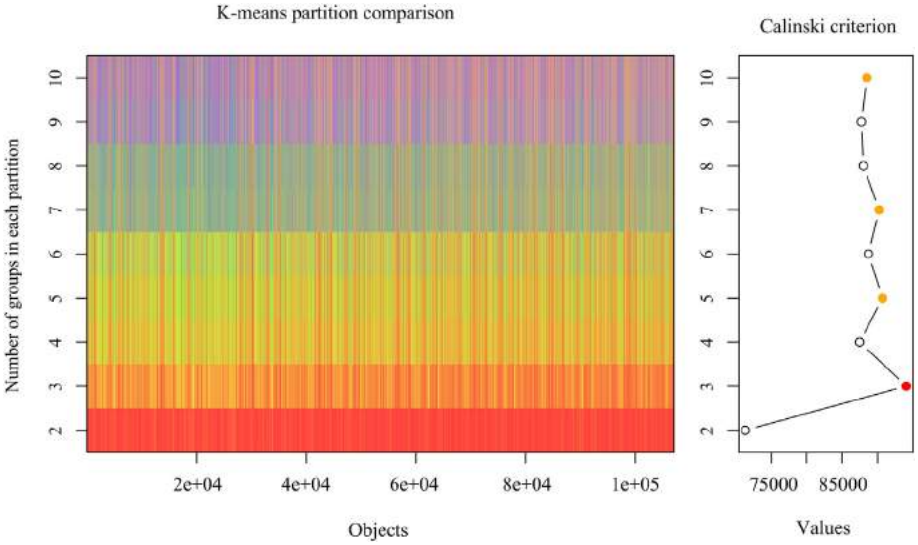

Fig. 3. Selection of clusters numbers.

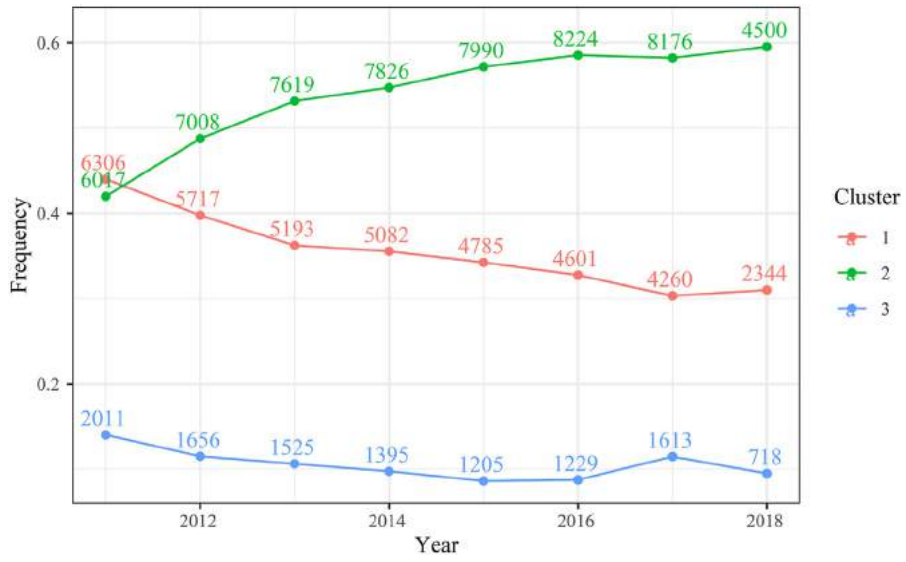

Fig. 4. The changes in the number of NH in each cluster over time.

Table 3
Descriptive results of all NH in 2018.

Variables	Total (n = 7562)	Cluster 2 (n = 4500)	Cluster 1 (n = 2344)	Statistics 1	*P*1	Cluster 3 (n = 718)	Statistics 2	*P*2	Statistics3	*P*3
Total beds, M (Q_1, Q_3)	102 (71, 131)	101 (70, 130)	112 (81, 137)	Z = 5.988	<0.001	86 (55, 120)	Z = −8.244	<0.001	χ^2 = 130.210	<0.001
Alzheimer unit, *n* (%)				χ^2 = 51.349	<0.001		χ^2 = 1.411	0.235	χ^2 = 51.322	<0.001
No	6506 (86.04)	3776 (83.91)	2115 (90.23)			615 (85.65)				
Yes	1056 (13.96)	724 (16.09)	229 (9.77)			103 (14.35)				
SCU, *n* (%)				χ^2 = 49.050	<0.001		χ^2 = 0.000	0.997	χ^2 = 50.928	<0.001
No	6366 (84.18)	3698 (82.18)	2078 (88.65)			590 (82.17)				
Yes	1196 (15.82)	802 (17.82)	266 (11.35)			128 (17.83)				
Medicaid, M (Q_1, Q_3)	64.81 (50.00, 76.30)	60.31 (44.63, 72.89)	69.65 (57.14, 78.43)	Z = 18.242	<0.001	74.58 (56.72,87.23)	Z = 15.786	<0.001	χ^2 = 490.228	<0.001
Medicare, M (Q_1, Q_3)	10.53 (6.00, 16.81)	11.28 (6.52, 18.15)	11.11 (7.08, 16.54)	Z = −1.286	0.198	4.35 (0.92, 8.33)	Z = −24.032	<0.001	χ^2 = 615.226	<0.001
Multifacility, n (%)				χ^2 = 1.994	0.158		χ^2 = 83.350	<0.001	χ^2 = 83.869	<0.001
No	2993 (39.58)	1680 (37.33)	916 (39.08)			397 (55.29)				
Yes	4569 (60.42)	2820 (62.67)	1428 (60.92)			321 (44.71)				
Profit, n (%)				χ^2 = 194.395	<0.001		χ^2 = 7.092	0.008	χ^2 = 224.923	<0.001
No	1994 (26.37)	1381 (30.69)	357 (15.23)			256 (35.65)				
Yes	5568 (73.63)	3119 (69.31)	1987 (84.77)			462 (64.35)				
Restrained residents, M (Q_1, Q_3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	Z = 7.751	<0.001	0.00 (0.00, 0.00)	Z = 7.530	<0.001	χ^2 = 90.419	<0.001
Average acuity index, mean ± SD	12.22 ± 1.35	12.19 ± 1.18	12.45 ± 1.26	*t* = 8.33	<0.001	11.65 ± 2.16	*t* = 6.51	<0.001	*F* = 102.089	<0.001
Physician extender, *n* (%)				χ^2 = 1.351	0.245		χ^2 = 61.203	<0.001	χ^2 = 70.165	<0.001
No	3227 (42.67)	1874 (41.64)	942 (40.19)			411 (57.24)				
Yes	4335 (57.33)	2626 (58.36)	1402 (59.81)			307 (42.76)				
Admission/bed, M (Q_1, Q_3)	1.69 (1.06, 2.65)	1.98 (1.28, 3.06)	1.55 (1.07, 2.30)	Z = −14.752	<0.001	0.69 (0.49, 0.93)	Z = −36.140	<0.001	χ^2 = 1477.763	<0.001
RN ratio, hours/day, M (Q_1, Q_3)	0.32 (0.21, 0.46)	0.35 (0.23, 0.49)	0.27 (0.17, 0.40)	Z = −15.183	<0.001	0.30 (0.18, 0.46)	Z = −5.292	<0.001	χ^2 = 232.312	<0.001
DCS, M (Q_1, Q_3)	3.46 (3.03, 3.99)	3.55 (3.13, 4.09)	3.32 (2.91, 3.83)	*t* = −8.41	<0.001	3.30 (2.76, 3.88)	Z = −8.224	<0.001	χ^2 = 186.781	<0.001
RN, hours/day, M (Q_1, Q_3)	0.39 (0.24, 0.59)	0.44 (0.28, 0.64)	0.32 (0.19, 0.50)	Z = −17.407	<0.001	0.33 (0.17, 0.51)	Z = −10.827	<0.001	χ^2 = 355.104	<0.001
LPN, hours/day, M (Q_1, Q_3)	0.83 (0.63, 1.02)	0.83 (0.63, 1.01)	0.85 (0.66, 1.04)	Z = 4.030	<0.001	0.73 (0.54, 0.95)	Z = −5.963	<0.001	χ^2 = 65.540	<0.001
CNA, hours/day, M (Q_1, Q_3)	2.21 (1.89, 2.59)	2.27 (1.96, 2.64)	2.12 (1.82, 2.49)	Z = −11.059	<0.001	2.18 (1.79, 2.66)	Z = −3.559	<0.001	χ^2 = 121.317	<0.001
Average RUGS NCMI, mean ± SD	1.29 ± 0.14	1.29 ± 0.11	1.32 ± 0.15	*t* = 7.43	<0.001	1.20 ± 0.25	*t* = 9.75	<0.001	*F* = 200.488	<0.001
Admissions from acute care, percent, mean ± SD	84.12 ± 13.25	86.67 ± 10.79	84.76 ± 11.34	*t* = −6.72	<0.001	66.08 ± 18.24	*t* = 29.43	<0.001	*F* = 936.794	<0.001
Long ADL (all admits), mean ± SD	16.84 ± 2.29	16.81 ± 1.90	17.26 ± 2.12	*t* = 8.51	<0.001	15.70 ± 3.99	*t* = 7.33	<0.001	*F* = 132.583	<0.001
CFS, M (Q_1, Q_3)	53.79 (43.90, 62.43)	56.82 (48.52, 64.69)	50.00 (40.59, 58.81)	*t* = −20.14	<0.001	39.18 (28.26, 50.82)	*Z* = −24.510	<0.001	χ^2 = 851.859	<0.001
Female, mean ± SD	57.48 ± 10.64	59.08 ± 9.16	55.61 ± 10.07	*t* = −13.93	<0.001	53.57 ± 17.15	*t* = 8.41	<0.001	*F* = 140.188	<0.001
White, M (Q_1, Q_3)	86.01 (65.31, 95.74)	89.51 (72.78, 96.63)	77.37 (54.67, 91.78)	Z = −18.827	<0.001	84.62 (59.26, 95.31)	*t* = 6.01	<0.001	χ^2 = 353.235	<0.001
Average age, years, mean ± SD	78.96 ± 6.87	80.44 ± 5.91	77.20 ± 5.91	*t* = −21.54	<0.001	75.43 ± 11.29	*t* = 11.63	<0.001	*F* = 298.289	<0.001
Long ADL, mean ± SD	16.56 ± 2.64	16.81 ± 2.28	16.61 ± 2.50	*t* = −3.37	<0.001	14.79 ± 4.07	*t* = 13.01	<0.001	*F* = 192.740	<0.001
Average RUGS NCMI, mean ± SD	1.18 ± 0.16	1.18 ± 0.13	1.18 ± 0.17	*t* = 0.00	0.999	1.10 ± 0.27	*t* = 8.38	<0.001	*F* = 93.824	<0.001
Bladder incontinent, mean ± SD	79.15 ± 13.48	80.03 ± 12.58	79.18 ± 13.01	*t* = −2.64	0.008	73.50 ± 18.27	*t* = 9.23	<0.001	*F* = 73.988	<0.001
Bowel incontinent, M (Q_1, Q_3)	63.92 (52.81, 74.71)	63.31 (52.78, 73.68)	66.67 (55.56, 78.09)	*t* = 8.86	<0.001	55.67 (43.33, 70.00)	Z = −9.277	<0.001	χ^2 = 196.800	<0.001
Hypertension, mean ± SD	76.49 ± 10.70	76.59 ± 10.04	78.06 ± 9.65	*t* = 5.90	<0.001	70.74 ± 15.14	*t* = 10.02	<0.001	*F* = 133.797	<0.001
Ventilator, M (Q_1, Q_3)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	Z = 8.217	<0.001	0.00 (0.00, 0.00)	Z = 3.857	<0.001	χ^2 = 67.045	<0.001
Obese, mean ± SD	28.98 ± 8.27	28.48 ± 8.16	29.16 ± 7.78	*t* = 3.37	<0.001	31.56 ± 9.86	*t* = −7.95	<0.001	*F* = 44.251	<0.001
Long stay with daily pain, M (Q_1, Q_3)	4.36 (0.49, 9.73)	4.55 (0.81, 9.81)	3.71 (0.00, 8.93)	Z = −3.843	<0.001	5.56 (1.88, 11.95)	Z = 4.141	<0.001	χ^2 = 40.121	<0.001
Long stay with pressure ulcers: high risk, M (Q_1, Q_3)	6.67 (3.85, 10.00)	6.25 (3.57, 9.38)	7.84 (4.76, 11.43)	Z = 12.254	<0.001	5.54 (2.78, 8.82)	Z = −3.776	<0.001	χ^2 = 189.020	<0.001
Successful discharge: observed, M (Q_1, Q_3)	0.59 (0.45, 0.69)	0.65 (0.56, 0.73)	0.52 (0.41, 0.61)	*t* = −36.27	<0.001	0.25 (0.09, 0.37)	Z = −38.585	<0.001	χ^2 = 2426.258	<0.001
Hospitalizations per resident year, M (Q_1, Q_3)	1.00 (0.72, 1.35)	0.94 (0.69, 1.24)	1.25 (0.97, 1.61)	Z = 26.184	<0.001	0.64 (0.46, 0.90)	Z = −18.795	<0.001	χ^2 = 1226.071	<0.001
Readmission rate, M (Q_1, Q_3)	0.17 (0.13, 0.21)	0.15 (0.12, 0.17)	0.23 (0.21, 0.26)	Z = 67.847	<0.001	0.15 (0.08, 0.20)	Z = 1.553	0.12	χ^2 = 4455.337	<0.001
Median LOS, days, M (Q_1, Q_3)	28.00 (22.00, 40.00)	25.00 (21.00, 32.00)	30.00 (24.50, 40.75)	Z = 21.040	<0.001	118.50 (88.00,120.00)	Z = 43.133	<0.001	χ^2 = 2301.625	<0.001

ADL, activities of daily living; CFS, cognitive function scale; CAN, certified nursing assistant; DCS, direct-care staff; LPN, licensed practical nurse; RN, registered nurse; RUGS NCMI, Resource Utilization Group Nursing Case Mix Index; SCU, special care unit; t, *t*-test; Z, Kruskal-Wallis H rank-sum test.
Cluster 1: high readmission rate and high length of stay (LOS); Cluster 2: low readmission rate and low LOS; Cluster 3: high readmission rate with low LOS.
*p*1: Cluster 1 vs cluster 2; *p*2: Cluster 3 vs cluster 2; *p*3: Cluster 1 vs cluster 2 vs Cluster 3.

and Alzheimer's unit on LOS and readmission rates may be attributable to the quality of care in the SCU and Alzheimer's unit.[19] A study by Luo et al.[20] showed that SCU residents had, in general, a better process of care than those in regular units and in NHs without an SCU, with SCU residents being less likely to have some adverse outcomes, such as hospitalization. Adlbrecht et al.[21] demonstrated that the care concept of the dementia SCU results in higher levels of relaxation, activities, and social interaction among residents. Since close to two-thirds of all US NH residents have some type of cognitive impairment,[22] an appropriate increase in Alzheimer's units and SCU may benefit residents in NH. The ownership of the NH was also associated with readmission and LOS. We found for-profit NH was associated with high readmission and LOS. For-profit NH tends to provide lower quality than not-for-profit NH.[23] In a study controlling for a range of facility characteristics such as age and size, care home and NH that were operated by non-profit organizations and those that are run by local authorities are, on average, of higher quality than those operated by for-profit providers.[24] When selecting an NH, it is advisable to consider the profit orientation of the institution. These findings have important and timely implications for health systems and care for older people, which highlights the role of NH facilities in NHs care, suggesting the importance of strengthening NH facilities to reduce readmission rates and LOS.

Previous research demonstrated connections between low nurse staffing and direct/indirect adverse patient events.[25] Insufficient resources in NH often mean insufficient types of staffing and the inability to make a multidisciplinary team decide and carry out suitable care plans.[26] Joynt and Jha found that hospitals with high RN staffing ratios had lower readmission rates.[27] Unsatisfactory nurse staffing can also lead to a greater risk of adverse events and, further, hospital admissions and readmissions.[28] Unauthorized people working in NH (i.e. care aides or personal support workers) provide up to 80% of general personal care.[29] A study by Arling et al. included facility characteristics in a comprehensive analysis of short-stay discharges in Minnesota found that higher nurse staffing levels were the predictor of community discharge. In this study, CNA in NH increased the risk of readmission and LOS. The ability of CNAs to carry out these roles is largely influenced by the work environment in which they practice.[30] In good work environments, there were adequate staff, supportive managers and resources, strong nursing foundations underlying care, better relationships with colleagues, large input of organizational affairs, and opportunities for advancement. Extensive research has shown that hospitals with these features have better patient outcomes, including lower mortality, reduced LOS, and higher satisfaction.[31] Where the nurse staffing was perceived as unsatisfactory, our study meant increasing the nurse coverage. In all NH, the findings meant decreasing the numbers of assistants or putting nurses into continuing education.[25] To shorten a patient hospital stay with better care and to prevent unplanned readmissions and long LOS, NH administrators and policymakers should focus on nurse retention and staffing quality.

This study found that nursing factors influence the LOS and readmission rate of NH residents. Policymakers and advocates should be cognizant that the LOS and readmission rates of NH

Table 4
Results of nursing factors on readmission rate and LOS.

Indicators	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Total beds						
Cluster 1 vs cluster 2	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.01)	0.397
Cluster 3 vs cluster 2	0.99 (0.98–0.99)	<0.001	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001
Alzheimer unit						
Cluster 1 vs cluster 2	0.77 (0.69–0.86)	<0.001	0.98 (0.87–1.09)	0.688	0.95 (0.84–1.06)	0.341
Cluster 3 vs cluster 2	0.49 (0.40–0.59)	<0.001	0.76 (0.62–0.92)	0.006	0.74 (0.60–0.91)	0.005
SCU						
Cluster 1 vs cluster 2	0.86 (0.78–0.95)	0.004	0.78 (0.70–0.87)	<0.001	0.88 (0.79–0.98)	0.022
Cluster 3 vs cluster 2	1.57 (1.32–1.88)	<0.001	1.13 (0.94–1.37)	0.191	0.99 (0.80–1.21)	0.887
Multifacility						
Cluster 1 vs cluster 2	0.93 (0.90–0.96)	<0.001	0.87 (0.85–0.90)	<0.001	0.87 (0.84–0.89)	<0.001
Cluster 3 vs cluster 2	0.69 (0.65–0.72)	<0.001	0.63 (0.60–0.67)	<0.001	0.68 (0.64–0.72)	<0.001
Profit						
Cluster 1 vs cluster 2	1.97 (1.90–2.03)	<0.001	1.47 (1.42–1.52)	<0.001	1.22 (1.17–1.26)	<0.001
Cluster 3 vs cluster 2	1.10 (1.04–1.16)	0.001	0.78 (0.73–0.83)	<0.001	0.73 (0.68–0.78)	<0.001
Admission/bed						
Cluster 1 vs cluster 2	0.85 (0.84–0.86)	<0.001	0.88 (0.87–0.89)	<0.001	0.89 (0.88–0.90)	<0.001
Cluster 3 vs cluster 2	0.05 (0.04–0.05)	<0.001	0.05 (0.05–0.06)	<0.001	0.12 (0.11–0.13)	<0.001
RN ratio						
Cluster 1 vs cluster 2	0.15 (0.14–0.18)	<0.001	0.23 (0.20–0.26)	<0.001	0.33 (0.29–0.38)	<0.001
Cluster 3 vs cluster 2	0.42 (0.34–0.53)	<0.001	0.71 (0.56–0.89)	0.003	1.09 (0.86–1.39)	0.467
RN						
Cluster 1 vs cluster 2	1.11 (1.04–1.18)	0.001	0.98 (0.92–1.04)	0.443	0.97 (0.90–1.04)	0.322
Cluster 3 vs cluster 2	0.95 (0.83–1.09)	0.488	0.75 (0.65–0.85)	<0.001	0.86 (0.74–1.01)	0.065
LPN						
Cluster 1 vs cluster 2	1.08 (1.04–1.12)	<0.001	1.04 (1.00–1.07)	0.044	1.02 (0.99–1.06)	0.244
Cluster 3 vs cluster 2	0.97 (0.90–1.04)	0.381	0.95 (0.88–1.02)	0.135	1.02 (0.96–1.09)	0.523
CNA						
Cluster 1 vs cluster 2	0.94 (0.92–0.96)	<0.001	0.99 (0.97–1.01)	0.199	0.98 (0.95–0.99)	0.028
Cluster 3 vs cluster 2	1.15 (1.11–1.19)	<0.001	1.21 (1.17–1.26)	<0.001	1.19 (1.14–1.24)	<0.001

CI, confident interval; Cluster 1, high readmission rate with high LOS; Cluster 2, low readmission rate with low LOS; Cluster 3, high readmission rate with low LOS; CNA, certified nursing assistant; LOS, length of stay; LPN, licensed practical nurse; OR, odds ratio; RN, registered nurse; SCU, special care unit.
Cluster 1 vs Cluster 2: Model 1 was unadjusted model, Model 2 adjusted for average age, the percent of female, and the percent of the White, Model 3 adjusted for average RUGS NCMI, admissions from acute care, cognitive function scale (CFS), bladder incontinent, bowel incontinent, hypertension, physician extender, obese, long stay with daily pain, long stay with pressure ulcers: high risk based on Model 2. Cluster 3 vs Cluster 2: Model 1 was unadjusted model, Model 2 adjusted for average age, the percent of female, and the percent of the White, Model 3 adjusted for average RUGS NCMI MDS 3, admissions from acute care, long activities of daily living (ADL), CFS, bladder incontinent, physician extender, ventilator, long stay with daily pain, average acuity index based on Model 2.

Table 5
Subgroup analysis of nursing factors on readmission rate and LOS.

