Public Health 220 (2023) 35–42

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Analysis of dietary patterns on cardiovascular risks in children: from a cross-sectional and a longitudinal study

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ARTICLE INFO

Article history:
Received 18 October 2022
Received in revised form
17 March 2023
Accepted 25 April 2023

Keywords:
Dietary patterns
Children
Cardiovascular disease
Risk factor
Cohort study

ABSTRACT

Objectives: Diet is one of the main risk factors for cardiovascular disease (CVD), while the evidence about the relationship between dietary pattern (DP) and CVD in children is scarce. This study aims to explore the association between DP and CVD risk in children.
Study design: This was a cross-sectional and longitudinal study.
Methods: This research was conducted among 4351 children aged 6–12 years old in 2014, then the subgroup children in 2014 were followed up in 2019. Dietary intakes were assessed using a food frequency questionnaire. DP was clustered based on 15 food items, and finally, four main DPs were obtained.
Results: Four major DPs were identified: (1) low intake of nuts and algae pattern, (2) low-energy intake pattern, (3) high-energy intake pattern, and (4) regular DP. Compared with the regular diet pattern, the low intake of nuts and algae pattern was associated with the increased risk of higher systolic blood pressure (107.71 mm Hg vs 105.78 mm Hg, $P < 0.001$), diastolic blood pressure (64.98 mm Hg vs 63.91 mm Hg, $P = 0.0056$), hypertension (odds ratio [OR]:1.44, 95% confidence interval [CI]: 1.10, 1.88; $P = 0.0036$), dyslipidemia (OR: 2.41, 95% CI: 1.28, 4.52; $P = 0.0194$), and obesity (OR: 1.48, 95% CI: 1.16, 1.89; $P = 0.0003$) in children from a cross-sectional aspect in 2014 and it was also found associated with an increased risk of hypertension (OR: 2.67, 95% CI: 1.45, 4.92; $P = 0.0017$) in 2019.
Conclusions: Low nuts and algae intake combinations in children seemed associated with increased CVD risk. Such findings are imperative for national development of dietary recommendation for the prevention of CVDs.

Introduction

Cardiovascular disease (CVD) is recognized as an increasingly serious public health problem and the leading cause of death globally.[1] There are many risk factors causing CVD.[2] High blood pressure (BP) and elevated blood glucose level are well-established risk factors for CVD.[3,4] Studies have shown that healthy diets have beneficial effects on CVD;[5] however, those only considering the effect of a single or several simple ingredients diets on CVD while ignores the synergistic effect among variety kind of foods.[6] Therefore, dietary pattern (DP) classification based on dietary habits can better explain the complexity of human diet and provide a more realistic evaluation of the relationship between diet and CVDs.[7]

Based on the DPs, there have been several studies focusing on CVDs in adults and children. Of all the DPs, representatives such as Mediterranean-style (MDS) diet and the Dietary Approaches to Stop Hypertension (DASH) diet have been extensively studied in relation to its influence on CVD. The Lyon Heart Study[8] and several cohort studies or cross-section study[9–11] all indicated that MDS diet plays a certain role in preventing the occurrence of CVDs in both adults and children. The DASH diet trial has acquired some solid evidence of the benefits on BP and other CVD risk factors as well.[6] In

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https://doi.org/10.1016/j.puhe.2023.04.018
0033-3506/

addition, the results from Framingham Offspring Study[12] identified proteomic and metabolomic correlates of the previous two DPs that may link diet to cardiometabolic health. Apart from that, other regional DP such as the Japanese DP,[13] the fast food and refined grains or poultry DP in Kuwaiti,[14] the New Nordic Diet (NND),[15] the Western DP in Iranian adolescents, and some identified DP[16] were reported, and those had different effect on CVD to varying degrees. Moreover, a research based on a population of mainly healthy children found that DP acquired in early life and persisting to later childhood was associated with markers of cardiometabolic health at school age.[17] Nevertheless, these research subjects were mainly adults and could not reflect the dietary characteristics of different countries and regions completely. Therefore, it is necessary to study the influence of DPs on children's cardiovascular risk factors in Southwest China.

In this study, the DPs of people aged 6–12 years in Chongqing were classified by latent variable classification, and the correlation between DPs and CVD was explored. In the present study, we hypothesize that different DPs can influence the risk of CVD risk factors from childhood to adolescence, and we would explore which DP has the most protective effect for cardiovascular outcomes. By analyzing the DPs of possible associations with CVD risk factors, this study aims to increase our insight to find out the protective and risk effects of DP on CVD.