Indicators	Model 1		Model 2		Model 3	
	OR	*P*	OR	*P*	OR	*P*
Age < 75						
Total beds						
Cluster 1 vs cluster 2	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.463
Cluster 3 vs cluster 2	0.99 (0.99–1.00)	0.007	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	0.000
Alzheimer unit						
Cluster 1 vs cluster 2	0.79 (0.65–0.97)	0.025	0.84 (0.69–1.01)	0.068	0.86 (0.70–1.07)	0.183
Cluster 3 vs cluster 2	0.47 (0.36–0.62)	<0.001	0.57 (0.43–0.75)	<0.001	0.74 (0.55–0.99)	0.049
SCU						
Cluster 1 vs cluster 2	0.91 (0.76–1.08)	0.270	0.96 (0.81–1.15)	0.664	1.04 (0.86–1.26)	0.690
Cluster 3 vs cluster 2	1.40 (1.11–1.78)	0.005	1.34 (1.05–1.71)	0.019	0.95 (0.73–1.23)	0.672
Multifacility						
Cluster 1 vs cluster 2	0.72 (0.67–0.77)	<0.001	0.76 (0.71–0.81)	<0.001	0.75 (0.70–0.81)	<0.001
Cluster 3 vs cluster 2	0.47 (0.43–0.53)	<0.001	0.50 (0.45–0.55)	<0.001	0.58 (0.52–0.65)	<0.001
Profit						
Cluster 1 vs cluster 2	1.22 (1.10–1.36)	0.001	1.19 (1.08–1.32)	0.001	1.08 (0.96–1.22)	0.176
Cluster 3 vs cluster 2	1.03 (0.88–1.20)	0.731	0.98 (0.84–1.14)	0.764	0.84 (0.71–0.99)	0.043
Admission/bed						
Cluster 1 vs cluster 2	0.85 (0.83–0.88)	<0.001	0.84 (0.81–0.86)	<0.001	0.83 (0.80–0.86)	<0.001
Cluster 3 vs cluster 2	0.07 (0.06–0.07)	<0.001	0.06 (0.06–0.07)	<0.001	0.12 (0.10–0.13)	<0.001
RN ratio						
Cluster 1 vs cluster 2	0.34 (0.27–0.45)	<0.001	0.38 (0.30–0.48)	<0.001	0.48 (0.36–0.64)	<0.001
Cluster 3 vs cluster 2	0.28 (0.19–0.42)	<0.001	0.37 (0.25–0.54)	<0.001	0.65 (0.43–0.98)	0.041
RN						
Cluster 1 vs cluster 2	0.95 (0.86–1.04)	0.263	0.97 (0.88–1.07)	0.539	0.96 (0.85–1.09)	0.494
Cluster 3 vs cluster 2	1.14 (0.94–1.38)	0.190	1.04 (0.86–1.26)	0.704	0.99 (0.79–1.25)	0.983
LPN						
Cluster 1 vs cluster 2	1.14 (1.06–1.23)	0.001	1.10 (1.03–1.17)	0.007	1.05 (0.97–1.13)	0.236
Cluster 3 vs cluster 2	0.91 (0.82–1.01)	0.088	0.92 (0.83–1.02)	0.106	0.97 (0.87–1.08)	0.578
CNA						
Cluster 1 vs cluster 2	0.97 (0.92–1.02)	0.256	0.97 (0.93–1.02)	0.239	0.89 (0.84–0.94)	<0.001
Cluster 3 vs cluster 2	1.13 (1.05–1.21)	0.001	1.13 (1.05–1.22)	0.001	1.18 (1.09–1.27)	<0.001
Age ≥ 75						
Total beds						
Cluster 1 vs cluster 2	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.000
Cluster 3 vs cluster 2	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001	0.99 (0.99–0.99)	<0.001
Alzheimer unit						
Cluster 1 vs cluster 2	0.97 (0.85–1.12)	0.702	0.99 (0.87–1.14)	0.952	0.97 (0.84–1.12)	0.648
Cluster 3 vs cluster 2	0.96 (0.69–1.32)	0.785	1.01 (0.73–1.40)	0.944	0.76 (0.53–1.08)	0.134
SCU						
Cluster 1 vs cluster 2	0.71 (0.62–0.81)	<0.001	0.75 (0.66–0.86)	<0.001	0.84 (0.73–0.97)	0.015
Cluster 3 vs cluster 2	0.91 (0.67–1.25)	0.573	0.88 (0.64–1.21)	0.423	0.97 (0.68–1.37)	0.856
Multifacility						
Cluster 1 vs cluster 2	0.95 (0.92–0.98)	0.002	0.93 (0.90–0.96)	<0.001	0.93 (0.90–0.96)	<0.001
Cluster 3 vs cluster 2	0.75 (0.71–0.80)	<0.001	0.72 (0.68–0.77)	<0.001	0.76 (0.71–0.82)	<0.001
Profit						
Cluster 1 vs cluster 2	1.90 (1.83–1.97)	<0.001	1.65 (1.59–1.71)	<0.001	1.35 (1.30–1.40)	<0.001
Cluster 3 vs cluster 2	0.91 (0.85–0.97)	0.003	0.81 (0.76–0.86)	<0.001	0.77 (0.72–0.83)	<0.001
Admission/bed						
Cluster 1 vs cluster 2	0.87 (0.86–0.88)	<0.001	0.87 (0.86–0.88)	<0.001	0.89 (0.87–0.90)	<0.001
Cluster 3 vs cluster 2	0.05 (0.05–0.05)	<0.001	0.05 (0.05–0.05)	<0.001	0.12 (0.11–0.13)	<0.001
RN ratio						
Cluster 1 vs cluster 2	0.14 (0.12–0.17)	<0.001	0.16 (0.13–0.18)	<0.001	0.25 (0.21–0.29)	<0.001
Cluster 3 vs cluster 2	1.07 (0.77–1.47)	0.701	1.14 (0.84–1.57)	0.401	1.15 (0.84–1.59)	0.377
RN						
Cluster 1 vs cluster 2	1.07 (0.98–1.17)	0.137	1.08 (0.99–1.17)	0.104	1.05 (0.96–1.15)	0.287
Cluster 3 vs cluster 2	0.49 (0.39–0.62)	<0.001	0.49 (0.39–0.62)	<0.001	0.83 (0.66–1.04)	0.101
LPN						
Cluster 1 vs cluster 2	1.03 (0.98–1.07)	0.239	1.01 (0.97–1.05)	0.723	1.00 (0.96–1.05)	0.851
Cluster 3 vs cluster 2	1.04 (0.96–1.14)	0.317	1.03 (0.95–1.12)	0.419	1.06 (0.98–1.15)	0.156
CNA						
Cluster 1 vs cluster 2	0.96 (0.94–0.98)	0.001	0.96 (0.94–0.99)	0.002	0.97 (0.94–0.99)	0.013
Cluster 3 vs cluster 2	1.24 (1.19–1.30)	<0.001	1.24 (1.18–1.30)	<0.001	1.18 (1.12–1.24)	<0.001

CI, confident interval; Cluster 1, high readmission rate with high LOS; Cluster 2, low readmission rate with low LOS; Cluster 3, high readmission rate with low LOS; CNA, certified nursing assistant; LOS, length of stay; LPN, licensed practical nurse; OR, odds ratio; RN, registered nurse; SCU, special care unit.
Cluster 1 vs Cluster 2: Model 1 was unadjusted model, Model 2 adjusted for average age, the percent of female and the percent of the White, Model 3 adjusted for average RUGS NCMI MDS 3, admissions from acute care, cognitive function scale (CFS), bladder incontinent, bowel incontinent, hypertension, physician extender, obese, long stay with daily pain, long stay with pressure ulcers: high risk based on Model 2. Cluster 3 vs Cluster 2: Model 1 was unadjusted model, Model 2 adjusted for average age, the percent of female and the percent of the White, Model 3 adjusted for average RUGS NCMI MDS 3, admissions from acute care, long activities of daily living (ADL) MDS 3.0, CFS, bladder incontinent, physician extender, ventilator, long stay with daily pain, average acuity index based on Model 2.

residents are affected by facility and nursing staffing, which can be a focus for the continuous improvement of NH. Decreased LOS and readmission rate can be accomplished when levels of staffing, skill mix, resources, services, and NH facilities are adequately allocated, which requires increasing NH total bed and SCU supplies, asking for input from non-profit organizations and ensuring nurse retention and staffing quality. Moreover, as nurses improve the quality of care for NH residents, other costs associated with care are likely to decrease, creating opportunities for additional cost savings to the NH industry. Our study may contribute to the improvement of facility care planning decisions, resource availability, nursing staffing, as well as cost savings in NH.

Our study is subject to several limitations. First, the study was a retrospective design, and the nature of a retrospective study design may lead to potential patient selection bias; therefore, all results have to be interpreted in an exploratory context and require further prospective evaluation. In addition, it is important to acknowledge the role that resident characteristics play in LOS and readmission rates in NH, which may have inevitably influenced our results. As we mixed readmission rates and LOS outcomes, the results of our subgroup analysis were not easy to explain. Moreover, the study provides insight into the possible associations between variables rather than demonstrating causation. Future well-designed prospective studies are needed to further evaluate the effect of nursing factors on LOS and readmission in NHs.

Our study indicates that LOS and readmission rate of NH residents were influenced by facility characteristics nursing staffing number and level. The findings of this study could be used by NH organizations to evaluate strategies that could play in improving residents' readmission and LOS.

Author statements

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Ethical approval

As the data sets included in the study were downloaded from public databases, the study did not need the approval of an ethics committee.

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Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Original Research

Real-time surveillance of severe acute respiratory infections in Scottish hospitals: an electronic register-based approach, 2017–2022

J. Wells [a, b], J.J. Young [a, *], C. Harvey [a], H. Mutch [a], D. McPhail [a], N. Young [a], L.A. Wallace [a], G. Ladbury [a], J.L.K. Murray [a, d], J.M.M. Evans [a, c]

[a] Public Health Scotland, Glasgow, Scotland, UK
[b] Dept. Mathematics & Statistics, University of Strathclyde, Glasgow, Scotland, UK
[c] Faculty of Health Sciences and Sport, University of Stirling, Stirling, UK
[d] School of Medicine, University of St. Andrews, St. Andrews, UK

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ABSTRACT

Objectives: The COVID-19 pandemic highlighted the importance of routine syndromic surveillance of respiratory infections, specifically new cases of severe acute respiratory infection (SARI). This surveillance often relies on questionnaires carried out by research nurses or transcriptions of doctor's notes, but existing, routinely collected electronic healthcare data sets are increasingly being used for such surveillance. We investigated how patient diagnosis codes, recorded within such data sets, could be used to capture SARI trends in Scotland.

Study design: We conducted a retrospective observational study using electronic healthcare data sets between 2017 and 2022.

Methods: Sensitive, specific and timely case definition (CDs) based on patient diagnosis codes contained within national registers in Scotland were proposed to identify SARI cases. Representativeness and sensitivity analyses were performed to assess how well SARI cases captured by each definition matched trends in historic influenza and SARS-CoV-2 data.

Results: All CDs accurately captured the peaks seen in laboratory-confirmed positive influenza and SARS-CoV-2 data, although the completeness of patient diagnosis records was discovered to vary widely. The timely CD provided the earliest detection of changes in SARI activity, whilst the sensitive CD provided insight into the burden and severity of SARI infections.

Conclusions: A universal SARI surveillance system has been developed and demonstrated to accurately capture seasonal SARI trends. It can be used as an indicator of emerging secondary care burden of emerging SARI outbreaks. The system further strengthens Scotland's existing strategies for respiratory surveillance, and the methods described here can be applied within any country with suitable electronic patient records.

Introduction

Syndromic surveillance aims to monitor disease indicators in near real time to detect trends and outbreaks of disease earlier than would otherwise be possible via traditional public health methods.[1] This is typically achieved using data from various sources – such as hospitals, emergency departments, primary care, health advice phone lines and pharmacies.[2–5]

The COVID-19 pandemic has highlighted the ongoing importance of routine syndromic surveillance of respiratory infections, specifically new cases of severe acute respiratory infection (SARI).[6,7] These cover a wide range of pathogens, including SARS-CoV-2, respiratory syncytial virus (RSV) and influenza. The World Health Organization defines a SARI case as an acute respiratory infection with history of fever or measured fever of ≥38 C° and cough, with onset within the last 10 days, that requires hospitalisation.[8] SARI cases are thus defined by the presence of symptoms (fever, cough) rather than by laboratory confirmation of a pathogen.

The collection of syndromic respiratory data for surveillance often relies on questionnaires carried out by research nurses or

* Corresponding author.
E-mail address: Johanna.young@phs.scot (J.J. Young).

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transcriptions of doctor's notes.[9–11] For example, in response to the 2009 influenza A (H1N1) pandemic, New Zealand established syndromic SARI surveillance within selected sentinel hospitals in 2012[9] as part of the Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance programme.[10] Overnight inpatients with suspected respiratory infections were screened daily, and if the World Health Organization SARI definition was met, a respiratory sample was laboratory tested for influenza. Similar syndromic SARI surveillance systems have been implemented in nine Eastern European countries.[11] These surveillance systems are often time consuming and labour intensive for clinicians collecting the data.

Existing, routinely collected electronic healthcare data sets are increasingly being used for real-time surveillance. Although symptoms data such as 'cough' or 'fever' are generally not routinely collected by these data sets, suspected or confirmed condition/disease (e.g. 'pneumonia'), are often recorded as electronic diagnosis codes (e.g. International Classification of Diseases, Tenth Revision [ICD-10] codes).[12] These codes can act as proxies for SARI presentations and hence be used to identify new SARI cases in real time.

John Hopkins University outlined a blueprint for SARI surveillance in the United States (Electronic Surveillance System for the Early Notification of Community-Based Epidemics).[13] This combines numerous data sets, including a validated set of ICD-9 patient diagnosis codes (predecessor to ICD-10), to achieve daily outbreak surveillance at both community and hospital levels.[14,15] In Australia, ICD-10 code–based surveillance for influenza was explored, using data from two sentinel hospitals, both before and during a pandemic.[16] In Canada, ICD-10 code–based case-finding algorithms were demonstrated to successfully identify influenza hospitalisations from discharge records, using influenza-specific diagnosis codes (J09 and J10).[17] Similarly, in Germany, an ICD-10 code–based SARI surveillance system was developed within a private network of sentinel hospitals.[18]

The ICD-10 codes J09-J22, including influenza, pneumonia and other acute lower respiratory infections, are the most commonly used for SARI and influenza-specific surveillance[17,19,20] (Table 1). Two new ICD-10 codes specifically for SARS-CoV-2 have since been introduced, U07.1 and U07.2, for confirmed and suspected COVID-19 cases, respectively.[21,22]

Set against the backdrop of the COVID-19 pandemic, Public Health Scotland developed a new surveillance system to monitor SARI presentations at hospital level within Scotland. The main goal was to use existing routinely collected ICD-10 code data, detailing Scottish hospital admissions, to monitor SARI admissions in close to real time. This would act as an indicator of the secondary care burden associated with future outbreaks of respiratory pathogens, help inform intervention policy and thereby minimise the burden on the National Health Service. In this article, we describe the development and validation of the surveillance system.

Methods

The SARI surveillance system uses ICD-10 codes listed in the routinely collected patient diagnosis fields of Scotland's two main national hospital data sets that collect data on every inpatient hospital admission in Scotland: The General Acute Inpatient and Day Case - Scottish Morbidity Record (SMR01)[25] and the Rapid Preliminary Inpatient Dataset (RAPID).[26] Both contain patient-level demographic details (treatment location, age, gender *etc*), and other variables related to a patient's stay in hospital are indexed by a Community Health Index. This unique patient identifier is used widely in other national data sets. Both SMR01 and RAPID contain six patient diagnosis fields, populated with ICD-10 codes, to document a patient's main condition and any comorbidities.

Table 1
ICD-10 codes used for severe acute respiratory infection, influenza-like illnesses and SARS-CoV-2 surveillance within the literature.

ICD-10 code	Corresponding condition	Literature used by
J00	Acute nasopharyngitis (common cold)	17,20
J01	Acute sinusitis	20
J02	Acute pharyngitis	17
J04*	Acute laryngitis and tracheitis	17
J06	Acute upper respiratory infections of multiple and unspecified sites	16,17,20
J09*	Influenza due to certain identified influenza viruses	9,17,18,20,23
J10*	Influenza due to other identified influenza virus	9,17,18,20,23
J11*	Influenza due to unidentified influenza virus	9,16–18 20,23
J12*	Viral pneumonia, not elsewhere classified	9,18,20,23
J13*	Pneumonia due to Streptococcus pneumoniae	9,18
J14*	Pneumonia due to Haemophilus influenzae	9,18
J15*	Bacterial pneumonia, not elsewhere classified	9,18
J16*	Pneumonia due to other infectious organisms, not elsewhere classified	9,17,18
J17*	Pneumonia in diseases classified elsewhere	9,18
J18*	Pneumonia, unspecified organism	9,16–18,20
J20*	Acute bronchitis	9,18,20,23
J21*	Acute bronchiolitis	9,18,23
J22*	Unspecified acute lower respiratory infection	9,16,18,20,23
J40	Bronchitis, not specified as acute or chronic	20
B34	Viral infection of unspecified site	16
B97.4	Respiratory syncytial virus as the cause of diseases classified elsewhere	23
R05	Cough	20
U07.1*	SARS-CoV-2 confirmed	21
U07.2*	SARS-CoV-2 suspected	21
J80*	Acute respiratory distress syndrome	24

ICD-10, International Classification of Diseases, Tenth Revision.
*ICD-10 codes part of SARI surveillance in Scotland.

SMR01 is a validated data set with ICD-10 coding fully complete. However, records are completed after hospital discharge, and therefore, long-stay patients may not be included in the data set for a significant period, with a fully complete data set having a time lag of around 3 months.

In contrast, the RAPID data set is updated weekly in each of the 14 local health authorities in Scotland, with ICD-10 codes continuously added for a fixed period, after which no further updates are made. This period varies by a local health authority, from 2 to 8 weeks. The level of completeness of the ICD-10 codes therefore also varies by health authority, ranging from <5% to >90%, although overall in RAPID, the patient diagnosis fields are completed for around 30% of all hospital admissions. However, no local health authority could be identified that could act as a sentinel health authority on its own, as those with the highest levels of completeness tended to have the longest time lag. Because RAPID is an unvalidated data set, it is also possible that ICD-10 codes are updated for SMR01.

Using the ICD-10 codes likely to be representative of a SARI case (J09-J22, J80, U07.1, U07.2 and J04; Table 1), three SARI case definitions (CDs) were defined using either SMR01 or RAPID:

1. Sensitive case definition (CD1): Any patient discharged from a Scottish hospital who had at least one of the specified ICD-10 codes listed in any of the six patient diagnosis fields in their SMR01 record for each individual hospital stay.
2. Specific case definition (CD2): Any patient discharged from a Scottish hospital who had one of the specified ICD-10 codes listed in the main/first patient diagnosis field in their SMR01 record for each individual hospital stay.

3. Timely case definition (CD3): Any patient admitted to a Scottish hospital who had at least one of the specified ICD-10 codes listed in any of the six patient diagnosis fields in their RAPID records for each individual hospital stay.

To assess how well their results matched known trends in seasonal data (representativeness), each CD was applied to historic SMR01 and RAPID data covering the period from 2017 to 2022. The number of weekly SARI cases collected by each CD was then compared with historical influenza and SARS-CoV-2 hospitalisation trends over these four seasons. These included all patients with a laboratory-confirmed test result either during their stay or within 7 days before admission for influenza and 14 days before admission for SARS-CoV-2. Patients with multiple laboratory-confirmed test results were counted separately for each infection.

In the absence of gold-standard symptoms data to definitively confirm an SARI diagnosis, we made the assumption that CD1 case counts most closely reflected the trueSARI hospital burden as all six patient diagnoses fields were used. The proportion of overall SARI cases captured by each CD (sensitivity) was estimated by calculating the weekly proportions of SARI cases (as a percentage) captured by the sensitive CD (CD1), which were also captured by the specific (CD2) and timely (CD3) CDs. The annual average of these percentages was then determined for each season (International Organization for Standardization (ISO) week 40 to week 39). A correlation analysis was conducted to examine the relation between the three CDs (CD1 vs CD2, CD1 vs CD3 and CD1 vs CD3 excluding weeks 10–23, 2020), by week.

As a further step in validation, the SARI cases were linked via Community Health Index number to the ECOSS (Electronic Communication of Surveillance in Scotland) data set that provides all laboratory test data for respiratory viruses (including SARS-CoV-2, influenza and RSV). SARS-CoV-2, influenza and RSV-confirmed SARI cases were defined as SARI cases with a laboratory-confirmed test result either during their hospital stay or 7 days before admission for influenza and RSV and 14 days before admission for SARS-CoV-2. These respiratory viruses were selected, as they are some of the most common viruses associated with SARI.[27–29]

R statistical software was used for all data analysis and the generation of the graphs.[30] Week 53 for non-leap years presented in the graphs was dealt with by averaging data for week 52 and week 1 of the subsequent year.

Results

Representativeness and sensitivity analyses

The representativeness analysis shows that all CDs identified similar seasonal peaks and trends compared with the laboratory-confirmed influenza and SARS-CoV-2 test results between week 40, 2017, and week 10, 2022 (Fig. 1). The number of identified SARI cases drops substantially in the most recent period, reflecting the 8- to 12-week time delay for the completion of SMR01. The decrease is less pronounced for RAPID data, which only ever captures a proportion of hospital admissions. The sensitivity analysis indicates that on average (from week 40, 2017, to week 10, 2022), CD2 captured 67.5% (42,388/62,752) of the SARI cases identified by CD1 and showed a strong correlation ($r = 0.98$). CD3 only returned 23.8% (14,815/62,752) of CD1's total case count (Table 2) and correlated moderately with CD1 ($r = 0.48$). However, CD3 still captured the overall trends of the other CDs, and this percentage increased to 33.3% (20,086/60,333) during the 2019–2020 season (Fig. 1). A strong correlation was found between CD1 and CD3 when weeks 10–23, 2020, were excluded, as the completion of ICD-10 codes in RAPID was significantly higher than any other period investigated ($r = 0.75$). The proportion of cases captured by CD2 did not vary significantly over time, but there was no additional advantage in using CD2 for the surveillance system.

All CDs identified the influenza outbreak that occurred in 2017–2018 and trends during this time were similar to confirmed influenza test results of hospitalised patients. The number of new SARI cases identified through CD1 was highest during this outbreak and higher even than during the peak of the COVID-19 pandemic. During the 2018–2019 winter season, CD1 and CD2 showed an increase in SARI cases before an increase in laboratory-confirmed influenza cases was observed. Similarly, at the start of the 2019–2020 season, SARI cases identified through CD1 and CD2 increased before an increase in laboratory-confirmed influenza cases was seen. Later that season, and at the start of the pandemic, an increase in SARI cases was observed with all three CDs, with CD3 picking up the rise in SARI cases slightly before the laboratory test result data, demonstrating its potential to identify changes in SARI hospital admissions that may occur before other signals. At the start of the 2021–2022 winter season, the number of admissions identified through CD2 was almost identical to the number of SARS-CoV-2 laboratory-confirmed tests of hospitalised patients, suggesting that during this time, all hospitalised patients with SARS-CoV-2 had a U07 (SARS-CoV-2) code in their main diagnosis field in SMR01. These analyses confirm that the selected CDs capture representative trends in SARI cases.

Laboratory-confirmed results

During the first two-and-a-half-year observation period, seasonal patterns were visible for SARI cases identified through CD3 that had a laboratory-confirmed influenza test result, whereas seasonal patterns for those with a laboratory-confirmed RSV test result were observed in winter 2018–2019 and 2019–2020 (Fig. 2). Minimal influenza and RSV were observed in 2020–2021 and 2021–2022, whereas there was a clear peak in SARI cases with a laboratory-confirmed SARS-CoV-2 test result around week 14, 2020.

Discussion

In Scotland, the CD3 is now being routinely used in parallel with the CD1 to identify SARI cases for this new SARI surveillance system. SARI surveillance (as opposed to pathogen-based surveillance) has the important advantage of identifying increased SARI activity arising from new variants or pathogens that are not yet part of routine testing procedures. Although the time lag associated with the availability of complete SMR01 data limits its use for achieving true real-time surveillance using either CD1 or CD2, CD1 and CD3 complement each other to provide both a complete and timely SARI surveillance system for Scotland. CD3 is being used to carry out weekly identification of SARI cases within RAPID at national level. Although ICD-10 codes have not reached their full level of completeness in the most recent 8-week period, and the actual numbers of SARI cases are uncertain, any increase in SARI numbers within these most recent weeks will always represent an increase in real-life cases and can thus act as an indicator of increasing burden in secondary care. Trends in overall SARI numbers can also be cross-checked with trends in the individual local health authorities that have the shortest time lag for full completion for early signals of localised increases in SARI admissions. CD1 using SMR01 data then provides a more complete, but retrospective, picture of overall number of admissions. This enables validation of the peaks and trends captured by CD3 retrospectively and also provides

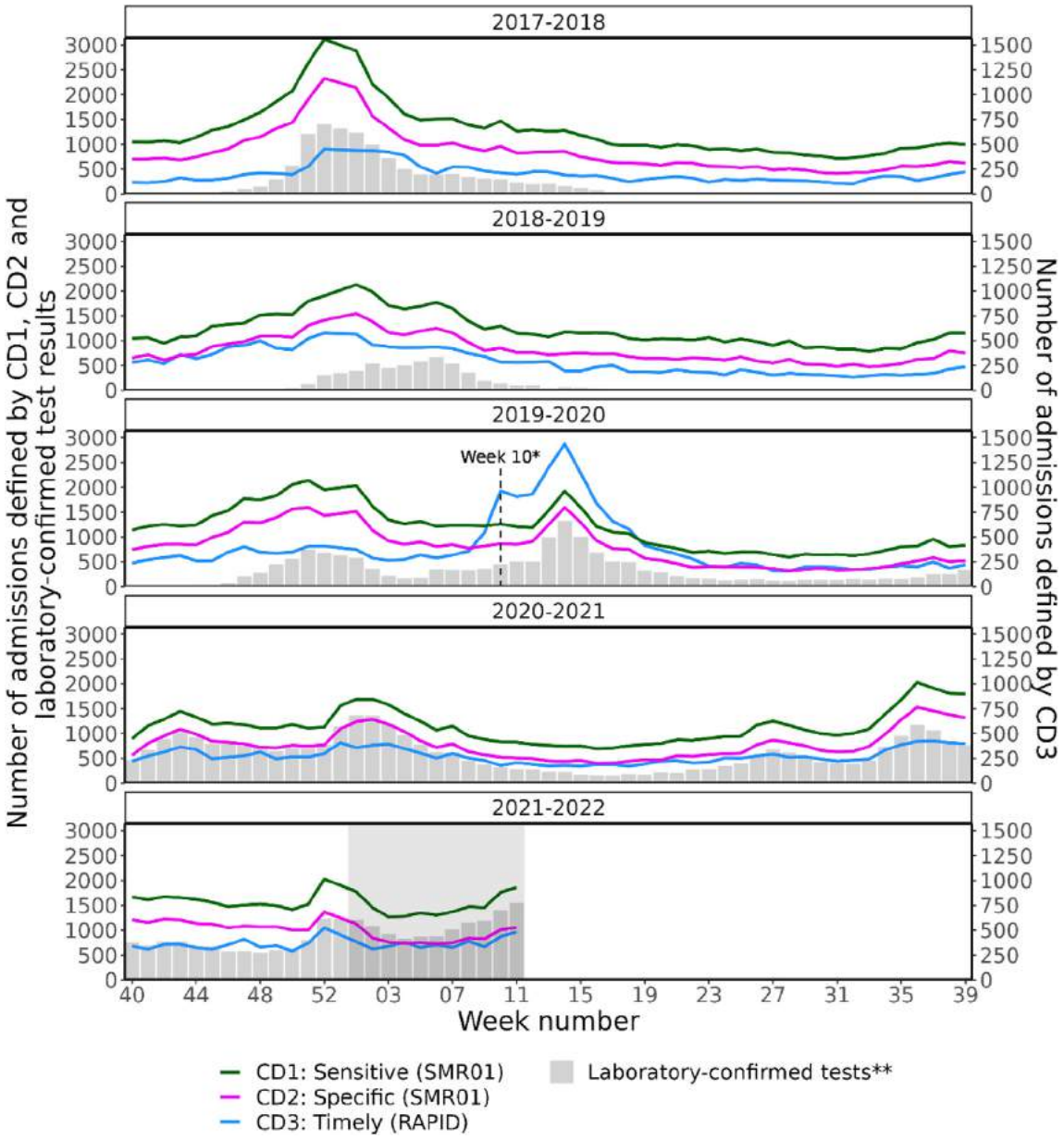

Fig. 1. Weekly number of SARI cases for each case definition and weekly number of laboratory-confirmed influenza and SARS-CoV-2 test results amongst hospital patients either during their stay or within 7 and 14 days before admission, respectively, by season, from week 40, 2017, to week 10, 2022. *Week 10, 2020, corresponds to the first case of community transmission of SARS-CoV-2. **Laboratory-confirmed test results of influenza and SARS-CoV-2; these correspond to positive results obtained during the patient's hospital stay or the 7 days before hospital admission for influenza or the 14 days before hospital admission for SARS-CoV-2. ***The CD3 SARI cases are scaled by two (with an appropriate y-axis provided on the right) to emphasise the patterns the case definition captures. ****The grey window highlights the maximum estimated time delay within the RAPID data set. Figures within this window (for CD3) are therefore liable to increase further.