Methods

Participants

Children enrolled in this study were invited to participate in two research visits for 5 years apart. More details about the study procedures have been previously published.[18,19] Participants who met the same criteria as reported before were recruited.[18,19] In total, 15,000 children in urban and rural areas were planned to be included; after excluding participants who refused to sign informed consent or had missing information in questionnaires, a total of 10,597 children with complete data were included in the final analysis sample at baseline as a cross-sectional study. The flowchart of inclusion/exclusion of participants is shown in Fig. 1. This study was approved by Children's Hospital of Chongqing Medical University with the ethics approval numbers 2013-86 and 2019-86.

Material collection

Physical examination

The same structured questionnaire was used at baseline (in 2014) and at the follow-up visit (in 2019) for collecting demographic variables, and the measuring methods of anthropometric variables, such as height, weight, and BP, were described in our previous publication.[20,21] Both data were gathered by well-trained pediatrics nurses or interviewers. BP and heart rate were measured with an OMRON arm-type electronic sphygmomanometer (HEM7051; Dalian Co. LTD, China) after they rested for at least half an hour. BP measurements were taken on three separate occasions, and the details of how measurements were performed were described in our previous publication.[18,21] When the children's BP met the criteria for hypertension for the first time, the second and third measurements were conducted in the following weeks.

Demographic variables

Demographic, socio-economic status, prenatal variables, family history, and physical activity information were collected, and the method was published in previous research.[18–21] The average physical activity time at baseline and the follow-up visit was used to represent the participants' regular physical activity.[21] A detailed description of the blood sampling and analysis procedures was published elsewhere.[18]

Diagnostic criteria

The hypertension diagnostic criteria described by Mi Jie were considered suitable for the growth characteristics of children and teenagers in this study. Hypertension was defined as mean measured systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) ≥95th percentile, based on age, sex, and height percentiles. Participants were diagnosed with hypertension if all three BP measurements met the criteria for hypertension at follow-up. The sex-specific Centers for Disease Control (CDC) and

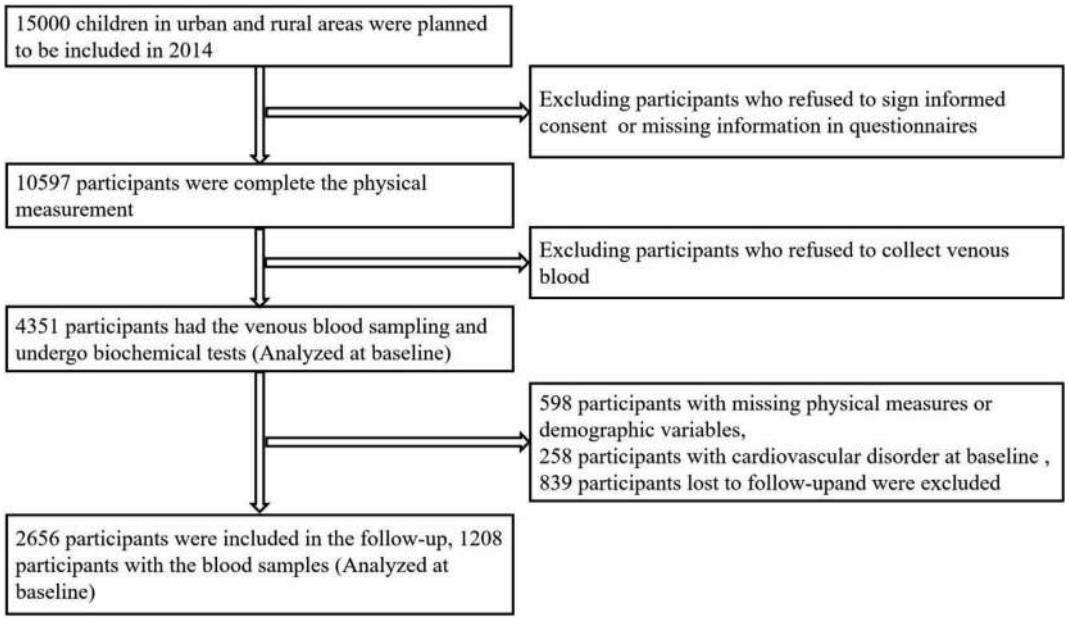

Fig. 1. The flowchart of the participants' inclusion.

Prevention charts body mass index (BMI)-for-age growth[22] and SAS code for the 2000 CDC Growth Charts were used to diagnose overweight and obesity.[23] Overweight was defined as a BMI at or above the 85th percentile and below the 95th percentile, and obesity was defined as a BMI at or above the 95th percentile. We calculated BMI z scores using the CDC's sex-specific BMI-for-age growth charts.[24] Children with the baseline blood glucose level FBG $\geq$5.6 mmol/L.[19] Children with triglyceride $\geq$ 1.24 mmol/L or serum high-density lipoprotein (HDL) cholesterol $\leq$ 1.03 mmol/L were considered dyslipidemia.[25] The mean arterial pressure (MAP, mm Hg) is calculated as MAP = DBP (mm Hg) + 1/3 (SBP [mm Hg] − DBP [mm Hg]).

Dietary intake

The questionnaire includes the children's food frequency questionnaires (FFQs), which was completed by the cooperation of parents and children, querying the children about their daily diet in the past, and the frequency they ate certain kinds of food. The FFQ includes 15 major categories. The kinds of foods analyzed were selected based on their health relevance and possible association with risk factors, such as obesity and hypertension.[26] The specific types of food and the corresponding frequency of food intake have been described in detail in previous studies.[27]

Statistical analyses

DP development

To minimize the impact of non-continuous variables from the food intake, each food variable was split into four categories according to the percentage of zeros: food subgroups that presented <20% of zeros were categorized in quartiles; food subgroups that had >20% of zeros were also divided into no consumption, and the others were separated in tertiles (Supplementary Table 2).

Latent class analysis model was used to identify DPs from the set of the 15 derived categorical food variables. Individuals were assigned to a certain DPs group with similar DPs. Latent class analysis for DP identification was conducted using a polytomous outcome variables (poLCA) package for the R language and software environment for statistical computation (version 4.0.2).

Models generated with increasing number of classes from two to seven were identified (Supplementary Table 3). Model selection was based on Akaike information criterion, Bayesian information criterion, entropy, and substantive interpretation of each model. Subjects were assigned to each pattern according to the highest probability of class membership. Each class of selected DP was then characterized based on the conditional probabilities of reported food subgroups.

Other statistical analyses

Continuous variables are presented as the means and standard deviations. Categorical variables are reported as the percentage (n [%]), and the Chi-squared test was used to test differences between groups.

The reference category was set as the class with highest proportion. The multivariate regression models testing the DP and different outcomes adjusted for variables are as follows: (1) SBP, DBP, or hypertension were adjusted for age, sex, region, breastfeeding, birth weight, gestational hypertension, house income, height, and physical activity; (2) BMI z score, levels of glucose, cholesterol, triglyceride, HDL and LDL, obesity, hyperglycemia, or dyslipidemia were adjusted for age, sex, region, breastfeeding, birth weight, house income, and physical activity. In the multivariate analyses of data from 2019, the models were additionally adjusted for the baseline values of dependent variables.

Univariate and multivariate linear regression models were performed to test the relationship between DPs and continuous outcomes. Logistic regression analysis adjusted odds ratios (ORs) and respective 95% confidence intervals (CIs) were performed to associate each DP with binary outcomes. Generalized linear models assuming Poisson distribution were used to examine the association of DPs with the incidence of the three outcomes, including hypertension, obesity, and dyslipidemia, generating adjusted incidence risk ratio and 95% CIs. Participants who already had the condition of interest at baseline were excluded.

The data analysis was conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). A significant difference was defined by an α level of 0.05 with two-sided tests.

Results

Dietary patterns

The four-class latent class analysis model was finally chosen to take forward in the analysis synthetically considering Bayesian information criterion, Akaike information criterion, entropy, and pattern interpretation. Finally, we chose the four categories as our DP and named each class due to type and quantity of food intake. The first class was followed by 11.05% of subjects and labeled as traditional diet consisting of low intake of nuts and alga; the second class was followed by 25.63% of subjects and labeled as elements of the traditional diet remain with decreasing range of foods consumed. The third class was followed by 22.02% of subjects and labeled as lower intake of most food group, and the fourth class was followed by 41.30% of subjects and labeled as ordinary diet with regular intake of each food group (Supplementary Table 2).