Table 2
Number and percentage of SARI cases captured by the sensitive case definition (CD1; n = 62,752), which were also captured by the specific (CD2) and timely (CD3) case definitions, by season, from week 40, 2017, to week 10, 2022.

Case definition	Number and percentage of CD1 cases captured									
	2017–2018		2018–2019		2019–2020		2020–2021		Average	
	n	%	n	%	n	%	n	%	n	%
CD1: sensitive (SMR01)	67,221	100	63,400	100	60,333	100	60,055	100	62,752	100
CD2: specific (SMR01)	44,530	66.2	42,329	66.8	41,387	68.6	41,306	68.8	42,388	67.5
CD3: timely (RAPID)	10,499	15.6	14,909	23.5	20,086	33.3	13,765	22.9	14,815	23.8

supporting evidence for any recent patterns that emerged using CD3. Further data linkage provides an in-depth analysis of the SARI cases and outputs on age groups, gender, laboratory pathogens detected and ICU/HDU admission. Weekly reporting from the system is used to help inform policy decisions at both local health authority level and within national government.

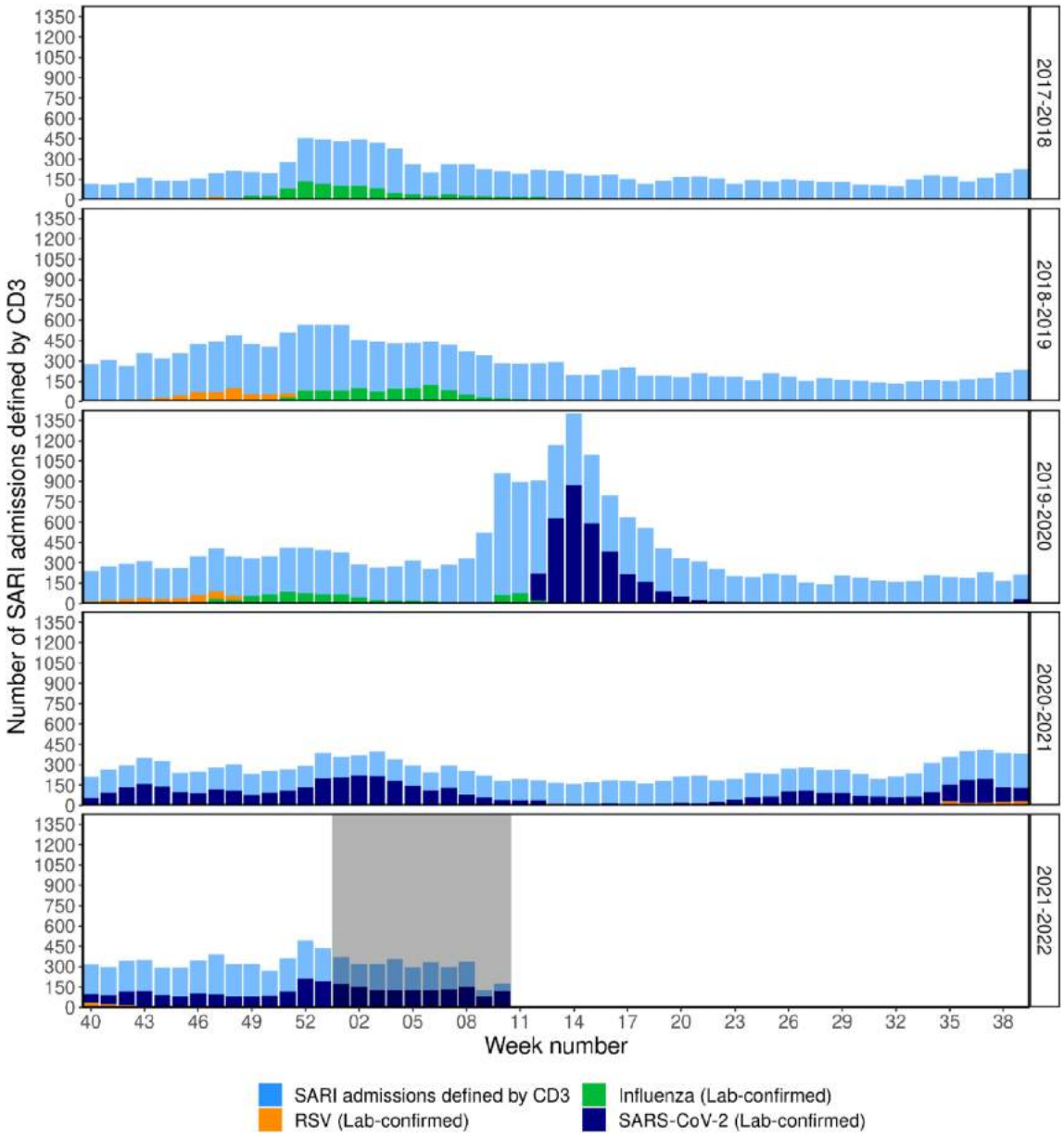

Fig. 2. Weekly number of SARI cases identified by CD3, by laboratory-confirmed pathogen and season, from week 40, 2017, to week 10, 2022. *The grey window highlights the maximum estimated time delay within the RAPID data set. Figures within this window (for CD3) are therefore liable to increase further.

The validation of the three CDs demonstrated that the number of SARI cases identified by CD3 was highest in 2019–2020 during the peak of the COVID-19 pandemic. CD3 picked up seasonal peaks after the introduction of SARS-CoV-2, but pre-SARS-CoV-2, these seasonal trends are less evident. This is likely due to the improvement of the data quality and completeness levels of ICD-10 codes in the RAPID data set as a response to the pandemic.

CD1 and CD2 demonstrate clear seasonal trends across the four seasons in line with the laboratory-confirmed influenza and SARS-CoV-2 test results. However, the number of SARI cases identified through both CDs reached their highest levels during the influenza epidemic in 2017–2018 and not during the pandemic, despite widespread reporting that health systems were experiencing unprecedented strain during this time. It may be that the threshold for an SARI hospital admission was higher during the pandemic. The Scottish population was directed to self-isolate and only seek care when absolutely essential, so only the most severe cases of COVID-19 patients were admitted to hospital, and these patients required high-level and resource-intensive care.[31–33]

Before the COVID-19 pandemic, it was observed that the data on laboratory-confirmed, positive influenza cases consistently fell significantly below the weekly case count numbers identified by CD1 and CD2 used by the SARI surveillance. It may be that fewer patients were tested for non-SARS-CoV-2 respiratory pathogens at this time. This changed in 2020–2021 when the increase in SARS-CoV-2 testing meant that the number of laboratory-confirmed cases was much closer to the CD1 and CD2 figures and is particularly obvious at the start of the pandemic in weeks 10–20, 2020, when the first case of community transmission was identified in Scotland,[34] and in the rest of the 2020–2021 season (Fig. 1).

Similarly, in 2020–2021, the high number of SARS-CoV-2 tests being recorded provides a useful platform for validation of the SARI

CDs. Almost all respiratory hospital admissions would have had a SARS-CoV-2 test, and so the testing figures could be assumed to capture a high proportion of SARS-CoV-2 hospital admissions. However, this is only applicable to SARI cases admitted for SARS-CoV-2 due to the low transmission of influenza and other respiratory pathogens during this same period, probably as a result of the nationwide lockdowns and social-distancing measures associated with the SARS-CoV-2 response.

The validation highlighted several periods of poor completion of ICD-10 codes within the RAPID data set. Nationally, between 2017 and 2019 (inclusive), the completion levels of these ICD-10 codes were around 10% but have increased to around 30% completion more recently. At the start of the COVID-19 pandemic, the ICD-10 completion levels in RAPID increased considerably but soon decreased when pressure in health care settings increased. This RAPID completeness issue is complex; partly caused by the collection of the ICD-10 codes not being mandatory; non-standardised policies, differing standards and multiple different reporting formats across the various regional local health authorities; alongside staffing constraints experienced within the data reporting teams. Completion of ICD-10 codes within the RAPID data set also varies between hospital and week by week, so timeliness and completeness of RAPID need to be continually monitored at local health authority level, and checks made for potentially biased completeness levels, for example, by ICD-10 code or over time. It is likely that similar variations and inconsistencies may occur in the data collection arena across countries worldwide. Thus, when developing this kind of electronic register-based surveillance, care should be taken to identify and understand any sources of variation, along with any other nuances of a chosen data set.

In summary, SARI surveillance using routinely collected, electronic hospital data sets has been shown to be viable and a valuable source of information for monitoring SARI trends across Scotland, given current levels of completion and timeliness. The quality of the real-time results could be further strengthened if levels of completeness were improved. Outputs provide detailed information without the need for additional data collection resources at hospital level and can easily be expanded upon, or linked to additional data sets, to provide further insight. This is a faster alternative for real-time SARI surveillance than traditional syndromic methods. Scotland's SARI surveillance system can act as an indicator of secondary care burden; be easily adaptable to include both existing and future emerging respiratory pathogens; reflect the broader picture of disease burden due to SARI; and provide data for further analyses, such as vaccine effectiveness for COVID-19 and influenza. SARI outputs presented here are updated routinely and presented in weekly Public Health Scotland reports. Further validation work is ongoing to assess and further enhance the performance of this surveillance system. From an international perspective, this type of surveillance could be applied within any country with similar electronic hospital data sets and could even evolve into a real-time worldwide SARI surveillance system, which could help strengthen SARI surveillance across the globe.

Author statements

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Ethical approval

No ethical approval was required for this study.

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Competing interests

None declared.

Author contributions

J.W., H.M. and G.L. developed the study protocol. J.W., C.H., H.M., D.M. and N.Y. analysed the data, with support from J.J.Y. and J.E. J.W., C.H., J.J.Y. and J.E. drafted the article. L.A.W. and J.M. critically reviewed the article. All authors revised the article critically and approved the final version.

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Review Paper

Smallpox vaccination and vaccine hesitancy in the Kingdom of the Two Sicilies (1801) and the great modernity of Ferdinand IV of Bourbon: a glimpse of the past in the era of the SARS-COV-2 (COVID-19) pandemic

M. Martini [a, *], M. Bifulco [b], D. Orsini [c]

[a] Department of Health Sciences, University of Genoa, Genoa, Italy
[b] Department of Molecular Medicine and Medical Biotechnologies, University of Naples "Federico II", Naples, Italy
[c] University Museum System of Siena (SIMUS), History of Medicine, University of Siena, Siena, Italy

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ABSTRACT

Objective: The current health emergency caused by COVID-19 disease shows several correspondences with well-known epidemics of the past. The knowledge of their management and overcoming could give us useful tools to face the present COVID-19 pandemic and future epidemics.
Study design: On 1 March 1801, the first smallpox vaccinations were carried out in Palermo, and a few weeks later, the vaccine was also administered in Naples and the various provinces of the Kingdom. We aim to study the mass vaccination programme initiated by the Bourbon king Ferdinand IV that was the first large-scale campaign to be conducted in Italy and one of the first in Europe.
Methods: The authors searched and examined historical testimony and different aspects linked to the public health issues on vaccination. It is a topical topic in the current period with the COVID pandemic.
Results: Albeit with the due differences determined by the passage of time and by the scientific and cultural advances of modern society, this testimony from the past can provide us with food for thought regarding how to face the present COVID-19 pandemic and to prepare for the future. Indeed, it shows us how the terrible smallpox epidemic was handled and finally overcome, thanks to vaccination.

Introduction

Exactly 220 years have passed since the history of vaccination in the dominions of Southern Italy began, when Ferdinand IV, King of Naples and Sicily (Fig. 1), initiated the fight against smallpox.

Today, despite the differences determined by the passage of time and by scientific advances, this history still has lessons to teach us as we face the current coronavirus pandemic. Indeed, it can show us how and by what means the tremendous smallpox epidemic was handled and finally overcome.

In those days, epidemic diseases were the leading causes of death. In the early years of the 21st century, by contrast, infectious diseases steadily and markedly declined as a cause of death – at least until the appearance of COVID-19. This is due to the fact that, over the years, fundamental public health measures have been implemented, such as mass vaccination campaigns, which have proved highly successful.

In this regard, David Salisbury, Associate Fellow of Global Health Security at Chatham House, the *Royal Institute of International Affairs in London*, asserted that 'Thanks to vaccinations, about 9 million deaths were avoided between 2000 and 2016'.[1]

Indeed, over the years, vaccination has proved to be the safest, and sometimes the only, means of protecting against possible epidemics and pandemics. Admittedly, adverse events and side-effects may occur, although these affect only a very small number of those who are vaccinated.

In the light of the history of vaccination and the impressive results achieved, the current antivaccination arguments appear not easy to understand. Interestingly, however, such arguments had already been levelled against the first smallpox vaccination campaigns at the beginning of the 19th century.[2]

In 1801, the whole of Sicily, and especially the city of Palermo – where the King had taken refuge after abandoning Naples at the

* Corresponding author.
E-mail address: mariano.yy@gmail.com (M. Martini).

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Fig. 1. Portrait of Ferdinando IV di Borbone (Napoli 1751–1825).

end of 1798, following the very brief experience of the French republic – were in the throes of a terrible smallpox epidemic, which killed over 8000 people and caused a veritable slaughter among children.[3,4]

Smallpox ('*variola*' in late Latin, derived from various, meaning '*varied, variable, mottled*') is an acute, infectious, contagious and epidemic viral disease characterised by a typical vesiculo-pustular rash.[5]

Reported since ancient times,[6] smallpox constantly reappeared in Europe after the middle of the 16th century, becoming the leading endemic disease in the following century.[7] It had a severe effect on society, striking younger age groups in particular and impacting negatively on the reproduction of the population. In the 18th and 19th centuries, smallpox was rife throughout Europe, being responsible for numerous epidemics, which broke out at intervals of 5–10 years, as soon as a sufficiently large population of non-immunised residents had been reconstituted.[8,9]

Ferdinand IV, whose brother don Filippo had died of smallpox in 1777, determined to seek some means of saving his people from this terrible disease. In 1778, he therefore ordered the court physician Angelo Maria Gatti to inoculate smallpox into him and his three children.[10,11]

In this case, it was inoculation of smallpox or variolation, an obsolete method of immunising patients against smallpox by infecting them with substance from the pustules of patients with a mild form of the disease (variola minor); it was basically a deliberate inoculation of an uninfected person with the smallpox virus (as by contact with pustular matter) that was widely practiced before the era of vaccination as prophylaxis against the severe form of smallpox, it was the method used before Jenner.

The vaccine with the 'Jenner method' was introduced in 1796, and it was the inoculation of exudate taken from vaccine smallpox pustules, which gave immunity both to this disease and to the more terrible human smallpox.

Indeed, the subject of inoculation was constantly present in Bourbon politics, so much so that the 1789 Code regulating the community of San Leucio contained an entire section devoted to inoculation against smallpox by means of the use of 'material' drawn from pustules of human smallpox.[13]

At the beginning of the 19th century, the King's wish was therefore to use the method designed in 1796 by the English physician Edward Jenner (1749–1823), whose book *The Origin of the Vaccine Inoculation* was published in 1801.[14]

Having observed that people who had recovered from 'cowpox' did not contract 'smallpox', Jenner deduced that the former disease could confer protection against the latter.[15,16] Indeed, as cattle farmers of the time used to say, 'I cannot take smallpox for I have had cowpox.[17] (See Fig. 2).

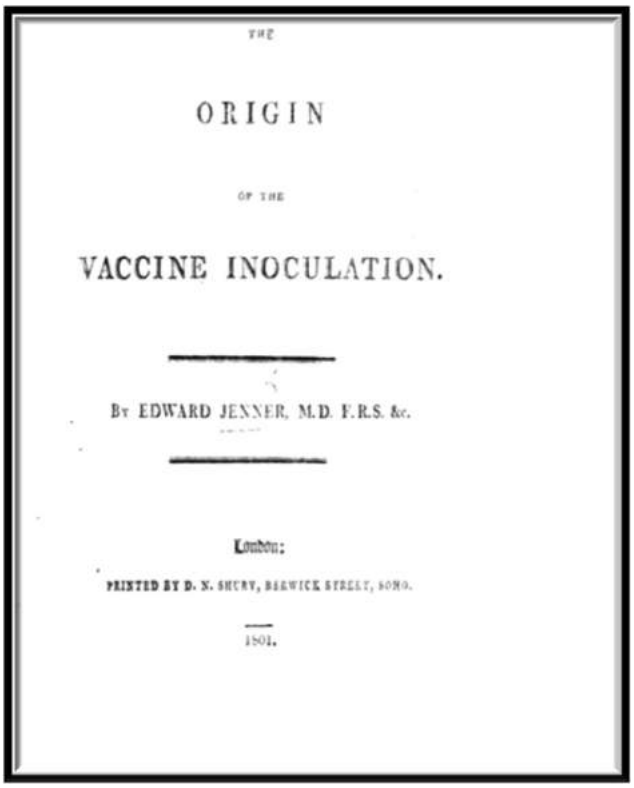
Jenner therefore put forward the hypothesis – which subsequently proved correct – that artificially infecting a healthy individual with material from a cowpox pustule would immunise that individual against smallpox. As was subsequently demonstrated, this phenomenon was due to the resemblance of the antigens of the two viruses. In other words, the antibodies active against cowpox were also active against smallpox. Thus, Jenner laid down the principles of vaccination (from the Latin word *vaccinus*, derived from *vacca*: cow), a preventive therapy against smallpox that proved more efficacious than inoculation and which had fewer complications.[12]

His discovery spread with surprising speed in Europe that, at the time, was at the beginning of the long years of the Napoleonic Wars. In the following years, it spread also to the Americas.[18] (See Fig. 3).

Smallpox vaccination in the kingdoms of southern Italy

Although Ferdinand IV did not have the possibility to produce Jenner's anti-smallpox vaccine in industrial quantities, he

Fig. 2. Portrait of Edward Jenner (1749–1823).



THE

ORIGIN

OF THE

VACCINE INOCULATION.

By EDWARD JENNER, M.D. F.R.S. &c.

London:

PRINTED BY D. N. SHURY, BERWICK STREET, SOHO.

1801.

Fig. 3. The origin of the vaccine and inoculation (1801).

nevertheless managed to stipulate an agreement with two physicians, Joseph Andrew Marshall and John Walker.

Both endorsed Jenner's method and had been commissioned by the Royal Navy to take part in a naval expedition to Egypt to inoculate the members of the crew and, at the same time, to spread the new method of prevention among the British troops stationed in the Mediterranean. After reaching Gibraltar, Minorca and Malta, the two physicians separated; Walker continued on the route towards Egypt, whereas Marshall headed for Palermo.[19]

With great ability, the King succeeded in getting vaccination extended to the populations of Palermo and Naples and provided funds and transport. On 14 March 1801, Joseph Andrew Marshall, on the invitation of Queen Maria Carolina of Austria, carried out the first vaccinations in Palermo; these were repeated publicly and free of charge on Mondays and Thursdays. Thus, Marshall was able to teach the new method to his colleagues Giovanni Vivenzio and Michele Troja, who were the Court Physician and the Surgeon of the King's Chamber, respectively.[20]

These two men would certainly have enjoyed considerable prestige in the local community and undoubtedly held great sway over the population; this was especially true of the Court Physician, who headed the entire health care organisation of the country.[21]

Moreover, to further spread knowledge of the new system of prophylaxis in the medical environment, Marshall published the treatise *Osservazioni sopra il vajuolo vaccino* in Palermo and opportunely dedicated it to King Ferdinand IV.[22]

To spread the word more effectively, public posters were distributed. Through Dispatch N° 228 of 23 June 1801, which was sent by the Minister for Ecclesiastical Affairs to the director of the General Police, 100 posters announcing Marshall's public inoculations at a centre in Monteoliveto were affixed in the city streets.[23]

The main targets of vaccination were children, who were the most severely affected by the disease. Indeed, they rarely survived, and when they did, they risked being left blind or deformed. From the report presented by Dr Marshall to the House of Commons in London in 1802, it emerged that, in collaboration with the Bourbon health system, he had managed to vaccinate over 10,000 children in less than 1 year. Moreover, according to the dates reported in the health care registers at the time, Ferdinand IVs vaccination programme was the first large-scale campaign to be conducted in Italy and among the first in Europe.[24]

Obviously, this vaccination programme was not exempt from criticism; heated arguments raged between supporters and opponents, often detractors, giving rise to an intense scientific and cultural debate. This is not surprising if we consider that even today, more than two centuries later, while the fate of our immediate future depends on a vaccine that was created in a very short time, there are still many people who oppose vaccination or remain hesitant. And this despite the far greater scientific knowledge available today, and the enormous success of mass vaccination campaigns that have led to the eradication of smallpox and have drastically reduced the incidence of many other epidemic diseases.[25,26]

Scepticism towards vaccinations is a phenomenon that has existed ever since this first vaccine became available and also during the 18th century towards inoculation. Today, however, it is certainly fuelled by the ease with which anyone at all can glean contradictory information from the Internet and also by many other bogus explanations that have nothing to do with vaccines.[27]

In English, this phenomenon is known as 'Vaccine Hesitancy'; in Italian, it is called 'esitazione vaccinale' (a term that combines the concepts of indecision, uncertainty, reluctance and procrastination).

It is a complex phenomenon that is strictly linked to different contexts with different determinants: historical period, geographical area, political situation. The vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services. Vaccine hesitancy is complex and context specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence.[28]

Thus, vaccine hesitancy constitutes only the latest chapter in a story that began in Italy in the middle of the 18th century, concomitantly with the first methods of smallpox prevention.[29] Indeed, back in the second half of the 18th century, the inoculation of smallpox (or 'variolation') elicited contrasting opinions in the various cities where this practice had been adopted.

After undergoing variolation, Ferdinand IV himself clashed with his father, King Charles III of Spain, who, being very religious, claimed that the practice conflicted with the will of God.

This idea was one of the most common reasons for opposition to the practice of inoculation, and later of vaccination; many people disapproved of the practice, in that they believed that their own death or the death of their children due to smallpox was merely the manifestation of God's will.

In those days, unlike today, doubts and rejection of vaccination were based on abstract beliefs. Another widely held belief was that vaccination was dangerous because smallpox disease needed an 'escape valve'. Indeed, according to a conviction that was rooted in the humeral tradition of Hippocrates, and later taken up by Galen, the manifestation of disease reflected a need for purification.

A further source of opposition to vaccination was the fear that inserting animal material into the human body could transmit animal diseases to people. Moreover, it was feared that the 'arm-to-arm' technique used in vaccination might spread diseases such as syphilis, as sometimes happened.

In 1821, vaccination was made obligatory in the Kingdom of the Two Sicilies (the first of the Italian states in which the obligation was introduced), whereas in the unified nation, this obligation was brought in by the Crispi-Pagliani law in 1888. Clearly, this step necessitated the implementation of specific strategies of health education to train doctors in the practice of vaccination, to inform the population, to answer the most frequent questions that arose and to reply to those who opposed vaccination.

The protagonists of the vaccination programme according to the 'Jenner method'

To better understand the measures implemented, it is useful to know something of the protagonists of the vaccination campaign that was initiated in southern Italy in 1801. These pioneers of vaccination operated at the same time as Luigi Sacco, who had been engaged since 1799 in spreading the practice of vaccination in the Cisalpine Republic, where smallpox deaths were drastically reduced, and Giacomo Barzellotti in Siena and in the Dipartimento (Department) dell'Ombrone (in Tuscany).

In the vaccination campaign conducted Southern Italy the name of Michele Troja (1747–1828) stands out. The king's personal surgeon, Troja had already been in charge of the 'Direzione Vaccinica' (Vaccination Directorate) created by Ferdinand IV in 1802 to coordinate vaccinations in the capital and in the provinces.

From the outset, Troja was flanked by his closest collaborator, the Salento physician Antonio Miglietta (1767–1826), who was the true architect of the project; the 'apostle of vaccination for the Kingdom of Naples', as he defined himself.[30,22] (See Fig. 4).

When the Direzione Vaccinica was transformed into the *Comitato Centrale di Vaccinazione* (Central Vaccination Committee) in 1807, its presidency was conferred upon Domenico Cotugno (1736–1822), the most famous southern Italian physician of the day, and Miglietta became the Secretary. Between the two, there was a perfect harmony with regard to the social objective that medicine should have to save the lives of as many people as possible.[31]

Fig. 4. Antonio Miglietta (1767–1826).

This objective fitted well with the illuminist vision, and with that of the Bourbon king, of the physical and moral well-being of all citizens, regardless of their social class.

This same view underlay the king's decision to promote free health care and to offer money prizes to those vaccinees whose names were picked out at random.[32]

Finally, another particularly prominent figure was Gennaro Galbiati (1766–1844), who promoted retrovaccination; that is to say, vaccination with a virus obtained from an animal previously inoculated with a human virus. Indeed, in agreement with Domenico Cotugno's idea that 'one who inoculates everything',[33] Galbiati strenuously opposed the 'arm-to-arm' method to avoid the possible transmission of venereal diseases during vaccination.

The important status of these two doctors testifies to the fact that smallpox was deemed to be a major issue that needed to be tackled directly by the State, and above all, that vaccination should be offered free of charge to all social classes.

On the basis of the indications provided by these physicians, the governors took some extremely effective decisions. To train future doctors in the practice of vaccination, they decreed that no student could graduate from the universities of the Kingdom without having demonstrated perfect knowledge of the mechanism of vaccination and of how to vaccinate.

Similarly, midwives were also obliged to undergo training in vaccination and to spread knowledge of the practice. Indeed, midwives were regarded as veritable 'social mediators', able to explain to mothers in simple language what vaccination was and how it would benefit their children. In addition, parish priests were requested to inform and convince their parishioners, especially those of the lower social classes, of the benefits of vaccination.

With a view to persuasion, Antonio Miglietta, director of the public Vaccination Establishments, responded to a precise request by the King (dispatch of 6 August 1806) by implementing a detailed project to overcome all resistance to vaccination; to this end, he produced three strategic documents, printed on 9 August 1806 at the expense of the Royal Treasury: *Istruzione sull'origine e il merito dell'inoculazione vaccina*, an informative brochure; *Ricordi salutari*, distributed to parents and godparents after a child's baptism; and *Omelia del vescovo di Goldstat, addressed to parish priests*.[24]

In the same period, similar interventions were undertaken by Luigi Sacco (1769–1836) in the Cisalpine Republic. Sacco recounted that: "priests could easily instruct and convince the faithful, from the pulpit or in their catechisms, of the need for this operation".[34]

This constituted an efficacious means of overcoming the diffidence of the many people, especially those of the lower classes, who superstitiously resigned themselves to the disease, convinced that there was no remedy for it, thereby hindering vaccination'. For this reason, in the territories where he planned to carry out vaccination, he distributed circulars and, above all, a copy of the 'Omelia' written by the zealous bishop of Goldstat explaining the valuable discovery of the inoculation of the anti-smallpox vaccine. '*The Omelia fits perfectly into Luigi Sacco's complex program, given that he himself is the author*'.[35]

Indeed, the Bishop of Goldstat, with his sound medical-scientific, as well as religious, knowledge did not really exist; he was invented by Sacco purely for the purpose of communication.

Through this fictitious character, Sacco was able to call on an incontestable and highly persuasive authority, while, at the same time, exploiting his own medical competence. Thus, he was able to persuade people to accept the vaccine as a remedy offered by divine Providence to save them, and especially their children, from the disease.

However, despite the many interventions undertaken within the framework of a sort of *ante litteram* information campaign, considerable prejudice against vaccination remained. To convince the most sceptical, in 1803, in the Santissima Annunziata Hospital in Naples, the Direzione Vaccinica organised a public demonstration, just as Jenner had been obliged to do in England.[36]

In front of a large audience, highly reputable surgeons who did not belong to the *Corpo de' pubblici Vaccinatori* (Body of Public Vaccinators) were invited to inoculate human smallpox into 18 orphan children who had already been vaccinated: six from the *Ruota degli Esposti dell'Annunziata*, six from the Real Albergo dei Poveri and six from the general population.

None of the children contracted the disease. As a result of this success, in Naples and the surrounding provinces between 1808 and 1819, almost 400,000 vaccinations were performed in over 17% of all live newborns in the Kingdom.

The organisation of the vaccination programme

Such a programme of mass vaccination necessarily involved many organisational problems, such as the production, conservation and distribution of the vaccine. To tackle these problems, the *Direzione Vaccinica*, on the advice of Miglietta, adopted the technique of 'arm-to-arm' vaccination, which involved taking material from the pustules of a recently vaccinated subject and injecting it directly into the subject to be vaccinated. In this way, those who had been vaccinated, particularly abandoned children and those housed in institutes, became veritable 'reservoirs'[37] of the vaccine.

However, in the setting of a normal, fruitful debate among men of science, doubt was cast on this technique by another Neapolitan scholar, Gennaro Galbiati, who was firmly convinced of the superiority of the practice of 'animal vaccine' (retrovaccination).

This involved taking exudate from vaccinated children and inoculating it into young cows, then drawing off material for further vaccinations from the pustules that formed on the cows.

Galbiati, who was fully conversant with the technique of vaccination, which he amply described in an 1803 publication, developed and regulated cow-based vaccine production, setting up in Naples a facility for the production of smallpox vaccine from heifers. In this way, he claimed, the vaccine had a greater immunising capacity and, above all, did not act as a vehicle for other human diseases, such as syphilis.

Aside from the vehement clash between Miglietta, the advocate of arm-to-arm vaccination, and Galbiati, the advocate of animal vaccine, the capital of the Kingdom of the Two Sicilies, found itself in the peculiar, and somewhat fortunate, situation of being able to use two vaccination services:

- one public and free of charge, run by Miglietta;
- the other, directed by Galbiati, reserved for the wealthier social classes who could afford an innovative vaccine, which was safer but certainly more costly.

Over the years, after the death of the two great physicians involved in this dispute, the superiority of the animal-based vaccine in terms of efficacy and safety was acknowledged.

Conclusions

In this article, the authors describe the first steps in the fight against smallpox, an extremely contagious infectious disease of viral origin that proved fatal in 30% of cases and for which no specific treatment existed, apart from prevention by means of vaccination.

For at least 3000 years, smallpox caused disastrous epidemics, killing over 300 million people in the 20th century alone.

To date, smallpox is still the only infectious disease to have been officially eradicated worldwide. This result was achieved through the efficacious implementation of mass vaccination throughout the world, which was rigorously carried out between 1958 and 1977, and particularly through a decisive worldwide vaccination campaign conducted by the World Health Organization between 1967 and 1979.

Vaccination was the main preventive measure for long years; it is an example in the collective imagination of modern times of the value of medicine and scientific research; it represents an effective strategy against the diseases that have afflicted humankind throughout history such as plague.

It is an excellent skill of prevention for individuals with at the same time a real effect for the entire community; compulsory vaccination was indeed an important aspect.

Today, we can observe a clear transformation of the cultural approach towards vaccination: individual choice prevails over collective one, and the idea of the concept of mandatory vaccination is deeply reduced. The subjective assessment of risks and benefits based on self-managed information becomes increasingly crucial and important.[38]

Certainly, this kind of topic cannot be treated lightly; in any framework, vaccine hesitancy and the refusal of vaccines belong to different reasons of a material, social, cultural, religious nature etc.

One of the fundamental issues is the possibility of having exactly data and the competence to read and interpret them. Today, several information is not checked by specialists in those scientific subjects, and moreover, it can spread very quickly, thanks to the advanced modern technologies.

Recently, the use of social networks such as Facebook, Twitter, and Sina Weibo has become an inseparable part of our daily lives. It is considered as a convenient platform for users to share personal messages, pictures, and videos. However, while people enjoy social networks, many deceptive activities such as fake news or rumors can mislead users into believing misinformation.[39,40]

Laurence Monnais, professor of history and Director of the Center for Asian Studies (CETASE) at Université de Montréal, Canada, in his book *Vaccinations Le mythe du refus*[41] focus on three statements used by different authors and often by media when dealing with the topic of vaccines and vaccination:

a) First of all 'the act of vaccine administration' (in particular, the process of immunisation); the vaccine induces active immunisation against infectious diseases, and it protect the population;
b) A second postulate often tend to confuse 'non-vaccination' (the fact of not being vaccinated) and 'refusal of vaccination' (when a subject does not want to be vaccinated);
c) focuses on the re-emergence of an infectious disease as certainly the direct result of vaccine refusal.[41] The question is therefore extremely complex.

Laurence Monnais states that the use of these postulates highlights 'a more or less shared ignorance of epidemiology, infectious diseases, immunological sciences, vaccinology and their common evolution; […] They are often based on data […] poorly contextualized and interpretable at will'.[41]

If, on the other hand, we approach the question with severe and careful scientific attention, we can affirm that: '*Vaccine hesitancy is complex and context specific, varying across time, place and vaccines.*

It is influenced by factors such as complacency, convenience and confidence'.[28]

> *Common concerns underlying hesitancy include uncertainty about the need for vaccination and questions about vaccine safety and efficacy. Sociodemographic factors associated with parental vaccine hesitancy vary across locations and contexts.*[42]

> *It's evident that "there is heterogeneity in vaccine hesitant individuals and a diversity of situations in which vaccine hesitancy can arise, thus requiring that interventions to address vaccine hesitancy be context-specific and problem-specific".*[43]

> *Albeit this, all mankind since the discovery of Edward Jenner, has taken advantage from vaccines to fight and sometimes downfall serious infectious diseases, even if the pathway towards successful vaccines has not been absolutely simple and without problems, e.g."the Cutter incident" regarding the polio vaccine.*[44] *In particular, in this case, it is essential that governments and vaccine pharmaceutical companies make correct, clear and immediate communication and announcement in order to explain the problem that has occurred, the possible effects and can therefore ensure fast results and solution of the causes.*

About the topic of the present article 'many of the issues salient in Jenner's era-such as the need for secure funding mechanisms, streamlined manufacturing and safety concerns, and deep-seated public fears of inoculating agents-have frequently reappeared and have often dominated vaccine policies'.[45]

In this sense, a narrative based on science could help to clarify the doubts of those who fear vaccines and above all to avoid a treatment, often with sensational effect, not based on evidence-based medicine. The case of the well-known and discussed case of Andrew Wakefield's publication of data on the correlation between the administration of the trivalent MMR vaccine (measles, mumps, rubella) and the onset of diseases such as autism and intestinal diseases is certainly significant: 'In 1998, a Lancet paper described 12 cases of children with autism, and having been vaccinated (MMR) in the United Kingdom; medias presented the information to the lay public, stating that a link was possible. In 2004, The Lancet published letters responding to allegations against the paper. Later, it was established that no link existed between MMR and autism; few years and many publications were necessary to conclude to the absence of evidence. In 2010, the General Medical Council published a report against Dr Wakefield, first author of the 1998 paper, and showing that the children hospital records did not contain the evidence; hospital records differed from the published paper; the Lancet retracted the 1998 paper'.[46] 'Despite the retraction, many autism advocacy groups and parents continue to defend Wakefield. […] The 'conspiracy theory' that vaccine manufacturers are hiding the truth about MMR and autism is fuelled by parents' need to know what is causing autism, says Margaret Spoelstra, executive director of Autism Ontario, despite the fact that no large study has replicated Wakefield's finding'.[47]

This situation has caused 'vaccine hesitancy' or 'vaccination refusal': in these cases, despite the evidence of the efficacy and safety of vaccinations, an increasing number of people have doubts about vaccination for themselves or their children;[48] this attitude and thinking can result a re-emergence of preventable diseases.[43,41] Non-vaccination can become a serious sociocultural problem and a major obstacle to public health goals.[49]

Moreover, as illustrated by the history of vaccination in southern Italy,[37] success can be achieved only through a concerted effort on the part of each one of us.

Donald A. Henderson, a recognised smallpox expert who served as the first director of the World Health Organization Smallpox Global Eradication Unit, clearly testifies to this.

In his book *Smallpox-the death* of a disease, Henderson […] provides a personal accounting of the strategies, decisions, and combined global efforts leading to the eradication of smallpox […].

He discusses the events leading to the World Health Assembly's (WHA's) decision to commit to a major global eradication effort.[50]

Henderson reports on the enormous international effort to achieve the eradication of smallpox.

International health experts from more than 70 countries have joined in the goal of eliminating this disease. Even the United States and the Soviet Union worked together during the darkest days of the Cold War.[51] This should set an example for the politicians of the States, who 'should be informed also about the large health and economic distributional impact that vaccines could have, and they should view vaccination policies as potentially important channels for improving health equity'.[52]

In the latest edition of Henderson's book (2021), there is a new introduction by Phillip K. Peterson, an expert on infectious diseases. He says that 'Dr. Henderson's smallpox campaign' could provide insights into the fight against COVID-19 and future global pandemics.[53]

Thus, while we continue to fight against COVID-19 and other epidemics spread around the world, several governments do not take clear positions on vaccination, and therefore, many people continue to reject this practice. The example cited in this scientific article, and other similar examples in the history of medicine could help clarify many doubts in those who fear or distress vaccines.

We believe that a more balanced reading of the 'history of vaccination' by those who do not recognise its efficacy and value is important and useful. We also believe that the 'history of medicine' and in particular the 'history of vaccines' and the 'history of vaccination' can help provide solutions for the future to current problems.[45]

Author statements

Ethical approval

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Original Research

The association between migraine and dementia – a national register-based matched cohort study☆

S. Islamoska [a, *], J.M. Hansen [b], Å.M. Hansen [a, c], A.H. Garde [a, c], G. Waldemar [d, e], K. Nabe-Nielsen [a]

[a] Department of Public Health, University of Copenhagen, Øster Farimagsgade 5, 1014 Copenhagen, Denmark
[b] Danish Headache Center, Rigshospitalet – Glostrup, Valdemar Hansens Vej 5, 2600 Glostrup, Denmark
[c] The National Research Centre for the Working Environment, Lersø Parkallé 105, 2100 Copenhagen, Denmark
[d] Danish Dementia Research Centre, Department of Neurology, Rigshospitalet, Inge Lehmannsvej 8, 2100 Copenhagen, Denmark
[e] Department of Clinical Medicine, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen, Denmark

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ABSTRACT

Objectives: Migraine and dementia, two major public health challenges, are associated, but more knowledge is needed to understand their relationship. Objectives of this study were to investigate 1) the association between non–self-reported measures of migraine and dementia, and whether dementia was associated with 2) migraine without aura (MO) and with aura (MA) in combination with migraine medication use, and 3) migraine severity operationalized as the number of migraine prescriptions.
Study design: Matched cohort study.
Methods: National register data were obtained from individuals born between 1934 and 1958. Migraine cases (aged 25–58 years) were identified by migraine diagnoses and redeemed migraine medication. Migraine cases were matched with non-cases (N = 340,850) and date of diagnosis or medication redemption was defined as index year. Dementia was identified by dementia diagnoses and redeemed dementia medication.
Results: We observed a 1.46 (95% CI: 1.26–1.69) times higher dementia rate in individuals with a migraine diagnosis and a 0.86 (95% CI: 0.76–0.97) times lower rate when using migraine medication. We found the highest dementia rate among individuals with MA, who also used migraine medication (HR = 2.23; 95% CI: 1.19–4.17), and the lowest rate among individuals with MO, who also used medication (HR = 1.25; 95% CI: 0.75–2.10). The number of migraine medication prescriptions was not associated with dementia.
Conclusions: Being registered with a migraine diagnosis was associated with a higher dementia rate, while use of prescribed migraine medication was not. The differences in the dementia rate among migraine cases identified via diagnoses versus medications warrants further investigation.

Introduction

Migraine and dementia are prevalent neurological disorders and leading causes of disability.[1] Several pathophysiological links between migraine and dementia are suggested,[2] including white matter hyperintensities, increased cortisol levels, deficits in nerve growth factors or neurotrophins, changes in amyloid plaque formation, infarct-like lesions, inflammation, cardiovascular disease (CVD), and volumetric changes in white and grey matter.[3,4] Still, the exact mechanisms are not well-established.[3,4] Previous studies reported higher dementia risk in self-reported migraine[5,6] or diagnosed migraine,[7–11] and one study found no risk in self-reported migraine.[12] A recent meta-analysis included all the mentioned studies on self-reported and diagnosed migraine, except one, and found a higher all-cause dementia risk.[13]

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* Corresponding author. Tel.: +45 3533 6070.
E-mail addresses: saim@sund.ku.dk (S. Islamoska), jakob.moeller.hansen.01@regionh.dk (J.M. Hansen), asemarie.hansen@sund.ku.dk (Å.M. Hansen), ahg@nfa.dk (A.H. Garde), Gunhild.Waldemar.01@regionh.dk (G. Waldemar), nabe@sund.ku.dk (K. Nabe-Nielsen).

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In Danish national data, a 50% higher dementia rate was found among individuals registered with migraine diagnosis in a hospital setting.[10] Hospital-based diagnoses may, however, only capture severe cases. In Denmark, most migraine cases are managed as outpatients and only 17% are registered in hospitals.[14] In addition, international recommendations suggest that non-specialist healthcare providers in primary care could meet 90% of individuals' needs when seeking headache treatment.[15] Thus, most migraine cases are likely treated in primary care and cannot be identified through hospital-based registers. Instead, redeemed migraine medication data can be used to obtain an objective measure of migraine cases treated outside the hospital sector, e.g., in general practice or by neurologists working in primary care.

To add to the scientific evidence of the migraine–dementia association, the objectives of this study were to investigate 1) the association between migraine and dementia by using information on migraine diagnoses and extending these data with information on redeemed migraine medication to define migraine cases, and whether dementia was associated with 2) migraine without aura (MO) and with aura (MA) in combination with migraine medication use, and 3) migraine severity based on number of migraine medication prescriptions.

Methods

Study population and design

The starting point for this matched cohort study was all inhabitants in Denmark born 1934–1958 (n = 1,878,914). In this population, we identified individuals with migraine diagnoses from 1988 onwards, as this was the inception year of the International Classification of Headache Disorders.[16] Specific migraine medication for acute migraine treatment became available in European countries from the 1990s,[17,18] and information on redemption of prescribed acute migraine medication was included from 1995 when medication registration was initiated.[19] As dementia is seldom in younger ages and validity of dementia diagnoses in younger patients is low, we considered individuals at dementia risk from age ≥60 years.[20,21] Thus, from they turned 60 years, individuals were followed in registers until death, emigration, dementia, or end of follow-up in 2018, whichever occurred first (Fig. 1).

Of 1,878,914 individuals, we excluded individuals who died (n = 153,101), emigrated (n = 26,734), had dementia before age 60 years (n = 9,577), or missed data on country of birth (n = 365) or education (n = 127,997). Among all individuals eligible for inclusion, we sex- and age-matched one individual with migraine to five individuals without migraine.[22] The included individuals were aged 28–58 years, when registered with migraine. Date of first migraine diagnosis or redemption of migraine medication was defined as index year for all six individuals in each matched set. After running the matching procedure, the population consisted of 396,765 individuals, yet, data were still missing on educational level (n = 6,891) and marital status (n = 49,024), because some information was not available for all years and individuals with missing information at this step were therefore deleted.[23] The final study population consisted of 340,850 individuals.

All data were obtained with approval from Statistics Denmark and the Danish Health Data Authority.

Migraine

Migraine was defined as being registered for the first time with a 1) migraine diagnosis without any registered redeemed migraine medication prescription for acute migraine treatment, 2) redeemed migraine medication prescription for acute migraine treatment without a registered migraine diagnosis, or 3) migraine diagnosis and redeemed migraine medication prescription for acute migraine treatment registered at any time (Table 1). Migraine diagnoses were obtained from the Danish National Patient Register (NPR) and Danish Psychiatric Central Research Register (PCR), which include hospital-based diagnoses based on the 8th and 10th revision of the International Classification of Diseases (ICD).[24,25] The first registered migraine diagnosis included a diagnosis of either: hemicrania ophthalmoplegica (ICD-8: 346.00), hemicrania alia definita (ICD-8: 346.08), hemicrania (ICD-8: 346.09), migraine (ICD-10: G43), MO (ICD-10: G43.0), MA (ICD-10: G43.1), status migrainosus (ICD-10: G43.2), complicated migraine (ICD-10: G43.3), other migraine (ICD-10: G43.8), or unspecified migraine (ICD-10: G43.9). Information on migraine medication was based on Anatomical Therapeutic Chemical (ATC) codes obtained from the Danish National Prescription Registry (DNPR)[19] and included the first redeemed medication of either Triptans (ATC: N02CC) or Ergotamine (ATC: N02CA).

Dementia

We defined all-cause dementia as the first registration with a dementia diagnosis or first redeemed antidementia medication. Dementia diagnoses were obtained from the NPR,[24] PCR,[25] and

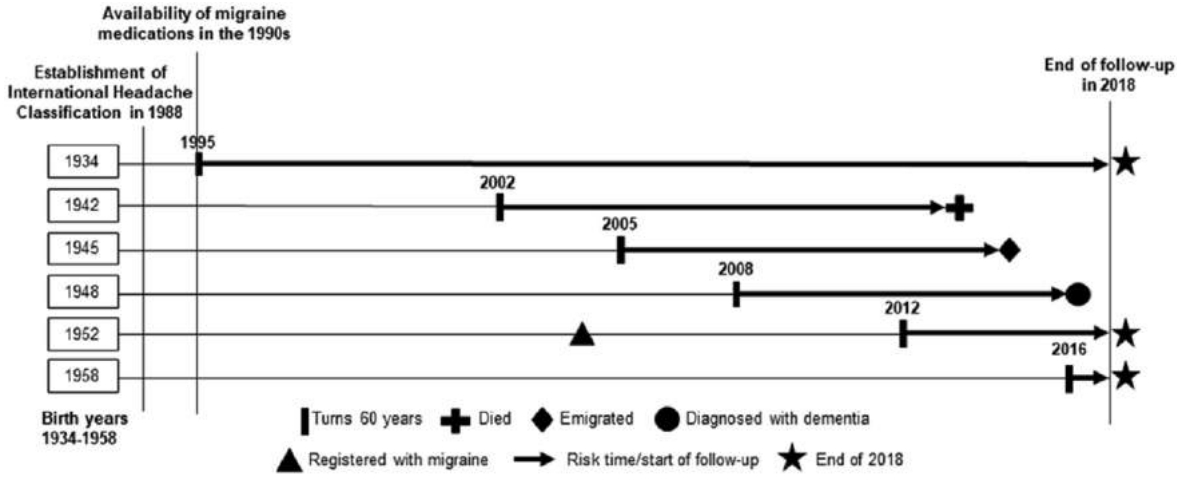

Fig. 1. Study design illustrated by six examples of individuals belonging to different birth cohorts.