General characteristics of four DPs in 2014

Overall, a total of 4351 children completed the FFQs and provided blood samples at baseline in 2014. The four identified clusters, which were categorized into four clusters based on 15 food items and children's relative consumption frequency, were labeled as follows (Supplementary Table 2): the low intake of nuts and alga (Class 1 = 481), the low-energy intake group (Class 2 = 1115), the high-energy intake group (Class 3 = 958), and the ordinary group (Class 4 = 1797). The mean age of four clusters were 9.66 ± 1.73, 8.94 ± 1.77, 9.39 ± 1.69, and 9.13 ± 1.77 years, respectively (Table 1). Among four DPs, we observed statistically significant differences in several characteristics. The SBP and DBP were highest in the Class 1 group, and the SBP and BMI z score was lowest in the Class 2. Apart from SBP, DBP, and BMI z score, the statistically significant differences were also found in height, region, house income, and physical activity ($P < 0.05$).

Table 2 presents that the Class 1 had higher fasting blood glucose (FBG) and low-density lipoprotein ($P < 0.05$) than other three DPs. There were no differences between four DPs in cholesterol and HDL. When hypertension, hyperglycemia, dyslipidemia, and obesity were taken into account, there were significant differences among four DPs (all $P < 0.05$). The proportion of hypertension, obesity, hyperglycemia, and dyslipidemia in the Class 1 (19.54%, 27.74%, 3.95%, and 34.51%, respectively) was significantly higher than those in the Class 4 DP. In contrast, the Class 3 contained the highest proportions of children with dyslipidemia (35.18%).

General characteristics of four DPs in 2019

In 2019, we followed up 1208 participants with blood sample (Supplementary Table 1), and their DPs were clustered as the same

Table 1
Baseline characteristics of population from 2014.

Variables	Class 1 (n = 481)	Class 2 (n = 1115)	Class 3 (n = 958)	Class 4 (n = 1797)	P
Age, years	9.66 (1.73)	8.94 (1.77)	9.39 (1.69)	9.13 (1.77)	<0.001
Birth weight, kg	6.65 (0.92)	6.61 (1.06)	6.60 (1.09)	6.64 (0.98)	0.718
Height, cm	137.3 (11.28)	133.7 (11.62)	136.5 (11.57)	135.5 (11.62)	<0.001
Gender, *n* (%)					
Male	264 (54.89)	545 (48.88)	492 (51.36)	949 (52.81)	0.092
Female	217 (45.11)	570 (51.12)	466 (48.64)	848 (47.19)	
Region, *n* (%)					
Rural	318 (66.11)	854 (76.59)	736 (76.83)	1440 (80.13)	<0.001
Urban	163 (33.89)	261 (23.41)	222 (23.17)	357 (19.87)	
Breast feeding, *n* (%)					
No	78 (16.22)	179 (16.05)	159 (16.60)	321 (17.86)	0.579
Yes	403 (83.78)	936 (83.95)	799 (83.40)	1476 (82.14)	
Gestational hypertension, *n* (%)					
No	473 (98.34)	1099 (98.57)	947 (98.85)	1776 (98.83)	0.784
Yes	8 (1.66)	16 (1.43)	11 (1.15)	21 (1.17)	
House income, RMB, *n* (%)					
~500	28 (5.82)	36 (3.23)	39 (4.07)	47 (2.62)	<0.001
~1000	60 (12.47)	83 (7.44)	66 (6.89)	110 (6.12)	
~2000	97 (20.17)	168 (15.07)	148 (15.45)	278 (15.47)	
~3000	116 (24.12)	287 (25.74)	210 (21.92)	404 (22.48)	
~4000	106 (22.04)	292 (26.19)	272 (28.39)	480 (26.71)	
>4000	74 (15.38)	249 (22.33)	223 (23.28)	478 (26.60)	
Physical activity, min/week, *n* (%)					
~120	203 (42.20)	463 (41.52)	334 (34.86)	649 (36.12)	0.002
~240	128 (26.61)	324 (29.06)	270 (28.18)	528 (29.38)	

Class 1 = traditional diet consisting of low intake of nuts and alga; Class 2 = elements of the traditional diet remain with decreasing range of foods consumed; Class 3 = lower intake of most food groups; Class 4 = ordinary diet with regular intake of each food group.

criterion as in 2014. The statistically significant differences were found in age, region, house income, and physical activity (all $P < 0.05$). Similar to 2014 (Table 2), the BMI z score in Class 3 was the lowest and tended to have statistically significant. The Class 1 had a higher prevalence of hypertension (16.33%) than the other three groups (9.52%, 6.22%, and 7.75%, respectively).