Table 1
Operationalization of the three different migraine exposures.

Purpose	Migraine operationalization	Migraine variable categorization
To investigate differences in dementia risk among individuals identified with migraine either by a registered migraine diagnosis, by a redeemed migraine medication, or both	Migraine cases based on either: first ever registered migraine diagnosis without a registered migraine medication prescription, first ever redemption of migraine medication without a migraine diagnosis, or registrations of both a migraine diagnosis and migraine medication at any time	1) No migraine (reference) 2) Any migraine diagnosis 3) Any migraine medication 4) Any migraine diagnosis and migraine medication
To investigate whether there were differences in dementia risk among individuals with MO and MA in combination with migraine medication	Migraine cases were defined by two variables: 1) first ever registration with migraine without aura (MO) and any registered migraine medication afterwards, or first ever registration with MO without any registered migraine medication afterwards; 2) first ever registration with migraine with aura (MA) and any registered migraine medication afterwards, or first ever registration with MA without any registered migraine medication afterwards. Individuals registered with both MA and MO were categorized as MA	1) No migraine (reference) 2) MO with migraine medication 3) MO without migraine medication 4) MA with migraine medication 5) MA without migraine medication
To investigate whether the risk of dementia increased with migraine severity	Migraine severity was defined as the total number of redeemed prescriptions of migraine medication used for acute migraine treatment before the age of 59	1) 1 prescription (reference) 2) 2 prescriptions 3) 3 prescriptions 4) ≥4 prescriptions

Danish Register of Causes of Death (DAR)[26] based on ICD codes of: unspecified dementia, Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia, and Lewy body dementia (Supplementary material). Based on ATC codes from the DNPR,[19] data on first redeemed prescriptions of antidementia medication included the cholinesterase-inhibitors Donepezil (ATC: N06DA02), Rivastigmine (ATC: N06DA03), and Galantamine (ATC: N06DA04), and the glutamate-receptor antagonist Memantine (ATC: N06DX01).

Covariates

We adjusted for covariates associated with migraine, dementia, and/or treatment-seeking behaviour, and other headache disorders and morbidities. We obtained this information one year before index year for all individuals to ensure that confounder information was obtained before migraine diagnosis or medication redemption.

We obtained information on 1) sociodemographic factors: birthdate, sex, country of origin (Denmark/Western countries/Non-Western countries),[27] marital status (unmarried/married), and highest attained educational level[28] (low educational level: primary school; medium educational: upper secondary education, business high school, and vocational education and training; high educational level: short-term further education, middle-range education, bachelor's degree, extended education, and research degree); 2) headache diagnoses: cephalalgia, other headache syndromes, cluster headache syndrome, vascular headache, tension-type headache, chronic post-traumatic headache, drug-induced headache, and other specified headache syndromes; 3) diagnoses of previous head injuries; 4) psychiatric diagnoses: schizophrenia, schizotypal and delusional disorders, mood affective disorders, psychoses, neuroses, and transient situational disturbances from NPR[24] and PCR;[25] and 5) morbidities registered in NPR[24] and PCR[25] potentially associated with migraine and dementia by using morbidities defined in the Charlson Comorbidity Index (CCI):[29,30] myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, renal disease, cancer, metastatic cancer, severe liver disease, and human immunodeficiency virus (Supplementary material).

Statistical analyses

We analysed the distribution of covariates among individuals with and without migraine (Table 2).

The association between migraine and dementia was investigated using a Cox regression model and estimated hazard ratios (HRs) of dementia with time since age 60 years as time scale (Table 3). As the probability of exposure misclassification may differ between birth cohorts, and we included individuals born from a wide range of years, all analyses were stratified on birth cohort to ensure comparisons were made among individuals with the same exposure misclassification probability. We adjusted for confounding in two steps: Model 1 included sex; Model 2 included sex, country of origin, marital status, educational level, headache, head injuries, psychiatric morbidities, and CCI. In sensitivity analyses, we postponed start of follow-up 5, 10, 15, and 20 years after index year to reduce reverse causation, i.e., that migraine reflected prodromal dementia.

We also investigated the associations of dementia with MO with or without migraine medication and MA with or without migraine medication (Table 3). Finally, we investigated dementia risk related to migraine severity operationalized as total number of redeemed migraine medication prescriptions (Table 4).

We tested the hazard proportionality[31] by using a Cox model including covariates of Model 2 and tested significance of a time-dependent interaction between time and covariates.[32]

For all analyses, we used SAS Enterprise Guide version 7.11 and a 5% significance level. Data underlying this article cannot by law be shared publicly, but accessed by employees at Danish research institutions after application to Statistics Denmark.

Results

We identified 59,436 (17%) migraine cases aged 28–58 years in a national sample of 1,878,914 individuals. Of these, 8,800 individuals were identified based on migraine diagnoses, 45,342 on use of redeemed migraine medication, and 5,294 had a migraine diagnosis and redeemed migraine medication at the same registration date (Table 2). Among migraine cases, 537 had dementia at a median age of 67 years, and among individuals without migraine, 2,345 individuals had dementia at a median age of 67 years. Most

Table 2
Baseline characteristics of the study population based on migraine diagnoses and redeemed migraine medication presented in percentages and medians with 25–75% interquartile ranges (IQR) ($N = 340,850$).

Characteristics		Comparison cohort	Migraine diagnosis cohort	Migraine medication cohort	Migraine diagnosis & medication cohort	Migraine without aura (MO)	Migraine with aura (MA)
		$n = 281,414$ (83%)	$n = 8,800$ (14%)	$n = 45,342$ (76%)	$n = 5,294$ (9%)	$n = 3,554$ (62%)	$n = 2,190$ (38%)
Age, median (IQR)	Years	50 (46–53)	50 (45–54)	50 (46–53)	46 (43–50)	48 (44–52)	49 (43–53)
Sex, *n* (%)	Female	216,598 (77)	6,025 (69)	35,277 (78)	4,314 (81)	2,806 (79)	1,566 (72)
Country/region of origin, *n* (%)	Danish	265,891 (94)	8,175 (93)	42,855 (94)	4,916 (93)	3,260 (92)	2,044 (93)
	Western	7,623 (3)	212 (2)	1,201 (3)	126 (2)	92 (3)	66 (3)
	Non-Western	7,900 (3)	413 (5)	1,286 (3)	252 (5)	202 (6)	80 (4)
Marital status, *n* (%)	Non-married	84,803 (30)	2,576 (29)	12,265 (27)	1,569 (30)	1,059 (30)	591 (27)
Educational level, *n* (%)	Low	89,313 (32)	3,283 (37)	12,499 (28)	1,592 (30)	1,110 (31)	658 (30)
	Medium	112,521 (40)	3,482 (40)	17,956 (40)	1,969 (37)	1,360 (38)	866 (40)
	High	79,580 (28)	2,035 (23)	14,887 (33)	1,733 (33)	1,084 (31)	666 (30)
Previous headache diagnoses, *n* (%)	Yes	3,247 (1)	820 (9)	1 543 (3)	285 (5)	273 (8)	136 (6)
Previous head injuries, *n* (%)	Yes	19,057 (7)	698 (8)	3,393 (8)	335 (6)	275 (8)	204 (9)
Previous psychiatric diagnoses, *n* (%)	Yes	16,174 (6)	825 (9)	2,850 (6)	373 (7)	256 (7)	172 (8)
Migraine prescriptions, median (IQR)	Total no.	–	–	5 (1–24)	23 (4–67)	33 (7–81)	11 (2–49)
Charlson Comorbidity Index, *n* (%)	0	261,179 (93)	8,065 (92)	41,664 (92)	4,930 (93)	3,261 (92)	1,990 (91)
	≥1	20,235 (7)	735 (8)	3,678 (8)	364 (7)	293 (8)	200 (9)

Table 3
Dementia rate ratios (HR) associated with migraine diagnoses and medication and their 95% confidence intervals ($N = 340,850$).

Migraine diagnoses or migraine medication	Dementia cases/person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)
None	2,345/1,884,700	1.00	1.00
Any hospital-based migraine diagnosis (no medication)	212/72,824	1.58 (1.36–1.83)	1.46 (1.26–1.69)
Any migraine medication (no hospital-based diagnosis)	280/293,485	0.85 (0.75–0.96)	0.86 (0.76–0.97)
Any hospital-based migraine diagnosis and medication	45/31,578	1.34 (0.99–1.80)	1.28 (0.95–1.72)
None	819/500,471	1.00	1.00
Migraine without aura and with use of migraine medication	15/11,512	1.28 (0.76–2.13)	1.25 (0.75–2.10)
Migraine without aura and no migraine medication	30/11,856	1.45 (1.01–2.09)	1.35 (0.93–1.94)
Migraine with aura and with use of migraine medication	10/4,080	2.46 (1.32–4.60)	2.23 (1.19–4.17)
Migraine with aura and no migraine medication	24/9,589	1.67 (1.12–2.51)	1.64 (1.09–2.46)
All other migraine diagnoses and use of migraine medication	20/15,986	1.07 (0.68–1.67)	1.00 (0.64–1.57)
All other migraine diagnoses and no migraine medication	158/51,378	1.57 (1.32–1.86)	1.40 (1.18–1.67)

Note. Model 1: adjusted for sex. Model 2: adjusted for sex, country of origin, marital status, educational level, headache diagnoses, headache injuries, psychiatric morbidities, and Charlson Comorbidity Index (CCI). Analyses on any migraine diagnoses and medication were based on 340,850 matched individuals. Analyses on migraine with or without aura, medication and other migraine diagnoses were based on 80,696 matched individuals and the follow-up started after ≥1 year.

Table 4
Dementia hazard rate ratios (HR) associated with number of redeemed migraine medication prescriptions and their 95% confidence intervals (95% CI) (N = 50,636).

No. of redeemed migraine medication prescriptions	Dementia cases/person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)
1 prescription	79/81,901	1.00	1.00
2 prescriptions	25/31,303	0.79 (0.51–1.25)	0.80 (0.51–1.26)
3 prescriptions	23/19,916	1.14 (0.71–1.81)	1.16 (0.73–1.85)
≥4 prescriptions	198/191,943	1.11 (0.85–1.45)	1.11 (0.85–1.45)

Note. The follow-up of individuals started after ≥1 year.

dementia cases were registered in national hospital patient data (92%), followed by prescription data (7%), and mortality data (1%).

Migraine cases with a hospital-based diagnosis had a dementia rate of 1.46 (95% CI: 1.26–1.69). Migraine cases identified based on their use of medication had a dementia rate of 0.86 (95% CI: 0.76–0.97). Individuals with a concurrent migraine diagnosis and use of migraine medication had a statistically non-significant dementia rate of 1.28 (95% CI: 0.95–1.72).

Among individuals with MO and redeemed migraine medication, the dementia rate was 1.25 (95% CI: 0.75–2.10) and 1.35 (95% CI: 0.93–1.94) when not having redeemed migraine medication. Individuals with MA and redeemed migraine medication had a dementia rate of 2.23 (95% CI: 1.19–4.17) and a rate of 1.64 (95% CI: 1.09–2.46) when not having redeemed migraine medication (Table 3).

We did not find a convincing dose–response relationship between number of redeemed migraine medication prescriptions and dementia rate (Table 4). Our sensitivity analyses showed that the direction and rate of dementia was unchanged among individuals registered with migraine diagnoses, migraine medication, or both with a time interval of 5–20 years between migraine registration and start of follow-up. Furthermore, the proportional hazards assumption could not be rejected meaning that the overall

dementia rate for migraine cases did not vary significantly with time after age 60 years.

Discussion

Main results

In this national register-based matched cohort study, we found 1) a higher dementia rate among individuals with a hospital-based migraine diagnosis (no redeemed medication prescriptions) and a lower dementia rate among individuals only registered as having redeemed prescribed migraine medication (no hospital-based diagnosis); 2) a higher dementia rate in individuals with MA with and without medication use; and 3) no association between number of redeemed migraine medication prescriptions and dementia rate. Adjusting for confounding or including longer time intervals between registration of migraine and dementia did not change direction and magnitude of the observed associations.

Comparison with previous research

To the best of our knowledge, this is the first study including migraine cases based on both hospital diagnoses and redeemed medication to obtain register-based information about severe and less severe migraine cases. Our results are in accordance with previous studies finding a higher dementia risk in self-reported migraine[5,6] and diagnosed migraine.[7–9] In the previous study using Danish data, an association was observed between hospital-based migraine diagnoses and dementia risk,[10] and in the present study, we extend these findings by adding information about migraine medication redemption. Our results are supported by several pathological mechanisms suggesting a link between migraine and dementia,[3,4] most markedly for MA.[4,33] A recent meta-analysis of nine (two case–control and seven cohort) studies reported a 33% higher dementia risk in individuals with migraine.[13] Earlier studies showed a three to four times higher risk of all-cause and vascular dementia specifically in individuals with self-reported migraine.[5,6] One explanation of the higher effect sizes in self-reports (compared with our findings) could be differential recall of migraine history, particularly if individuals at a mean age of 75 years already had memory issues at the time of data collection.[5] Some studies collected information on both migraine and dementia when participants were above age 60 years,[7,9] which increase the reverse causation risk and confounding due to CVD leading to an overestimation of the migraine–dementia association. Other studies reported comparable or lower dementia risks in diagnosed migraine.[7–9] However, if severe tension-type headache is misclassified as migraine, this may influence the observed association, as tension-type headache is also associated with dementia.[34] Furthermore, too short follow-up time may yield an underestimation of dementia incidence, as it often develops over decades.[28] This may explain why some studies did not report a higher risk of cognitive decline[35] or dementia[11,36] in self-reported migraine.

One explanation for the higher dementia rate in those registered only with a migraine diagnosis, but a lower rate in those only registered with migraine medications could be that those using medications may reflect a patient group with well-managed and/or less severe migraine. Also, those only with migraine diagnoses may be patients with contraindications for migraine treatment, e.g., CVD. Thus, these patients may have an increased dementia risk because of other reasons. Another explanation is that individuals redeeming medication only 1–2 times may not represent actual migraine cases. Because migraine can remit over time,[37] using only one and first registration of either diagnosis or medication may not necessarily reflect recurring migraine attacks.

Apart from reflecting a potential effect of migraine itself (due to increasing severity), one could also speculate whether a higher dementia risk in individuals with several prescriptions could reflect adverse migraine side-effects. Current evidence does not suggest a significant association between the most frequently used migraine medication, triptans, CVD events,[38] and dementia, whereas some studies found that the migraine medication, Ergotamine, is associated with ischemic complications.[39] Nevertheless, despite that cardio- and cerebrovascular mechanisms play a role in dementia aetiology, our data did not provide any substantial support for the hypothesis of a higher dementia risk in individuals with more redeemed prescriptions. Non-steroidal anti-inflammatory drugs (NSAID) are also used for migraine treatment, but evidence regarding its association with dementia shows mixed results.[40] We did not have available information on NSAIDs in this study, as these are over-the-counter medications, which are not registered in DNPR.

Strengths and limitations

The use of national registers to investigate the association of migraine based on both diagnoses and medication with dementia risk is novel. We increased validity of our exposure measures by using register data on migraine diagnoses starting from 1988[16] and prescriptions from 1995. Dementia data consisted of valid, clinical diagnoses from hospitals,[41] or dementia prescriptions. The risk of loss to follow-up was low because individuals were followed in national registers. Furthermore, the large study population enabled a 1:5 exposure-matching procedure and, thereby, reasonable statistical power. We ensured that information on covariates, including comorbidities, was obtained before migraine registration for them to be considered as confounders. In our register data, we did not, however, have access to information on health behaviour (e.g., smoking, physical activity, dietary habits), which could therefore not be controlled for. Migraine severity was explored by using number of prescriptions, which has not been investigated before. To reduce reverse causation risk, we only included migraine cases below age 59 years and dementia cases above age 60 years. Thus, we strictly separated the timing of a migraine diagnosis/prescription from the timing of a dementia diagnosis/prescription, and we also included longer time intervals between migraine and dementia in sensitivity analyses.

Current evidence gives no clear indications of treating mild cognitive impairment (MCI) with antidementia medications as this treatment is possibly ineffective in reducing progression to dementia.[42] However, as treatment choice is up to the individual physician,[42] we cannot rule out that some patients treated with antidementia medication had MCI rather than dementia, although we expect that this number is limited.

Expert recommendations state that general practitioners or neurologists in primary care should treat individuals with uncomplicated migraine and specialized neurologists in hospital-based centres should treat complicated migraine.[15,43] This highlights the suggested differences between migraine cases who are only in contact with primary health care, while cases diagnosed at hospitals apparently belong to a more severely affected patient group. Even though migraine medication can be prescribed by both general practitioners and at hospitals, we observed that 80% of the migraine cases were identified only via redeemed migraine medication. Thus, most migraine cases were not in contact with hospitals due to migraine, but were managed in primary healthcare.[15,43]

In this study, 48 individuals were simultaneously diagnosed with MO and MA showing that individuals may have mixed symptoms emphasizing the complexity in diagnosing migraine. We included migraine patients based on the first registered migraine diagnosis. Yet, this only reflects the time of seeking hospital

contact. Consequently, age at migraine diagnosis may not reflect the actual age of migraine onset, but solely when the patient sought treatment, or when a specialist set the migraine diagnosis.

In our study, 17% of the study population were registered with migraine. On a global level, the migraine prevalence has been estimated to 14%.[44] Thus, our data corresponds to data from other studies, although migraine in general seems to be underdiagnosed. As regards to the outcome of this study, there are about 60% undiagnosed dementia cases in Denmark, thus, register data also underestimate the actual dementia incidence.[45] The dementia incidence peaks at age 80–90 years,[46,47] yet, in our study, the oldest individuals were followed up until age 74 years, and we cannot conclude on dementia risk beyond this age. In addition, being in frequent hospital contact due to migraine or other morbidities may increase the likelihood of being diagnosed with dementia as well and may have yielded an overestimation of the association between migraine diagnoses and dementia.

Conclusion

In conclusion, findings of our study support the notion that individuals with a migraine diagnosis are at higher risk of dementia than individuals without a migraine diagnosis. Furthermore, the findings reassure that most migraine cases, who are represented by individuals using migraine medication, but who do not have a hospital-based diagnosis, are not at higher risk of dementia than individuals without migraine. Further studies are needed to understand if the higher dementia risk in patients seeking hospital treatment can be prevented by improved migraine treatment, regular follow-ups, and management of migraine attacks to prevent or delay dementia onset. In addition, the mechanisms between MA, migraine medication and dementia need to be investigated further to elucidate the underlying pathology with the purpose of preventing dementia among individuals with severe migraine.

Author statements

Ethical approval

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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.2022.09.018.

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Short Communication

The role of altruism vs self-interest in COVID-19 vaccination uptake in the United Kingdom

C. Jones*, M.S. Bhogal, A. Byrne

School of Psychology, Faculty of Education, Health and Wellbeing, University of Wolverhampton, United Kingdom

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ABSTRACT

Objectives: The aim of the present study was to explore self-interest, kin altruism and non-kin altruism reasons that influence people to vaccinate against COVID-19.
Study design: This was a cross-sectional study using a fully repeated measures design.
Methods: Participants ($N = 178$) answered questions on perceived threat and likelihood of infection, vaccination status and opinion on mandatory vaccination. Participants also rated a set of statements that asked how likely these would influence them and others to vaccinate against COVID-19. Statements reflected self-interest, kin altruism or non-kin altruism.
Results: Just more than half of the sample (50.8%) reported the likelihood of infection as somewhat or extremely likely, and almost three-fourths (74.2%) reported that COVID-19 posed a minor or moderate threat to their physical health. Almost three-fourths (74.3%) of the sample were vaccinated, with just more than half (56.2%) in favour of mandatory vaccination. A 2 (self/other) × 3 (self-interest/kin altruism/non-kin altruism) fully repeated measures analysis of variance showed that kin-altruistic reasons were rated most highly, regardless of whether this was regarding oneself or others. Participants rated others as having greater self-interest reasons for vaccination compared with oneself, whereas non-kin altruism reasons for vaccination were rated higher for oneself, compared with others.
Conclusion: Highlighting the benefits of vaccination for close relatives and vulnerable others in the population would be a useful strategy for government to use when urging the public to vaccinate against COVID-19.

Introduction

The impact of the COVID-19 pandemic has been felt worldwide. Global attempts to control the spread of the virus have included imposing restrictions on behaviour with the hope of returning to normality in the United Kingdom by focusing on vaccinating the population.

Vaccination protects not only the individual but also others, either directly (by reducing transmission) or indirectly (via herd immunity).[1] Nonetheless, vaccine uptake depends on a variety of factors and has been shown to be highly variable across different vaccines.[2] It has been estimated that to achieve herd immunity, approximately 80% of the population would need to receive the COVID-19 vaccination to reduce the spread of the disease and to offer protection to those unimmunised,[3] although this figure may vary with the emergence of new variants of the virus. Therefore, it is imperative that empirical research is conducted to examine ongoing factors that contribute to vaccine uptake.

Research suggests that prompting altruism may be a useful strategy to encourage vaccination against COVID-19.[4,5] Ultimately, receiving a vaccine can be seen as an altruistic act because the benefit would be greater to wider society than to the individual.[6] Unvaccinated individuals would receive greater protection as the number of vaccinated individuals increase. However, the cost of infection would be higher for an unvaccinated individual when fewer people have been vaccinated overall.[7]

This study aimed to investigate motivations for vaccine uptake in the United Kingdom and whether factors such as altruism contribute to this. Furthermore, altruism can vary depending on the recipient. From an evolutionary perspective, high levels of altruism are more prominent towards kin (those who share genetic material with us) compared with non-kin.[8] The theoretical reasoning lies in evolutionary theory, suggesting altruism increases inclusive fitness (genetic fitness and survival of those who share genetic code with

* Corresponding author. Millennium City Building, Wulfruna Street, Wolverhampton, WV1 1LJ, UK
E-mail address: Claire.Jones@wlv.ac.uk (C. Jones).

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us). We examined whether there were differences between kin altruism, non-kin altruism (altruism towards non-genetic relatives) or self-interest reasons for having the COVID-19 vaccine. We also examined which reasons were perceived to be important for oneself and which reasons were perceived to be important for others.

Methods

Participants

One hundred seventy-eight participants took part (42 male, 134 female, and 2 non-binary). The mean age was 33.31 (standard deviation = 12.28; see supplementary materials for demographic information). Participants were recruited from the general population via social media platforms (such as Facebook and Twitter) and undergraduate students via the host universities' research participation scheme. Data were collected between April 2021 and November 2021. This study did not form part of a larger research project.

Materials and procedure

Once informed consent was provided, participants completed the following measures online:

Demographic information

Participants provided their age, gender, education, nationality, and ethnicity.

Perceived threat of infection and vaccine uptake

Two questions were used to assess the participants' perceived likelihood of infection in terms of personal susceptibility ("how likely do you believe it is that you will get infected with Covid-19?") and threat to physical health ("If you got infected with Covid-19, how threatening would it be to your physical health?"). These were rated on a 5-point scale (*1= not at all to 5= extremely*).

Two questions were asked about vaccine uptake for participants that may have already received the vaccine ("Have you been vaccinated for Covid-19?" Yes/No) or intentions to receive the vaccine ("If you have not yet received the vaccine, how likely is it that you would get vaccinated for Covid-19 in the future?" *1=Highly unlikely − 5=Highly likely*).

Finally, one question examined opinions on mandatory vaccination adapted from Reiger,[5] "What do you think of a mandatory Covid-19 vaccination?" (*1= strongly oppose to 4= strongly favour*).

Reasons for vaccination

Participant's reasons that influence their decision to vaccinate for COVID-19 was measured using two sets of statements adapted from Robertson et al.[9] First, participants were asked, "How likely is it that the following reasons would influence **you** to vaccinate against Covid-19?" The statements reflected kin altruism, non-kin altruism or self-interest. For example, participants rated self-interest statements such as "To prevent me catching coronavirus or getting very ill from it," non-kin altruistic statements such as "To protect others that are clinically vulnerable" and kin-altruistic statements such as "Because a member of my family is vulnerable." Second, participants were asked, "How likely do you think it is that the following reasons would influence **others** to vaccinate against Covid-19?" The statements were amended to reflect this perspective (e.g. "To prevent them from catching coronavirus or getting very ill from it"). These were rated on a 5-point scale (*1= extremely unlikely to 5= extremely likely*).

Results

This research examined participants' perceptions of COVID-19 and reasons for vaccination for both oneself and perceptions of why others would get vaccinated. When asked about perceived likelihood of infection and threat to physical health, 50.8% of participants reported that likelihood of infection was 'somewhat/extremely likely' with most participants (74.2%) reporting that COVID-19 posed a minor or moderate threat to their physical health. In the current sample, 74.3% were vaccinated ($N = 133$), and 25.7% ($N = 46$) were not yet vaccinated. Of the participants not yet vaccinated, 38.9% ($N= 21$) said it was 'highly likely' that they would get vaccinated compared with 25.9% ($N= 14$) who said it was 'highly unlikely' that they would get vaccinated in the future. When asked about mandatory vaccine, 56.2% ($N = 100$) somewhat/strongly favoured mandatory vaccines, whereas 43.8% ($N = 78$) somewhat/strongly opposed mandatory vaccine.

A two-way repeated measures analysis of variance was used to analyse reasons for vaccination for both self and others. The first factor was perspective with two levels (self/others). The second factor was vaccination motives with three levels (self-interest/kin-altruism/non-kin altruism). The dependent variable was the ratings across the reasons for vaccination that influenced participants' motives to get vaccinated.

There was no significant main effect of perspective (F (1, 170) = 2.59, $p = .11$,$\eta_p^2 = .015$). The main effect of vaccination motives was significant (F (2, 170) = 114.42, $p < .001$,$\eta_p^2 = .402$). The interaction was also significant (F (2, 340) = 64.54, $p < .001$, $\eta_p^2 = .275$). Simple contrasts reveal significant differences between self-interest and kin altruism reasons ($p < 001$) and between self-interest and non-kin altruism reasons ($p < .001$). As can be seen from Fig. 1, kin-altruistic reasons were rated most highly, regardless of whether this was for self or others; however, participants rated others as having greater self-interest reasons for vaccination compared with themselves, whereas non-kin altruism reasons were rated higher for self, compared with others. Follow-up tests confirmed these difference were significant for self-interest reasons (t (170) = −5.56, $p < .001$, $d = -.42$) and for non-kin altruistic reasons (t (170) = 2.8, $p = .006$, $d= .21$).

Discussion

These findings offer a novel contribution to the literature by highlighting the reasons *why* people choose to vaccinate against COVID-19. First, kin-altruistic reasons were rated most highly, regardless of whether this was regarding oneself or others. This is consistent with previous research demonstrating that high levels of altruism are more prominent towards kin and fit within an evolutionary framework.[8] Second, we found that participants rated others as having greater self-interest reasons for vaccination compared with themselves, whereas non-kin altruism reasons were rated higher for oneself, compared with others. This suggests that people see others as having the vaccine for self-interest (possibly selfish) reasons but see themselves having the vaccine for the benefit of others. This aligns with previous research demonstrating that altruistic acts and feeling good about oneself may motivate people to vaccinate.[10] Furthermore, our findings are consistent with Cucciniello et al.[4] and Reiger[5] who found that individuals are responsive to altruistic notions.

Given that one-fourth of our sample were not yet vaccinated, and 25% of these said they were unlikely to vaccinate in the future; findings such as these are vital to inform strategies for public health messaging that may encourage more people to vaccinate against disease. Emphasising the benefits of vaccination for those close to us and how this could potentially help vulnerable others would be a

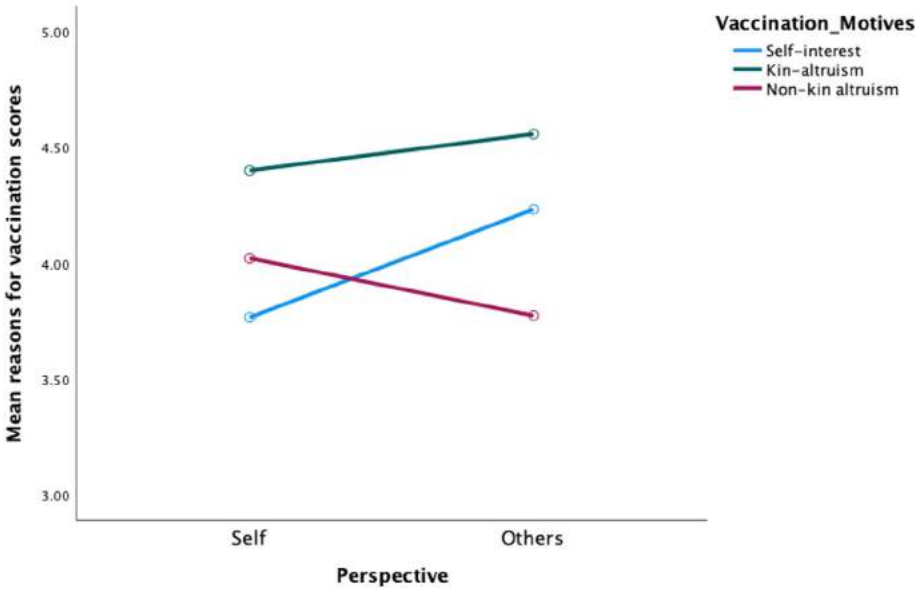

Fig. 1. A graph to show self-interest, kin-altruistic and non-kin altruistic reasons for vaccination for self and others.

beneficial strategy for government to adopt[4] as opposed, or in addition to, emphasising the positive effects of vaccination to the self.

There are some limitations of this research. First, we did not use established psychometric scales when constructing our variables. Second, there was not an equal number of vaccinated and unvaccinated participants in each group, meaning we were unable to run additional parametric analyses. Third, although our results align with existing data on the role of altruistic motives in vaccination uptake, more research is needed to establish the role of altruism in COVID-19 vaccine uptake, with the use of various methodologies and statistical analyses. Future research aimed at identifying strategies for public health messaging are important, particularly with the continued need for booster vaccinations against COVID-19.

Author statements

Ethical approval

Ethical approval was granted by the Faculty of Education, Health and Wellbeing's ethics committee at the University of Wolverhampton.

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Competing interests

None.

Data availability statement

Data available on request from the authors.

Appendix A. Supplementary data

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Original Research

Trends in sexually transmitted infection screening during COVID-19 and missed cases among adolescents

S. Bonett [a, *], D. Teixeira da Silva [b], N. Lazar [b, c], S. Makeneni [d], S.M. Wood [b, c, d]

[a] School of Nursing, University of Pennsylvania, USA
[b] Perelman School of Medicine, University of Pennsylvania, USA
[c] Craig-Dalsimer Division of Adolescent Medicine, Children's Hospital of Philadelphia, USA
[d] PolicyLab, Children's Hospital of Philadelphia, USA

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ABSTRACT

Objective: The COVID-19 pandemic disrupted sexual health services for young people, with potential consequences of decreasing preventive screening and increasing undiagnosed sexually transmitted infections (STIs). This study aimed to assess trends in asymptomatic screening among patients receiving STI testing and to estimate the number of STI cases that were missed during the early months of the pandemic.

Study design: A cross-sectional study of electronic health records for chlamydia, gonorrhea, and trichomonas testing encounters from six pediatric primary care clinics in Philadelphia, July 2014 to November 2020.

Methods: A total of 35,548 testing encounters were analyzed, including 2958 during the pandemic. We assessed whether testing at each encounter was performed as asymptomatic screening, risk-based testing, or symptomatic testing. We evaluated screening trends over time and estimated the number of missed STI cases during the pandemic.

Results: The mean monthly testing encounters decreased from 479 per month prepandemic to 329 per month during the pandemic. The percent of tests performed as asymptomatic screening dropped from 72.5% prepandemic to a nadir of 54.5% in April 2020. We estimate that this decrease in asymptomatic screening would represent 159 missed cases (23.8% of expected cases) based on patient volume from the previous year.

Conclusions: During the pandemic, the total volume of STI testing encounters and the proportion of tests performed as asymptomatic screening decreased, potentially resulting in missed diagnoses. Undiagnosed STIs can result in severe sequelae and contribute to community transmission of STIs. Efforts are needed to re-establish and sustain access to STI services for adolescents in response to disruptions caused by the pandemic.

Introduction

Chlamydia trachomatis (CT) and *Neisseria gonorrhea* (GC) are the most common bacterial sexually transmitted infections (STIs) in the United States, and adolescents and young adults are the age groups with the highest incidence of infection.[1] The rates of STIs have been on the rise for six consecutive years and have now reached an all-time high.[1] Chlamydia and gonorrhea can be detected using nucleic acid amplification tests and treated with readily available antibiotics.[2] However, untreated STIs can lead to serious sequelae, including pelvic inflammatory disease,[3] adverse outcomes during pregnancy,[4] and increased susceptibility to HIV.[5] In addition, untreated STIs contribute to increased community transmission of these pathogens. Routine screening for bacterial STIs among adolescents is an evidence-based Centers for Disease Control and Prevention guideline strategy for mitigating the public health impact of these communicable diseases.[6]

The COVID-19 pandemic has the potential to severely disrupt access to sexual health services for young people. Emerging evidence suggests that rates of STI testing, both as symptomatic

* Corresponding author. School of Nursing, University of Pennsylvania, 418 Curie Blvd, Philadelphia, PA, 19104, USA. Tel.: +215-573-4299.
E-mail address: stepdo@nursing.upenn.edu (S. Bonett).

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testing and asymptomatic screening, decreased during the initial months of the pandemic.[7–10] Several studies also found that among the tests that were conducted, greater test positivity was observed.[7–9,11] This pattern could be attributed to a shift toward treating symptomatic patients and deferring asymptomatic screening[12] and/or increasing population prevalence and community transmission of STIs during the pandemic.[13] Systematic decreases in STI screening during the pandemic may have resulted in missed STI cases, with significant consequences for individual health, healthcare costs,[14] and the epidemiology of these STIs.

Research to date has not yet determined how the pandemic has affected patterns of asymptomatic STI screening for adolescents. This study aimed to assess trends in asymptomatic screening among patients receiving STI testing in pediatric primary care settings in Philadelphia. In addition, this study estimates the number of STI cases that were missed during the pandemic based on changes in asymptomatic screening.

Methods

We analyzed electronic health record (EHR) data from six pediatric primary care clinics located within the city of Philadelphia, including two clinics funded through the Title X Federal Family Planning program to provide confidential sexual health services and comprehensive family planning for low-income and uninsured people. Our study sample consisted of all patient encounters with a patient address in Philadelphia or the surrounding counties (Bucks County PA, Chester County PA, Delaware County PA, Montgomery County PA, New Castle County DE, Burlington County NJ, Camden County NJ, Gloucester County NJ, and Salem County NJ) that included CT, GC, or *Trichomonas vaginalis* testing at any anatomic site (i.e. urine, vaginal swab, urethral swab, throat swab, or rectal swab) from July 1, 2014, to November 30, 2020. Trichomonas testing was included; recently, guidelines have suggested that screening should be considered in settings with high prevalence of STIs, such as the Philadelphia area.[2] Testing for syphilis was not included because, based on the 2015 Centers for Disease Control and Prevention guidelines,[15] routine screening among adolescents was only recommended for men who have sex with men, and we could not ascertain sexual orientation via EHR data. To compare outcomes from the period before the COVID-19 pandemic in the United States to the period after pandemic onset, we defined July 1, 2014, to February 29, 2020, as the prepandemic period and March 1, 2020, to November 30, 2020, as the pandemic period.

Measures

Testing type category

We used the *International Statistical Classification of Diseases, Tenth Revision,* order diagnosis associated with each STI testing encounter to classify encounters as asymptomatic screening, risk-based testing, or symptomatic testing. Order diagnoses that would not indicate clinical suspicion for an STI were classified as asymptomatic. In addition, diagnoses that indicate sexual activity (without identifying a specific risk), diagnoses that refer to counseling or education, and diagnoses that indicate that non-standard guidelines should be used for STI screening (e.g. pregnancy, men who have sex with men), but which do not necessarily indicate higher risk, were classified as asymptomatic. Order diagnoses that might lead a primary care provider to consider an STI as part of differential diagnosis were classified as symptomatic. These include symptoms of genitourinary infection (including abnormal urine findings), rectal infection, pharyngeal infection, as well as systemic symptoms consistent with acute HIV (e.g. weight loss, fever). Laboratory results and other signs that are often associated with symptoms of an STI, such as pyuria, were classified as symptomatic. Non-specific gastrointestinal complaints (e.g. abdominal pain) were classified as symptomatic, as they could be related to pelvic inflammatory disease. Diagnoses related to irregular bleeding or other menstrual symptoms were classified as symptomatic. Order diagnoses that indicated that the patient was at increased risk for an STI based on specific events, behaviors, and circumstances were classified as risk based. This includes those who were the victim of sexual assault, experienced a needlestick injury, reported injection drug use, had a sexual partner with a recent STI, or reported condomless intercourse. To minimize misclassification bias, two physician members of the research team (S.W. and D.T.S.) independently reviewed the 1547 distinct order diagnoses and encounter reasons associated with encounters in the data set and classified each diagnosis or reason as indicative of one of the three testing type categories. When there was disagreement on classification, discrepancies were solved by consensus. Consensus on classification was reached for 1468 diagnoses. A third member of the research team (N.L., nurse practitioner) was consulted to determine the final classification for the remaining 79 diagnoses.

When no order diagnosis was recorded for an encounter, the encounter reason (i.e. visit indication as noted by the staff member scheduled the visit) was used. For encounters with missing data for both order diagnosis and encounter reason, the testing type category was classified as "missing."

Encounter-level characteristics

Age at encounter was measured in years as reported in the EHR. Sex was measured as sex assigned at birth, as reported in the EHR. Gender identity data were not routinely collected by the health system during the study period. Race (i.e. Black, White, Asian, or multiracial/other) and ethnicity (i.e. Latinx or non-Latinx) were extracted from the EHR and thus likely represent staff perceptions of the race/ethnicity of patients or parents at registration rather than self-identification by the patient. Race is a sociopolitical construct and included in the analysis as a measure of potential exposure to racism and discrimination. Insurance status at each encounter was categorized as private insurance, Medicaid, or uninsured. Laboratory results for all STI testing performed at each encounter were extracted and classified as either positive or not positive.

Statistical analysis

Descriptive statistics were calculated for all measures, and comparisons were made between the prepandemic and pandemic periods using Chi-squared tests for categorical variables, *t*-tests for normally distributed continuous variables, and Mann–Whitney U tests for non-normal continuous variables. Monthly trends in asymptomatic screening were investigated by calculating the proportion of encounters each month that were classified as asymptomatic screening. Locally estimated scatterplot smoothing was used to visualize trends over time, with a 95% confidence interval displayed for the fitted curve.[16]

To estimate the number of potential missed STI cases during the nine-month pandemic period, we first identified the *expected screening estimate*—the number of asymptomatic screening encounters using the observed number of asymptomatic screening encounters from the analogous 9-month period the previous year. To account for decreased overall patient volume (i.e. all patient encounters for any visit reason) during the pandemic, we also calculated a *patient-volume-adjusted expected screening estimate* by multiplying the *expected screening estimate* by the ratio of patient volume during the pandemic period over the patient volume during the analogous 9-month period the previous year (57,103 encounters/68,001 encounters = 0.84). The number of *estimated*

missed cases and the *patient-volume-adjusted estimated missed cases* were calculated by multiplying the *expected screening estimate* and the *patient-volume-adjusted expected screening estimate*, respectively, by the observed STI test positivity rate for asymptomatic screening encounters during the pandemic (14.2%). Finally, the total number of *expected cases* and the *patient-volume-adjusted expected cases* were calculated by adding the number of observed cases during the pandemic (n = 510) to the *expected missed cases* and *patient-volume-adjusted missed cases*, respectively. This research was reviewed and deemed exempt by the institutional review boards at the Children's Hospital of Philadelphia and Access Matters.

Results

A total of 35,548 STI testing encounters (14,158 unique patients) were analyzed, including 2958 (2289 unique patients) during the pandemic period. The median patient age at encounter was 17.5 (interquartile range: 16.3–18.6), and 57.4% of patients were assigned female sex at birth. Most patients' race was recorded as Black/African American (84.2%), and most patients' ethnicity was recorded as non-Hispanic/Latinx (95.1%). At their first encounter in the data set, more than half of the participants were enrolled in a Medicaid insurance plan (55.3%), 34.3% had private insurance, and 10.0% were uninsured. Most encounters included testing for chlamydia (99.1%) or gonorrhea (98.3%); only 25.6% of encounters included testing for trichomonas. During the pandemic, a smaller proportion of the STI testing encounters were among uninsured patients compared with the prepandemic period (3.9% vs 13.0%). A summary of the characteristics of the STI testing encounters by the pandemic period is presented in Table 1.

During the prepandemic period, an average of 479 STI testing encounters occurred each month, dropping to an average of 329 encounters per month during the pandemic period. Asymptomatic screening was relatively stable during the prepandemic period, with 72.5% of STI tests being performed as asymptomatic screening. The percentage of tests performed as asymptomatic screening declined during the pandemic, reaching a low of 54.5% in April 2020 (Fig. 1). STI test positivity for any STI from all asymptomatic screening encounters was 11.3% over the entire study period, 11.1% during the prepandemic period, and 14.2% during the pandemic period. CT test positivity for asymptomatic screening encounters that included CT screening was 9.9% over the entire study period, 9.7% during the prepandemic period, and 11.9% during the pandemic period. GC test positivity for asymptomatic screening encounters that included GC screening was 1.8% over the entire study period, 1.6% during the prepandemic period, and 3.3% during the pandemic period. Trichomonas test positivity for asymptomatic screening encounters that included trichomonas screening was 3.6% over the entire study period, 3.7% during the prepandemic period, and 3.3% during the pandemic period.

From March to November of 2019, 3112 asymptomatic screening encounters occurred. Thus, the *expected screening estimate* during the pandemic period is 3112, and the *patient-volume-adjusted expected screening estimate* during the pandemic is 2613. We observed 1994 asymptomatic screening encounters during the pandemic period, corresponding to 1118 fewer screening encounters than expected based on patient volume from the previous year and 619 fewer screening encounters than the patient-volume-adjusted estimate. Given that 14.2% of asymptomatic screening encounters resulted in a positive STI test during the 9-month pandemic period, this translates to 159 *estimated missed cases* (23.8% decline from *expected cases*) based on patient volume from the previous year and 88 *patient-volume-adjusted missed cases* (14.7% decline from *patient-volume-adjusted expected cases*).

Discussion

This study assessed changes in asymptomatic screening for STIs among adolescents and young adults who were associated with the COVID-19 pandemic. We found that during the pandemic, the total volume of STI testing encounters decreased, corroborating previous research.[7–9] Furthermore, the proportion of tests performed as asymptomatic screening also decreased during this time. This finding is consistent with a previous study among patients of all ages at an STI clinic in Rhode Island, where researchers found that testing volume declined during the pandemic overall, and the largest declines were among screening visits for patients without symptoms.[10]

Our study suggests that this pattern of decreased screening also affected adolescents and young adults. It is likely that during the

Table 1
Description of STI testing encounters at six pediatric outpatient clinics, July 1, 2014, to November 30, 2020.

Variable	Overall	Prepandemic (July 1, 2014– February 29, 2020)	Pandemic (March 1, 2020– November 30, 2020)	*P*
n	35,548	32,590	2958	
Age (years), median (IQR)	17.47 (16.28, 18.61)	17.48 (16.27, 18.62)	17.44 (16.41, 18.46)	0.82
Insurance status (%)				<0.01
Medicaid	20,421 (57.4)	18,611 (57.1)	1810 (61.2)	
Private	10,652 (30.0)	9635 (29.6)	1017 (34.4)	
Uninsured	4336 (12.2)	4222 (13.0)	114 (3.9)	
Missing	139 (0.4)	122 (0.4)	17 (0.6)	
Race (%)				<0.01
Asian	419 (1.2)	357 (1.1)	62 (2.1)	
Black/African American	31,754 (89.3)	29,212 (89.6)	2542 (85.9)	
Other/multiracial	1545 (4.3)	1364 (4.2)	181 (6.1)	
White	1830 (5.1)	1657 (5.1)	173 (5.8)	
Ethnicity (%)				<0.01
Hispanic/Latinx	1303 (3.7)	1157 (3.6)	146 (4.9)	
Not Hispanic/Latinx	34,183 (96.2)	31,378 (96.3)	2805 (94.8)	
Refused/unknown	62 (0.2)	55 (0.2)	7 (0.2)	
Male sex (%)	9927 (27.9)	9069 (27.8)	858 (29.0)	0.18
Testing type (%)				<0.01
Asymptomatic	25,636 (72.1)	23,642 (72.5)	1994 (67.4)	
Missing	1265 (3.6)	1147 (3.5)	118 (4.0)	
Risk	1596 (4.5)	1454 (4.5)	142 (4.8)	
Symptomatic	7051 (19.8)	6347 (19.5)	704 (23.8)	

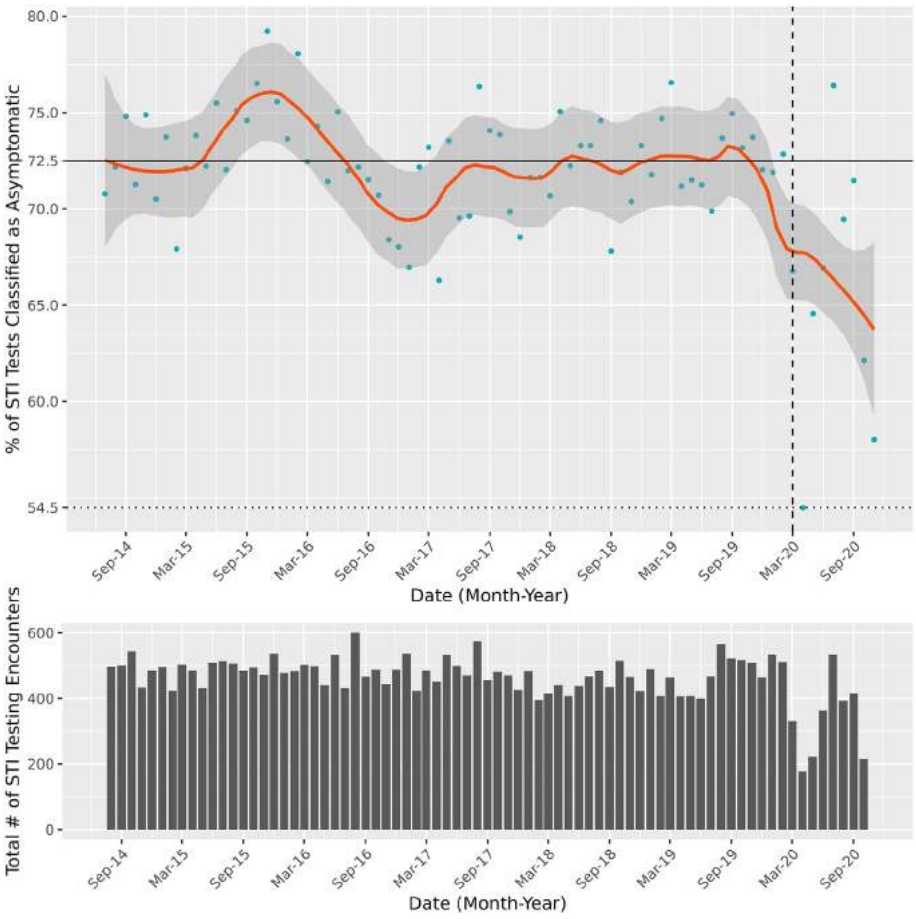

Fig. 1. Top panel: percent of STI tests classified as asymptomatic screening over time. Horizontal solid line denotes prepandemic average, horizontal dotted line denotes nadir of screening rate, and vertical dashed line denotes the start of the pandemic. Bottom panel: number of STI testing encounters by month over time.

pandemic, providers and health systems prioritized testing symptomatic patients and may have opted to defer routine preventive health appointments that would have included asymptomatic screening for STIs. Many clinical guidelines for STI management during the pandemic recommend that providers defer asymptomatic screening due to the risk of exposure to COVID-19 during a clinical visit.[17,18] These pressures to limit routine screening were exacerbated in the fall of 2020 when a national shortage of testing supplies and competition for laboratory resources severely constrained clinical capacity to provide STI testing.[19] Our study shows that these strategic responses to the evolving pandemic had a demonstrable effect on how STI services were delivered to young people. Innovative and flexible strategies for providing sexual health services to young people will be needed as we confront these shocks to the healthcare systems. Protocols to continue STI screening with limited contact between patients and providers, such as the "express visits," recommended by DiMarco et al. in their guidelines for STI screening during disruptions to in-person care.[20] The use of home-based STI testing with self-collection of specimens is another promising strategy for expanding the reach of testing in contexts where in-person care is not feasible.[21]

This pattern of decreased screening raises concerns about undetected STI cases, as deferred routine screening for STIs can be expected to result in undiagnosed STIs. Routine screening is a foundational strategy for the management of bacterial STIs.[6] This is especially important for managing chlamydia and gonorrhea, as most cases of these infections present asymptomatically.[22] One modeling study estimated that 16% of untreated CT infections would result in pelvic inflammatory disease.[23] Untreated STIs also increase susceptibility to HIV[5] and enhance forward transmission of HIV,[24] leading to increased community transmission of both infections. The diagnosis of STIs is also a key opportunity to link young people to pre-exposure prophylaxis (PrEP) against HIV. Youth with a recent STI are eligible for PrEP,[25] and recent estimates suggest that only 11% of eligible adolescents and young adults were prescribed PrEP;[26] missed diagnoses of STIs also represent missed opportunities for PrEP counseling and linkage. In addition, the cost of untreated STIs is substantial. Kumar et al. found that 64% of the cost of lifetime medical costs of chlamydia infections could be attributed to untreated asymptomatic infections.[14] Considering that the total medical costs for chlamydia and gonorrhea combined are estimated at nearly $1 billion per year nationwide,[27] strategies to optimize the diagnosis and treatment of asymptomatic infections could significantly lessen the economic burden of these infections.