Multivariable adjusted levels of CVD risk factors

In the year of 2014 and 2019 (Table 3), after adjusted age, sex, breastfeeding, birth weight, gestational hypertension, house income, and physical activity, the SBP (mean [standard error (SE)]: 107.74 [0.72] and 109.28 [1.38]) and DBP (mean [SE]: 64.98 [0.60] and 66.47 [1.05]) in Class 1 were higher than in Class 4. In 2014, children in Class 2 had lower BMI z score than those in Class 4 (mean [SE]:0.16 [0.04] vs 0.30 [0.03], $P = 0.0014$) after adjusting for age, sex, breastfeeding, birth weight, house income, and physical activity.

The glucose level in Class 3 (mean [SE]: 0.95 [0.02] vs 1.00 [0.02]; $P = 0.0352$) was higher than that in Class 4 after adjusting for age, sex, breastfeeding, birth weight, house income, and physical activity.

The relationship between four DPs and the prevalence and incidence of CVD factors

Tables 4 and 5 show the results of the multivariable logistic regression model and Poisson regression model of the hypertension, obesity, hyperglycemia, and dyslipidemia in the other three DPs after adjusting for covariates. Compared with the Class 4, the Class 1 was associated with an increased risk of higher hypertension (OR [95% CIs]: 1.44 [1.10, 1.88], $P = 0.0036$), obesity (OR [95% CIs]: 1.48 [1.16, 1.89], $P = 0.0003$), and dyslipidemia (OR [95% CIs]: 2.41 [1.28, 4.52], $P = 0.0194$) in 2014. The risk of hypertension was also higher in Class 1 than in Class 4 in 2019 (OR [95% CIs]: 2.48 [1.28, 4.84], $P = 0.006$). The Class 3 was associated with a decreased risk of lower obesity (OR [95% CIs]: 0.85 [0.70, 1.04], $P = 0.001$) and hyperglycemia (OR [95% CIs]: 0.88 [0.74, 1.03], $P = 0.0287$) when compared with the Class 4. From a prospective aspect, the incidences of obesity had no significant difference among four DPs in 2019. The relative risks of hypertension (OR [95% CIs]: 2.67 [1.45, 4.92]) and obesity (OR [95% CIs]: 1.84 [1.02, 3.31]) in the Class 1 were increased compared with Class 4.

Discussion

Among children aged 6–12 years, four DPs were identified based on the FFQs: the low intake of nuts and alga, the low-energy intake, the high-energy intake, and the ordinary diet DP. The present study has shown that the DPs were associated with CVDs in children. Our study revealed that who intake lower nut and algae was associated with an increased risk of BP and lipid disorder, whereas the lower energy DP was mainly associated with a decreased risk of obesity.

DPs can be classified and named in many ways. In the present study, we named the DPs by energy intake and picked out one unique type of DPs for discussion. Common DPs can be named in three categories based on their calories: low carbohydrate (carbohydrates, ≤40% kcal; protein, approximately 30% kcal; fat, 30–55% kcal; e.g. Atkins, South Beach, Zone), low fat (carbohydrates, approximately 55–60 kcal; protein, approximately 15% kcal; fat, 21 to ≤30% kcal; e.g. Biggest Loser, DASH, Jenny Craig, MDS, Portfolio, Slimming World, Volumetrics, and Weight Watchers), and moderate macronutrient (carbohydrates, approximately 60 kcal; protein, approximately 10–15% kcal; fat, ≤20% kcal; e.g. Ornish, Rosemary Conley).[28] The three categories of DPs, named after calorie intake, are similar to the DPs we clustered. We also investigated the children's long-term eating habits and divided them according to their energy intake. This way of naming method can directly reflect the characteristics of DPs in the Southwest China.

Except for the DPs named by calories intake, there were also some DPs that combined with local unique diets. For example, the Japanese DP takes natto and other special products into consideration, and the Nordic diet consists principally of a high intake of foods locally produced such as salmon and cod.[5] These DPs varies were depended on the diet habits of each country and its

Table 2
Basic characteristics analyses of the CVD risk in 2014 and 2019.