In our study, we estimated that between 14.4% and 23.8% of expected STI cases were missed during the pandemic due to decreases in asymptomatic screening. Patterns observed in our study are consistent with another study of STI testing in the United States,[8] suggesting a substantial number of undiagnosed STI cases nationwide. In 2019, 2.4 million cases of chlamydia and gonorrhea were reported, including more than 1.3 million among adolescents and young adults.[1] Our results have significant local implications for adolescent health, community health, and healthcare costs; additional research is warranted to determine if these patterns of decreased screening may have similar implications nationwide.

A decrease in asymptomatic screening may also be masking increases in STI incidence during the pandemic. Several studies have found lower rates of STI incidence in the early months of the pandemic.[8,10,12] However, these studies also note lower testing volume, which suggests the possibility that decreased screening could account for much of the decline in incidence.[12] One modeling study showed that disruptions to STI screening could have offset the impact of changes in sexual behavior during the pandemic, resulting in an overall increase in incidence of chlamydia among men who have sex with men in the Netherlands.[28] Our findings suggest that stable or even decreased levels of STI incidence within clinic-based study samples during that pandemic could still be indicative of increasing STI population prevalence due to decreases in screening.

This study is subject to several notable limitations. First, we were unable to assess the prevalence of STI screening among patients eligible for testing. Data on patient's sexual activity are not well captured in the EHR, limiting our ability to identify the total population of patients eligible for testing. Instead, we used the proportion of STI tests performed as asymptomatic screening to assess the degree to which routine screening was taking place relative to symptomatic and risk-based testing. Although this measure is a proxy for the STI screening rate, it does not account for potential changes in the number of patients indicated for screening based on age, gender, and sexual activity. Second, our method for estimating missed STI cases assumes that prevalence and forward transmission of bacterial STIs was similar during the 9-month pandemic period explored in this study and the corresponding 9-month period in the previous year. It is possible that COVID-related public health ordinances (i.e. school closures, limits on public gatherings, social distancing recommendations) may have resulted in reduced risk for STIs among adolescents, which would result in an overestimation of missed STI cases. However, recent data suggest that by the end of 2020, STI prevalence nationwide had rebounded to equal or greater levels than the previous year.[29] Third, despite using a system for classifying encounter testing type that drew on the expertise of adolescent health providers and multiple fields of EHR data, there remains potential for misclassification due to inaccuracies and missing data in the EHR. Finally, this study is limited to a single pediatric health system in a large US city, and the results may not be generalizable to other settings.

Conclusion

The COVID-19 pandemic has introduced new challenges for young people in getting connected to STI-related services. In addition, adolescent health providers were forced to make hard decisions about how to allocate and prioritize in-person care and testing supplies in the face of widespread community transmission of COVID-19 and disruptions to the medical supply chain. In this context, routine preventive sexual health screenings for adolescents may have been delayed or missed. As healthcare systems become better equipped to serve patients in the setting of the ongoing pandemic, we may observe an increase in the incidence of STIs and their sequelae related to the undiagnosed cases during the pandemic. Health systems that serve adolescents should use this opportunity to enhance routine STI screening to diagnose and treat these infections. A systematic review and meta-analysis of strategies to improve STI screening rates found that universal collection of urine specimens, patient reminders for screening, and additional staffing resources dedicated to STI screening programs all proved to be effective strategies.[30] A multicomponent quality improvement intervention implemented in pediatric primary care clinics, which including universal urine specimen collection and EHR-based prompts to remind clinicians to order STI screening, was associated with a significant increase in chlamydia screening rates of adolescent and young adult women in Philadelphia.[31] As we adapt and strengthen our public health systems to respond to COVID and prepare for future public health emergencies, efforts are needed to minimize delays and mitigate disruptions to preventive sexual health care for adolescents.

Author statements

Ethical approval

This research was reviewed and deemed exempt by the institutional review boards at [blinded].

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Competing interests

The authors have no conflicts of interest or financial disclosures relevant to this article to report.

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Unacceptable persistence of territorial inequalities in avoidable under-five mortality in Colombia between 2000 and 2019: a multilevel approach

M.L. Rojas-Botero [a], J.A. Fernández-Niño [b, c, *], Y.E. Borrero-Ramírez [a]

[a] Universidad de Antioquia. Facultad Nacional de Salud Pública. Medellín, Colombia
[b] Johns Hopkins Bloomberg School of Public Health. Baltimore MD, USA
[c] Universidad Del Norte, Barranquilla, Colombia

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ABSTRACT

Objectives: This study aimed at evaluating territorial inequalities in avoidable mortality in children under 5 years of age in Colombia between 2000 and 2019.
Study design: This was an ecological study.
Methods: An ecological, longitudinal, multigroup study was conducted using secondary sources. Because of the hierarchical structure of the data, the effect of territorial characteristics on the count of avoidable under-five deaths was estimated using a three-level negative binomial regression model with random intercepts for municipality and fixed intercepts for time and departments.
Results: Between 2000 and 2019, there were 216,809 avoidable under-five deaths in Colombia (91.3% of all registered deaths of children under 5 years of age). A total of 1117 municipalities located in 33 departments were analyzed over five 4-year periods. Ecological relationships were found between avoidable under-five mortality and the percentage of adolescent births, female illiteracy, and multidimensional poverty at the municipal level (standardized mortality ratio: 1.43 95% confidence interval: 1.33–1.54 for the group with the highest level vs the group with the lowest level of poverty). Furthermore, multidimensional poverty was a confounding factor for the association between the percentage of the population living in rural areas and avoidable child mortality.
Conclusions: Systematic and avoidable gaps were observed in mortality in children aged under 5 years in Colombia, where the territory constitutes an axis of inequality. Implementing strategies and programs that contribute to improving the conditions of women and socio-economic conditions in the territories should be a priority.

Introduction

Avoidable mortality in children is an indicator of premature, unnecessary, and unfair deaths in a population, insofar as they can be amenable or prevented by providing individual health care and collective interventions that address the social determinants of health. This concept was introduced in 1976 by Rutstein et al., who identified sentinel health events as those in which "if everything had gone well, the condition would have been prevented or managed" and proposed a list of diseases or events that should not—or only rarely—lead to death.[1]

In the case of child mortality, the literature has reported high percentages of avoidable deaths, especially in the Global South, with figures as high as 97.0%[2] in Uganda. In contrast, the United Kingdom was reported to have classified 35.0% of child and adolescent deaths as avoidable.[3]

While the percentage is also high in Colombia, a downward trend has been seen over the last two decades, with 93.5% of deaths registered in the country having been avoidable in 2000 vs 88.5% in 2018.[4] However, the distribution is highly heterogeneous at the territorial level. The percentage of availability in Páramo (Santander) was the lowest, with 33.3% between 2000 and 2018, whereas in another 99 municipalities, 100% of deaths among children under 5 years of age were classified as avoidable.[4]

In fact, some conceptual models suggest that the territory is a social determinant of health and an axis of inequality.[5] The

* Corresponding author. 615 N. Wolfe Street, Room E8532, Baltimore, MD 21205, USA.
E-mail address: jferna53@jhu.edu (J.A. Fernández-Niño).

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organization, infrastructure, services, and other characteristics of a territory directly influence the opportunities that its population actually has to attain the highest possible level of health and well-being. Theoretical and methodological tensions currently exist about how the territory is conceived in social research,[6] which correspond to the different theoretical models of geographical thought.

In addition, most of the available evidence on multilevel determinants of inequalities in avoidable mortality in children and other populations has come from high-income countries such as Canada,[7] Korea,[8] and several European countries.[9] Fewer studies have been carried out in middle-income countries, and particularly in Latin America, with the exception of Mexico[10] and Brazil.[11] Therefore, it is relevant to study the determinants of avoidable mortality in other low- and middle-income countries in Latin America, such as Colombia, where socio-economic inequalities are also high at the territorial level (regions, departments, and municipalities).[12]

Urban–rural socio-economic inequalities in Colombia are well known, as are their consequences, which include health inequities. These are expressed as disparities not only among departments but also among the municipalities that are located within them. To the best of our knowledge, no previous longitudinal analyses on the determinants of inequities in avoidable mortality have been conducted in Colombia at different territorial levels of analysis.

In this research, the territory has been operationalized according to Colombia's political-administrative divisions as well as its sociogeographical dimensions, where the characteristics of the interactions between territory and population converge, namely, demographic structures, geographical conditions, and socio-economic characteristics (Fig. 1).

In previous analyses, we identified an inequality gradient in avoidable childhood mortality related to multidimensional municipal poverty. While avoidable child mortality was 13.6 deaths per thousand live births in the Colombian municipalities in the wealthiest quintile, this rate was nearly double in the poorest quintile, with 24.7 avoidable deaths per thousand live births. We also identified female illiteracy, the percentage of the population living in rural areas, and the border area as axes of inequality.[13]

Nevertheless, it is worthwhile to go beyond the bivariate study by advancing a joint analysis of the conditions that have been identified as social determinants of inequality at the ecological level while also considering the data's natural hierarchical structure.

Therefore, this study was aimed at using a multilevel approach to jointly analyze territorial inequalities in avoidable mortality in children aged under 5 years in Colombia over a period of 20 years (2000–2019).

Methods

Design, study population, and rationale for the multilevel approach

An ecological, longitudinal, and multigroup study was conducted in Colombia.

Colombia, located in the northwest portion of South America, covers an area of 1,141,748 km^2 and has a population of 51.6 million inhabitants, according to the 2018 census projection for the year 2022 (7.6% children aged under 5 years), 76.3% of whom reside in

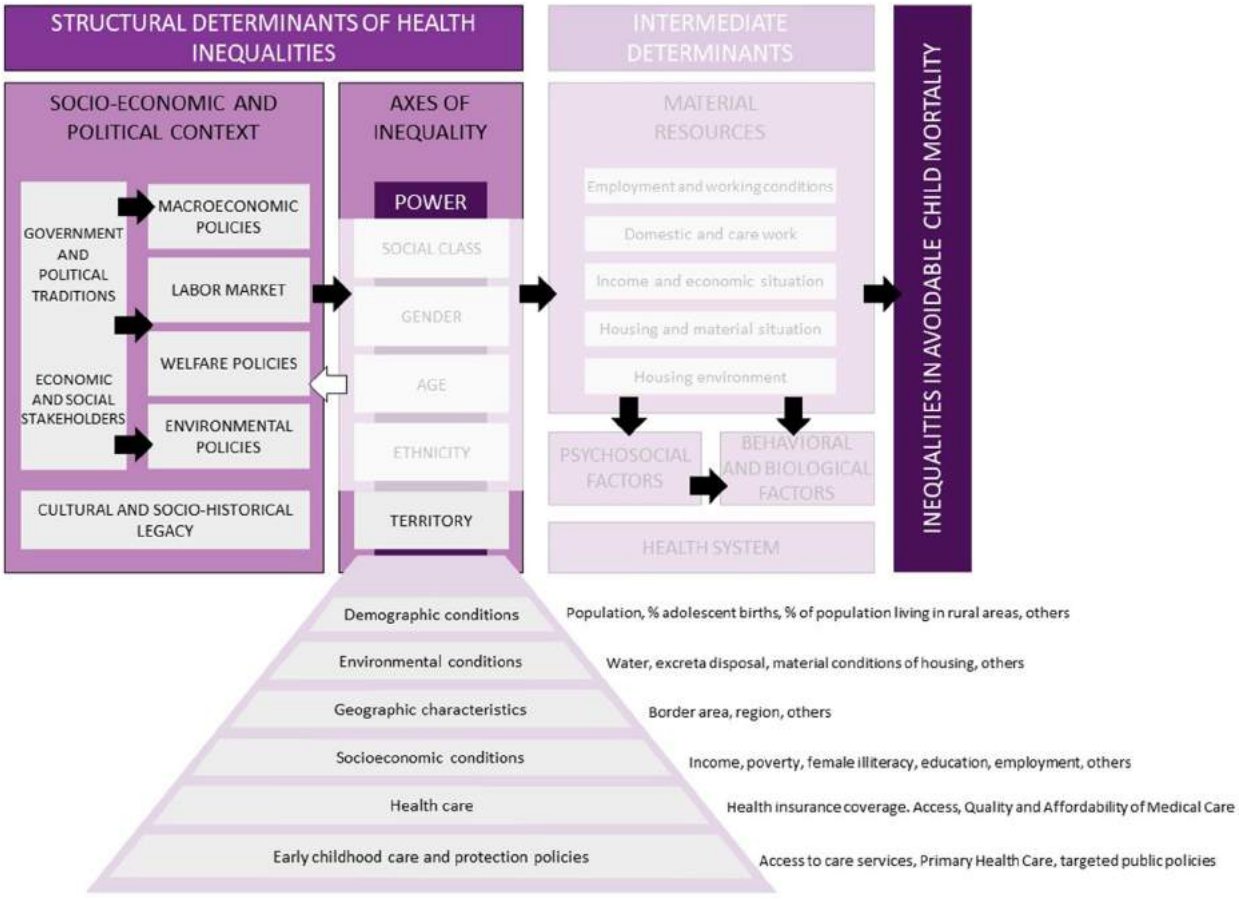

Fig. 1. Conceptual framework of the determinants of health inequalities proposed by this study. Adapted from: Commission to reduce social inequalities in health in Spain, 2010.[5]

urban areas.[14] It is an upper middle-income country with a Gross Domestic Product (GDP) per capita in 2021 of US$6131.2 and has been identified as one of the most unequal countries in the world, with a Gini index of 0.523.[15] In 2018, female literacy (ages ≥15 years) was 93.9%, 19.8% of births occurred among adolescents, 40.7% of households were headed by women, and multidimensional poverty at the national level was 19.6%.[14] Fig. 2 shows the distribution of multidimensional poverty at the municipal level based on the 2018 census.

The unit of analysis was the territory over time, specifically, the municipality during each 4-year period between 2000 and 2019. The political-administrative distribution of Colombia as of 2005 was used. Data from the municipalities that were created after that year were reintegrated into the municipalities to which they belonged in 2005. Finally, 1117 municipalities were analyzed during five 4-year periods: 2000–2003, 2004–2007, 2008–2011, 2012–2015, and 2016–2019.

A multilevel approach was necessary, given the hierarchical structure of the data. This study used repeated measures over time for each municipality; therefore, the approach first had to consider the correlation among the units over time,[17] where municipality time was the smallest unit of analysis. Although municipalities in Colombia (the smallest administrative entities) may present internal variability, each has its particular policies, administrative capacities, and resources, and therefore, the populations within each municipality tend to present more homogeneous socio-economic conditions than those in other municipalities. The municipalities in turn are nested in departments, each one with its specific policies and resources that the municipalities in the same department have in common. This reflects a hierarchical structure that the methodology needs to take into account, for which a multilevel analysis is appropriate, as has been done in previous studies.[18]

Information sources

This study used anonymized microdata of vital statistics from the National Department of Statistics (DANE in Spanish) for 2000–2019, specifically, the municipality of residence and year of occurrence of the vital event. Quality analysis and database preparation have been described elsewhere.[4]

Outcome

The outcome was avoidable under-five mortality, operationalized as the number of avoidable deaths in children from 0 to 59 months for each municipality and 4-year period, with the number of live births for the same municipality and 4-year period as the exposure (offset) variable. To classify observed deaths as avoidable or not, the list of potentially avoidable causes of death in childhood proposed for Colombia was used.[19] This is an inventory of 6168 potentially avoidable causes of death in children under 5 years of age (four-character *International Classification of Diseases, Tenth Revision*, codes) that enables classifying those deaths as amenable, preventable, or mixed. The list was proposed based on the literature review through consensus and validation by experts.

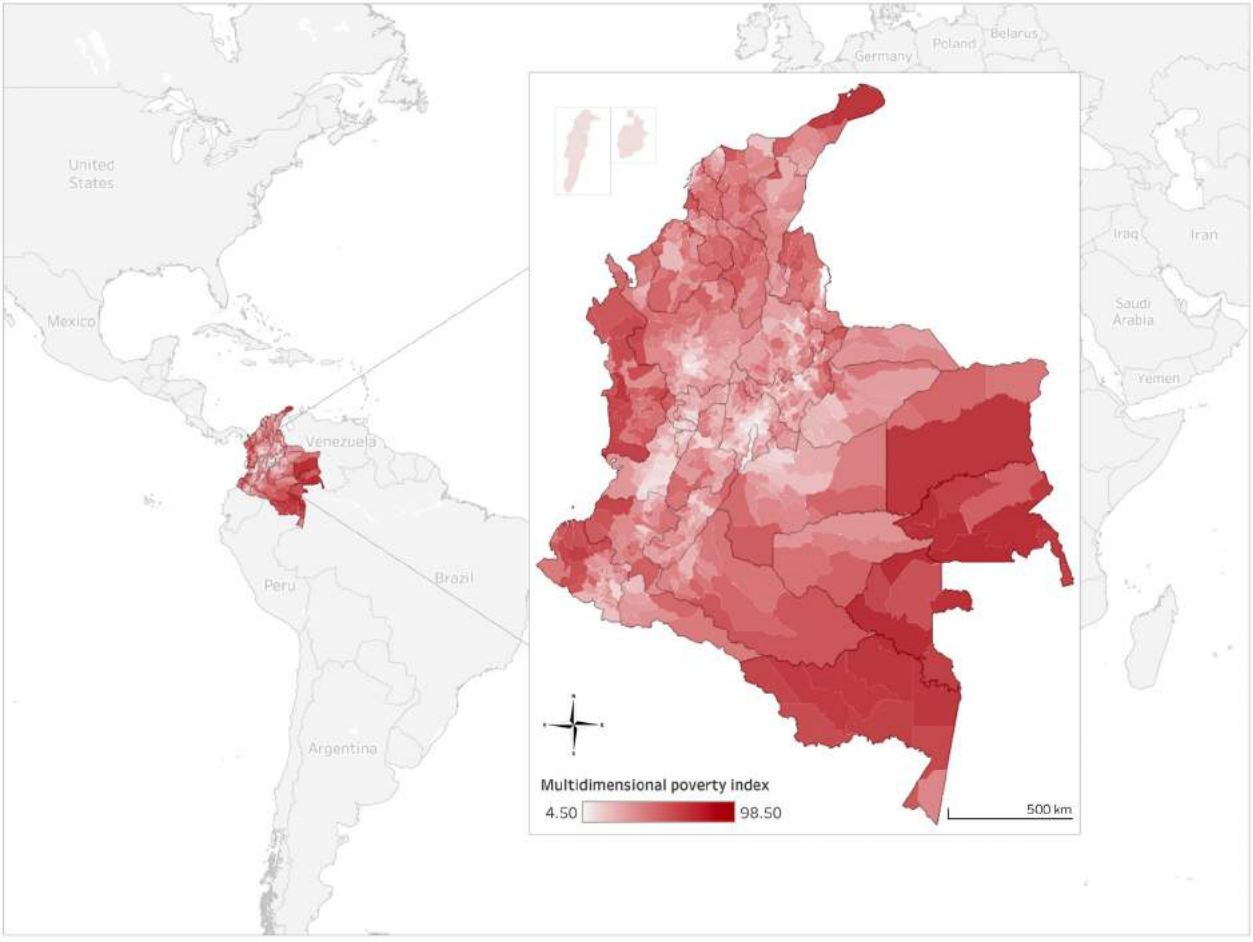

Fig. 2. Location of Colombia and distribution of multidimensional poverty at the municipal level. Source: Multidimensional poverty index estimated by DANE, 2020.[16]

Exposure

The exposure of interest was the territory, which was operationalized as the municipality of residence over time (unit of analysis) and its demographic, geographical, and socio-economic conditions (Table 1).

The percentage of adolescent births was obtained by dividing the number of births to women aged under 19 years by the total number of births. Data on female illiteracy (in those aged ≥15 years) were available only for 2018, a measurement obtained from that year's census. This corresponded to the percentage of women aged ≥15 years who could not read or write out of the total women in the same age group. The rural population corresponded to the percentage of people residing in rural centers and dispersed towns to the total projected population. Border areas were categorized as municipalities adjacent to Colombia's borders whose economic and social activities were directly influenced by border dynamics (Law 191 of 1994).

The municipal category considered the population and the current income of the territory. Municipal poverty, which used the DANE census as a source of information, was based on the Alkire and Foster methodology and included 15 indicators reflecting five dimensions: household educational level, conditions involving childhood and youth, work, health, housing, and household access to public services. Households with deprivation in at least 33.3% of the indicators were considered to be in a situation of multidimensional poverty.[16]

Data processing and statistical analysis

First, an exploratory analysis of the data was performed. This was followed by building a negative binomial regression model since overdispersion was observed. In the negative binomial regression model, the Poisson distribution measure is a random variable drawn from the Gamma distribution, which introduces an additional free parameter. The hierarchical structure of the data required a multilevel approach. Therefore, time (municipality-quadrennium) was used as level 1, the municipality as level 2, and the department of residence as level 3.

Four negative binomial regression models were adjusted for the number of avoidable under-five deaths for each municipality and 4-year period. The offset variable was the total live births in each municipality per each 4-year period, which represented the number of children susceptible to death during this period within each ecological unit of observation. This made it possible to compare death counts among the different departments and municipalities. Therefore, the association measures obtained from each model corresponded to standardized mortality ratios (SMRs) with 95% confidence intervals (CIs).

The first model was fixed as a standard negative binomial model without specifying any hierarchical data structure. It included the following explanatory variables: percentage of adolescent births, percentage of the population living in rural areas, municipalities in border areas, female illiteracy, and municipal category. The second model included the explanatory variables from the first model, but the hierarchical structure of the data was also defined, which included random intercepts at the municipality level. In the third model, a fixed intercept was added at the departmental level. Finally, the fourth model included municipal multidimensional poverty as a new variable. Many previous studies have traditionally associated poverty at the municipal level with infant and maternal mortality. The work herein is interested in going further by also exploring other relevant variables, such as the presence of the border area or female illiteracy, which are also very important social determinants. Therefore, since the greater role of poverty was already known a priori, we decided to explore the first models without including this factor and then see if the associations held when adding this variable to the models.