Variables	Class 1	Class 2	Class 3	Class 4	*P*
The univariate analysis of cardiovascular risk in 2014					
n	481	1115	958	1797	
SBP	106.68 (11.23)*	102.88 (10.39)*	103.85 (10.04)	103.87 (10.18)	<0.0001
DBP	64.66 (7.49)*	63.25 (7.63)	63.54 (7.67)	63.27 (7.66)	0.003
BMIz	0.42 (1.16)	0.19 (1.17)*	0.36 (1.11)	0.35 (1.12)	<0.0001
TG	1.02 (0.56)	0.96 (0.54)	0.95 (0.54)	0.99 (0.60)	0.0946
FBG	4.25 (0.71)*	4.17 (0.61)	4.19 (0.67)	4.14 (0.61)	0.0035
CHOL	3.54 (0.64)	3.55 (0.70)	3.51 (0.66)	3.51 (0.65)	0.2577
HDL	1.20 (0.26)	1.25 (0.27)	1.22 (0.28)	1.23 (0.27)	0.0093
LDL	1.81 (0.56)*	1.76 (0.57)	1.74 (0.55)	1.73 (0.53)	0.0285
Hypertension, *n* (%)					
No	387 (80.46)	957 (85.83)	827 (86.33)	1545 (85.98)	0.0133
Yes	94 (19.54)	158 (14.17)	131 (13.67)	252 (14.02)	
Obesity, *n* (%)					
No	362 (75.26)	940 (84.30)	775 (80.90)	1472 (81.91)	0.0003
Yes	119 (24.74)	175 (15.70)	183 (19.10)	325 (18.09)	
Hyperglycemia, *n* (%)					
No	462 (96.05)	1095 (98.29)	938 (97.91)	1774 (98.72)	0.0016
Yes	19 (3.95)	19 (1.71)	20 (2.09)	23 (1.28)	
Dyslipidemia, *n* (%)					
No	315 (65.49)	786 (70.56)	621 (64.82)	1206 (67.11)	0.0323
Yes	166 (34.51)	328 (29.44)	337 (35.18)	591 (32.89)	
The univariate analysis of cardiovascular risk in 2019					
n	98	361	214	535	
SBP	108.6 (11.47)	107.5 (10.69)	106.8 (10.65)	107.6 (9.41)	0.5063
DBP	65.42 (7.69)	63.83 (6.99)	63.27 (7.29)	63.78 (7.17)	0.1044
BMIz	0.48 (1.07)	0.19 (1.20)	0.24 (1.18)	0.30 (1.11)	0.1428
TG	1.09 (0.65)	1.03 (0.49)	1.05 (0.45)	1.09 (0.57)	0.3346
FBG	4.39 (0.39)	4.41 (0.39)	4.41 (0.41)	4.42 (0.43)	0.9075
CHOL	3.48 (0.61)	3.59 (0.72)	3.48 (0.56)	3.51 (0.59)	0.1045
HDL	1.40 (0.29)	1.45 (0.32)	1.42 (0.30)	1.43 (0.30)	0.4225
LDL	1.82 (0.41)	1.88 (0.45)	1.81 (0.39)	1.84 (0.43)	0.2316
Hypertension, *n* (%)					
No	82 (83.67)	323 (90.48)	196 (93.78)	488 (92.25)	0.0216
Yes	16 (16.33)	34 (9.52)	13 (6.22)	41 (7.75)	
Obesity, *n* (%)					
No	79 (80.61)	293 (82.07)	175 (83.73)	450 (85.07)	0.5576
Yes	19 (19.39)	64 (17.93)	34 (16.27)	79 (14.93)	
Hyperglycemia, *n* (%)					
No	97 (98.98)	359 (99.45)	211 (98.60)	530 (99.07)	0.7779
Yes	1 (1.02)	2 (0.55)	3 (1.40)	5 (0.93)	
Dyslipidemia, *n* (%)					
No	82 (83.67)	303 (83.93)	186 (86.92)	447 (83.55)	0.7068
Yes	16 (16.33)	58 (16.07)	28 (13.08)	88 (16.45)	

BMIz, BMI z score; CHOL, cholesterol; CVD, cardiovascular disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglycerides.
*$P < 0.05$ after multiple comparison correction. The reference group is Class 4.

geographical location. This article represented the DPs in Chongqing, the city located in the Southwest area of China, where the dietary habits had unique characteristics. People in Chongqing often like to consume cooked vegetables with salt or pickled,[29,30] as well as this phenomenon was also reflecting the dietary habit of children in our previous research.[31] In this research, we pay attention to different DPs in children aged 6–12 years in Chongqing. Only by combining local DPs characteristics, corresponding policies can be formulated to prevent CVD risks in children.