To determine the applicability of the multilevel approximation, the intraclass correlation index was calculated for the linear model, and the chi-squared test was used for the final model. Precision was evaluated with the standard error of the explanatory variables. At the municipality level, the Hausman test was used to compare each random intercept model with their equivalent fixed intercept model.[20] No statistically significant systematic differences in the estimated coefficients were found by comparing these models ($P > 0.10$). Therefore, random patterns were chosen to maintain

Table 1
Explanatory variables included in the analysis at the municipal level.

Variable	Years with available data	Type of data	Categories	Ecological measurement level	Source
Percentage of adolescent births[a]	2000–2003, 2004–2007, 2008–2011, 2012–2015, 2016–2019	Qualitative, ordinal	1. 0.0%–21.2% 2. 21.3%–25.8% 3. 25.9%–29.9% 4. 30.0%–100.0%	Aggregate	Live birth, DANE
% female illiteracy (>15 years)[a]	2018	Qualitative, ordinal	1. 0.6%–4.9% 2. 5.0%–6.7% 3. 6.8%–9.1% 4. 9.2%–27.1%	Aggregate	Census, 2018, DANE
% rural population in the municipality[a]	2000–2003, 2004–2007, 2008–2011, 2012–2015, 2016–2019	Qualitative, ordinal	1. 0.0%–42.0% 2. 42.1%–62.2% 3. 62.3%–76.7% 4. 76.8%–100.0%	Aggregate	Population projection, DANE
Municipality in border area	2000–2019	Qualitative, nominal	1. Yes 2. No	Global	Law 191 of 1994
Municipal category[b]	2000–2003, 2004–2007, 2008–2011, 2012–2015, 2016–2019	Qualitative, ordinal	1. Categories Special and 1 2. Categories 2, 3, 4, and 5 3. Category 6	Global	Law 136 of 1994 General Accounting Office of the Nation
Municipal multidimensional poverty[a]	2018	Qualitative, ordinal	1. 4.5–30.2 2. 30.3–40.8 3. 40.9–52.4 4. 52.5–98.5	Global	Census, 2018, DANE

[a] The categorization was based on the observed distribution of the variable by quartiles.
[b] The modal category was assigned for each 4-year period.

Table 2
Demographic, geographic, and socio-economic characteristics of the municipalities analyzed.

Socio-economic characteristics	Quadrennium				
	2000–2003	2004–2007	2008–2011	2012–2015	2016–2019
Avoidable deaths in children <5 (n)	62,308	50,922	40,704	32,499	30,376
Live births (n)	2,878,293	2,857,370	2,721,212	2,659,695	2,573,785
Avoidable mortality rate in children <5 per thousand live births	21.6	17.8	15.0	12.2	11.8
Percentage of deliveries by adolescents[a]					
$\bar{x}$ (*SD*)	24.6 (7.2)	26.1 (7.4)	26.9 (6.6)	26.5 (7.4)	24.1 (7.3)
Minimum to maximum	0–100	0–100	0–52.7	0–100	0–100
Percentage of rural population[a]					
$\bar{x}$ (*SD*)	59.9 (24.0)	58.9 (24.0)	58.0 (24.0)	57.2 (23.9)	56.3 (24.0)
Minimum to maximum	0.2–100	0.2–100	0.1–100	0.1–100	0.1–100
Municipal category (%)					
Special – Cat 1	1.8	1.9	2.0	2.3	2.9
Cat 2, 3, 4, and 5	12.4	7.3	7.6	8.3	8.1
Cat 6 and not categorized	85.8	90.9	90.4	89.1	89.0
Multidimensional poverty **(2018)**					
$\bar{x}$ (*SD*)	41.7% (17.3%)				
Minimum to maximum	4.5–98.5				
Female illiteracy (>15; **2018)**					
$\bar{x}$ (*SD*)	7.2% (3.5%)				
Minimum to maximum	0.6%–27.1%				
Border area	11.2%				

$\bar{x}$ = *Average*; *SD* = *Standard Deviation*
[a] This variable was categorized according to its quartiles to include them in the regression models.

statistical consistency but not to find a correlation between the independent variables and the random component. Random patterns are known to be more effective, that is, they have lower variance estimators.

Unlike the municipal level, at the departmental level, the models with fixed intercepts did show systematic differences with the random intercepts, so it was decided to keep fixed intercepts, which are conceptually known to be less biased. This is also explained because at this level, there are only 33 units (departments), and it is known that this number of units is very small for random intercept models.

The Wald statistic was used to determine the importance of the parameters, and the Akaike information criterion and Bayesian information criterion were used to evaluate the models' goodness of fit, where lower values indicate a better fit.

The statistical program StataMP v17 was used for the data analysis (Stata license 501709220598).

Results

Between 2000 and 2019, there were 216,809 avoidable deaths in children aged under 5 years in Colombia (91.3% of all registered deaths of children aged under 5 years). A total of 1117 municipalities located in 33 departments were analyzed over five 4-year periods. The characteristics of the municipalities are presented below.

The distribution of avoidable deaths for all municipalities for all the study years shows that avoidable deaths have very high overdispersion, with a mean of 38.8 and a variance of 46,476.5, with 3.9% being zero and 50.3% being 10 or less.

As mentioned, four negative binomial models were built to explain avoidable under-five mortality at the municipal level over time in Colombia. The first model (Table 3) was used to identify associations between avoidable child mortality and the percentage of births in adolescents (e.g. SMR = 1.21; 95% CI: 1.16–1.25 for the highest category vs the lowest), female illiteracy (e.g. SMR = 1.46; 95% CI: 1.40–1.52 for the highest category vs the lowest), the percentage of the population living in rural areas (e.g. SMR = 1.05; 95% CI: 1.01–1.09 for the highest category vs the lowest), border areas (e.g. SMR = 1.13; 95% CI: 1.09–1.17), and the municipal category (e.g. SMR = 1.10; 95% CI: 1.03–1.18 for the municipalities in category 6 vs those in the category 1).

Afterward, the second model, with the multilevel approach, resulted in a better approximation for the analysis (χ^2, $P = 0.000$). This model presented a considerable decrease in the magnitude of the association with births in adolescents (e.g. SMR = 1.09; 95% CI: 1.05–1.13 for the highest category vs the lowest), and the association with the municipal category disappeared (SMR estimates were not statistically different from one in all the categories analyzed). Other estimates of association remained very similar to those obtained with the first model.

The third model had a higher likelihood and particularly modified the magnitude of the association between avoidable mortality in children and the border area (e.g. SMR = 0.99; 95% CI: 0.92–1.08). Slight changes were observed in the other estimates in comparison to the two previous models.

Finally, with model 4, which was also adjusted by multidimensional poverty, the association remained between avoidable mortality in Colombian children and 30% or more births by adolescents (SMR = 1.05; 95% CI: 1.01–1.08), as well as between avoidable mortality and female illiteracy greater than 6.8% (SMR = 1.07; 95% CI: 1.01–1.13 for the third category; and SMR = 1.13; 95% CI: 1.05–1.20 for the last category). Meanwhile, the association with the population residing in rural areas and with border area disappeared (SMR estimates were not statistically different from one for all the categories analyzed), suggesting a confounding effect at the ecological level with the first three models (Table 3).

As shown in model 4 and Fig. 3, there is a strong association between municipal multidimensional poverty and avoidable under-five mortality (e.g. SMR = 1.43; 95% CI: 1.33–1.54 for the highest category vs the lowest), with a marked inequality gradient and worse results in the municipalities with the highest multidimensional poverty.

SMR obtained from a multilevel negative binomial model, with a random intercept at the municipal level and fixed intercepts over time at the department level

Thus, when comparing extremes, the standardized ratio of avoidable mortality in children was 43% higher in the

Table 3
Multivariate and multilevel negative binomial regression models.[a]

Independent variables	Model one SMR (95% CI)	Model 2 SMR (95% CI)	Model 3 SMR (95% CI)	Model 4 SMR (95% CI)
Percentage of deliveries by adolescents				
0.0%–21.2% (Ref)	–			
21.3%–25.8%	1.04 (1.01–1.08)	1.01 (0.98–1.04)	1.00 (0.98–1.03)	1.00 (0.97–1.03)
25.9%–29.9%	1.09 (1.05–1.13)	1.02 (0.99–1.05)	1.01 (0.98–1.05)	1.00 (0.97–1.03)
30.0%–100.0%	1.21 (1.16–1.25)	1.09 (1.05–1.13)	1.07 (1.03–1.11)	1.05 (1.01–1.08)
Female illiteracy				
0.0%–4.0% (Ref)	–	–	–	–
4.1%–6.7%	1.07 (1.03–1.11)	1.06 (1.00–1.13)	1.07 (1.02–1.12)	1.03 (0.98–1.08)
6.8%–9.1%	1.21 (1.17–1.26)	1.18 (1.11–1.26)	1.16 (1.10–1.23)	1.07 (1.01–1.13)
9.2%–27.1%	1.46 (1.40–1.52)	1.41 (1.32–1.50)	1.32 (1.24–1.40)	1.13 (1.05–1.20)
Percentage of rural population				
0.0%–42.0% (Reference)	–	–	–	–
42.1%–62.2%	0.92 (0.89–0.96)	0.98 (0.93–1.03)	0.99 (0.95–1.03)	0.96 (0.92–1.00)
62.3%–76.7%	0.95 (0.92–0.99)	0.98 (0.93–1.03)	1.01 (0.97–1.16)	0.96 (0.91–1.00)
76.8%–100.0%	1.05 (1.01–1.09)	1.06 (1.00–1.12)	1.09 (1.03–1.15)	1.00 (0.95–1.06)
Border area	1.13 (1.09–1.17)	1.12 (1.05–1.20)	0.99 (0.92–1.08)	1.02 (0.95–1.11)
Municipal category				
Special and category 1 (Reference)	–	–	–	–
Categories 2, 3, 4, and 5	1.08 (1.01–1.16)	1.05 (0.98–1.13)	1.04 (0.97–1.11)	1.03 (0.97–1.10)
Category 6 and not categorized	1.10 (1.03–1.18)	1.07 (0.99–1.16)	1.04 (0.97–1.12)	1.03 (0.96–1.11)
Multidimensional poverty				
4.5–30.2 (Reference)				–
30.3–40.8				1.09 (1.03–1.15)
40.9–52.4				1.16 (1.09–1.23)
52.5–98.5				1.43 (1.33–1.54)
Random components				
Marginal means		37.24	37.35	37.12
Municipality (Variance)		0.09	0.05	0.04
Municipality (Intraclass correlation coefficient)		0.25	0.12	0.10
Model fitting				
Akaike information criterion	4730.3	2995.0	2457.4	2358.1
Bayesian information criterion	4849.6	3120.9	2795.3	2716.0

CI, confidence interval; SMR, standardized mortality ratio.
[a] Model 1: negative binomial model without specifying the hierarchical structure and including the following explanatory variables: percentage of adolescent births, percentage of the population living in rural areas, municipality in a border area, female illiteracy, and municipal category. Model 2: first model + random intercepts at the municipal level. Model 3: second model + fixed intercepts at the department level. Model 4: model 3 + municipal multidimensional poverty.

municipalities with the highest poverty than in those with the lowest poverty (model 3). Similarly, the children's standardized avoidable mortality ratio increased 5.0% when 30% or more births in the municipality occurred among adolescents. The increase in this same ratio was 7.0% when female illiteracy was between 6.8% and 9.1% and reached 13.0% when female illiteracy exceeded 9.2%.

Regarding the random parameters, the table presents the variance components and the intraclass correlation coefficient estimate for the multilevel models. As seen in model 3, by adding the fixed intercept at the department level, the intraclass correlation coefficient decreased substantially (from 0.25 to 0.12), as expected, and it decreased more in model 4 when multidimensional poverty was added.

Discussion

The differences in the magnitude of avoidable under-five mortality between socially constituted groups serve as a reference for the degree of health inequities in a population. Thus, the gaps found in this work not only indicate the presence of inequalities in health care but also represent structural injustices and the need to implement public policies that positively impact the social determinants that are responsible for these differences.

In the previous analysis, which was based on a bivariate analysis, the socio-economic, geographic, and demographic determinants in the territories were found to be related to the heterogeneous distribution of avoidable mortality in children under 5 years of age in Colombian municipalities. The present study advances our understanding of this phenomenon by jointly considering the different social determinants of health and the hierarchical structure of the data.

As seen in the results, when only recognizing the absence of independence in the observations, the association with the municipal category and the border area disappeared (models 2 and 3). Then, by adjusting for multidimensional poverty, the association with the percentage of the population residing in rural areas also disappeared. These findings coincide in that they show that physical space alone is not a determinant of health, but rather, the determinants involve the sociocultural nature of a territory, that is, the socially constructed space: educational and work conditions, the quality and affordability of health services and access to them, public services, and opportunities for the population, including for children and youth. These must be addressed, and all the actors in society need to be involved to ensure that the risk that children under 5 years of age will die from avoidable causes does not increase due to their place of birth or residence.

It is worth noting that the variability that is explained by the municipal level is low, which may be due to models 3 and 4 having incorporated variables from the municipal level (such as multidimensional poverty) that are closely related to the avoidable under-five mortality outcome and with differences among the municipalities.

One association that remained after adjusting the models was the relationship between the percentage of births by adolescents and avoidable mortality in children, although it was modified with the multivariate analysis. This relationship has been repeatedly reported in the literature. At the individual level, children of adolescent mothers have been reported to have a higher risk of dying, especially in poor households.[21] Moreover, from the ecological perspective, higher mortality rates (neonatal, infant, and children) have been observed in states with high percentages of

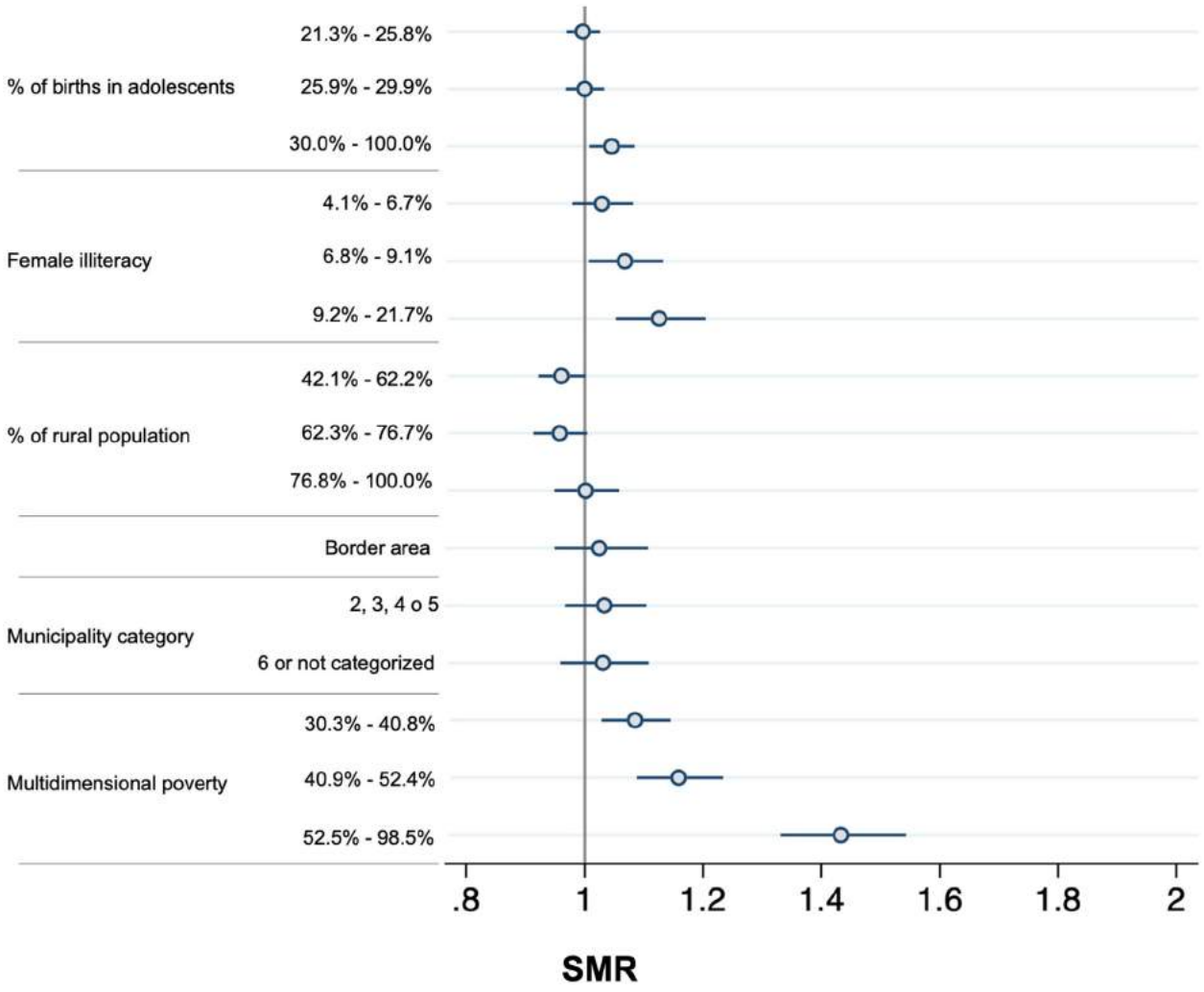

Fig. 3. Avoidable mortality and its association (SMR with 95% CI) with demographic, geographic, and socio-economic conditions.

births by adolescent mothers[22] and in countries with high adolescent fertility rates.[23]

Neal et al. obtained similar results when they evaluated evidence on the impact of maternal age on neonatal mortality in 45 low- and middle-income countries. These authors found that the offspring of adolescent mothers (aged under 16 years) presented a higher risk of neonatal death than children of adult mothers, with marked differences among countries. Furthermore, this association was maintained after adjusting for socio-economic conditions, demographic characteristics, and healthcare access.[24]

Similar results were reported by Sharma et al.,[25] who found that children of adolescent mothers aged between 12 and 15 years living in rural areas of Nepal experienced greater neonatal mortality than children of older women, adjusting for socio-economic factors, low birth weight, preterm birth, and small size for gestational age.

Several biological and physiological causal pathways have been suggested for this association at the individual level. This association can be exacerbated by adverse socio-economic conditions and barriers to accessing prenatal care. An increased risk of low birth weight and prematurity in children of adolescent mothers has been associated with several factors, including biological immaturity during pregnancy;[26,27] nutritional deficiencies induced by maternal–fetal nutrient competition;[28,29] increased risk of hypertensive disorders and preeclampsia in pregnant adolescents;[30,31] and factors related to physiological immaturities, such as reduced blood supply to the uterus and cervix[32] and reduced placental transport in adolescents.[33]

The present study also found a strong association between female education and infant and child mortality. This relationship has been frequently reported in the literature, both individually and collectively. Higher child mortality rates have been observed among children of women with less education,[34] and a systematic review of female education and child health in 175 countries between 1970 and 2009 indicated that approximately half of the reduction in child mortality could be attributed to increased schooling among young women.[35]

It is worth mentioning that some studies involving low-income countries have shown that the mother's education can explain more of the variations in infant and child mortality than household economic resources.[36,37] Similarly, studies have concluded that this association remains after adjusting for other socio-economic conditions. Research considering both determinants has found that maternal education and household wealth are independently associated with infant mortality.[37]

One possible explanation that has been proposed for the finding regarding education is that the mothers' education increases health awareness and high-order cognitive skills, which encourages them to seek health services in a timely way and to engage in practices that benefit the child's well-being.[38,39] Furthermore, some researchers have argued that in addition to developing skills and

competencies that facilitate interaction with health bureaucracies, education leads to more equitable gender attitudes and greater autonomy.[40] This has a positive impact on the empowerment of sexual and reproductive health and better living conditions for children.

This study presents some limitations that are inherent to the use of secondary sources of information. It should also be noted that the scope of ecological studies cannot definitively explain whether the determinants have the same direction and magnitude of association at an individual level. In this case, the limitation affects the ability to explain whether the sociogeographical determinants have a greater or lesser effect on the risk of a child dying before reaching the age of 5 years due to an avoidable cause. The joint distribution of the characteristics of the study at the individual level is unknown, making it impossible to determine whether the children who died from avoidable causes were the same ones with the highest exposure to poverty, mothers' low education, or whether they were children of adolescent mothers. Therefore, the reader should be aware that the findings related to the municipalities should not be applied to individuals, thereby avoiding cross-inference among the levels, that is, avoiding the ecological fallacy.

Furthermore, the present study found that the main determinant of avoidable mortality in children corresponds to multidimensional municipal poverty. However, this indicator is exclusively for 2018 and is not comparable with other poverty measurements in the territories. Therefore, it is impossible to adjust for variations in this measurement over time, which may decrease reliability and result in underestimating the association. Nevertheless, the socioeconomic conditions of the territories do not vary greatly over short periods.

In addition, we want to emphasize that the statistical models are not perfect. There are multiple possible valid models for explaining the observed phenomena. In this case, we worked with the available information for the Colombian territories. However, this does not mean that the determinants in this study are the only ones that have an important effect on avoidable under-five mortality in Colombian municipalities. Thus, it is pertinent to continue with the analysis of this phenomenon using other theoretical-methodological approaches.

This study also has its strengths. Among them, the grouping by 4-year periods made it possible to observe a greater number of avoidable deaths and births for each municipality, thus controlling the problem of having a small number.[41] Another strength is that by recognizing the hierarchical structure of the data, our approach addressed the lack of independence of the observations. The adjustment of the models is also a strength, as is the application of the list of avoidable causes of death proposed for Colombia, which is specific to classifying avoidable deaths in children under 5 years of age.[19] Other lists that have previously been applied in the country are for the general population, and they omit causes of death that can be avoided in childhood.[42] This list is based on the literature review, and all its codes were analyzed and validated by a panel of more than 30 experts, such as pediatricians with clinical experience and training in pediatric intensive care, neonatology, genetics, epigenetics, infectious diseases, pediatric pulmonology, child neurology, palliative care, public health, epidemiology, clinical sciences, and obstetrics and gynecology, who recommended its use for the Colombian context.[19]

Conclusion

This study confirms that sociogeographical inequalities in avoidable under-five mortality exist among municipalities in Colombia. At the same time, it shows that the socially constructed space is important to the actual opportunities to live a dignified life and survive early childhood. This study also highlights the impact that socio-economic gaps among territories have on the unjust distribution of avoidable mortality. It confirms that avoidable under-five mortality is independently associated with female education, births in adolescents, and poverty in a territory, which are factors that should be targeted for interventions to close the unfair gaps and achieve compliance with children's rights, especially for the most disadvantaged population.

Author statements

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Ethical approval

According to Resolution 8430 of 1993 of Colombia, this research was classified as risk free because we used secondary and anonymized sources of information. In addition, by making use of data grouped by territories, the data protection of the subjects was guaranteed. Therefore, it was not necessary to obtain informed consent to participate in the study. Finally, this study is part of a doctoral thesis endorsed by the Research Ethics Committee of the Facultad Nacional de Salud Pública of the Universidad de Antioquia (CI 341-2018).

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Competing interests

The authors declare no competing interests.

Authors' contributions

M.L.R.B. and J.A.F.N designed and conceptualized the study, conducted data analysis, and drafted the article. J.A.F.N. and Y.E.B.R. have guided the formulation of the research gap, supported during study conceptualization and in analysis, reviewed and edited the writing, and contributed to production of the final version of the article. All authors read and approved the final article.

Consent for publication

Not applicable.

Availability of data and materials

The data sets supporting the conclusions of this article are all available on the web. Microdata with the births and non-fetal deaths of children between 0 and 5 years are available on the DANE VitalStatistics website (https://www.dane.gov.co/index.php/estadisticas-por-tema/demografia-y-poblacion/nacimientos-y-

defunciones). The indicators from the 2018 census are available at https://www.dane.gov.co/index.php/estadisticas-por-tema/demografia-y-poblacion/censo-nacional-de-poblacion-y-vivienda-2018, population projections are at https://www.dane.gov.co/index.php/estadisticas-por-tema/demografia-y-poblacion/proyecciones-de-poblacion, and the categorization of the municipalities is available on the webpage of the General Accounting Office of the Nation (https://www.contaduria.gov.co/categorizacion-de-departamentos-distritos-y-municipios).

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