The DP 'low intake of nuts and alga' was characterized by a low intake of nuts and alga, which were both considered to be correlated with CVDs. Higher nut intake was associated with lower mortality risk from both cardiovascular and other causes in low-, middle-, and high-income countries.[32] Our previous research identified the importance that taking appropriate amount of nuts had beneficial effect on BP level and indicated that intake of 50–100 g/d nuts had the optimal daily nuts dosage of cardioprotection in children.[27] The algae also has beneficial effects on CVD. According to a cross-sectional study in Japan, 1.76 g/d of nori to the diet over 10 weeks significantly decreased DBP in boys.[33] Given 12 and 24 g/d of seaweed fiber for 4 weeks could improve Swedish patients with mild hypertension compared with placebo treatment.[34] It is likely that unique biologically such as dietary fiber, minerals, vitamins, polyunsaturated fatty acids from alga, which may play an important role on protecting cardiovascular.[35] The results were similar to the conclusion of both our previous study and this study. Moreover, we also found that this pattern is more like the opposite of NND. NND emphasizes intake abundance of algae, wild plants such as fungi, and the nuts.[36] Several studies showed that NND lowed BP level, the reason may duo to the effect of fruit, vegetable, fiber, and nut consumption.[15,37] This suggests that both nuts and algae are effective in lowering the level of BP and HDL, which could protect the health of cardiovascular, no matter being eaten alone or with other kinds of food in DPs even in children.

The DP 'low-energy intake' involves low consumption of all kinds of food. This pattern is more like a weight loss pattern. In fact, we observed that it had an effect on obese children indeed. Obesity is a risk factor for cardiovascular disease, and controlling body weight reduces the incidence of cardiovascular disease.[38] The DP

Table 3
Multivariable adjusted levels of cardiovascular disease factors.

Variables	Class 1, mean (SE)	Class 2, mean (SE)	Class 3, mean (SE)	Class 4, mean (SE)
In 2014				
SBP	107.74 (0.72)[1]*	105.56 (0.66)	105.43 (0.67)	105.78 (0.64)
DBP	64.98 (0.60)[2]*	64.08 (0.54)	64.06 (0.55)	63.91 (0.53)
BMIz	0.40 (0.05)	0.16 (0.04)[5]*	0.32 (0.04)	0.30 (0.03)
TG	4.26 (0.03)	4.24 (0.02)	4.24 (0.02)	4.21 (0.02)
FBG	1.02 (0.03)	0.98 (0.02)	0.95 (0.02)[6]*	1.00 (0.02)
CHOL	3.56 (0.03)	3.58 (0.02)	3.54 (0.02)	3.55 (0.02)
HDL	1.22 (0.01)	1.26 (0.01)	1.24 (0.01)	1.24 (0.01)
LDL	1.83 (0.03)	1.80 (0.02)	1.78 (0.02)	1.78 (0.02)
In 2019[a]				
SBP	109.28 (1.38)[3]*	108.45 (1.13)	107.61 (1.20)	108.03 (1.12)
DBP	66.47 (1.05)[4]*	65.23 (0.86)	64.53 (0.92)	64.98 (0.85)
BMIz	0.54 (0.11)	0.21 (0.07)	0.27 (0.08)	0.31 (0.06)
TG	4.45 (0.05)	4.41 (0.03)	4.40 (0.04)	4.41 (0.03)
FBG	1.19 (0.06)	1.07 (0.04)	1.08 (0.05)	1.13 (0.03)
CHOL	3.53 (0.07)	3.56 (0.04)	3.53 (0.05)	3.55 (0.04)
HDL	1.41 (0.04)	1.44 (0.02)	1.40 (0.02)	1.41 (0.02)
LDL	1.81 (0.05)	1.88 (0.03)	1.83 (0.04)	1.86 (0.03)

BMIz, BMI z score; CHOL, cholesterol; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; TG, triglyceride.
SBP and DBP were adjusted for age, sex, breastfeeding, birth weight, gestational hypertension, house income, height, and physical activity.
BMIz was adjusted for age, sex, breastfeeding, birth weight, house income, and physical activity.
$P < 0.05$, 1 < 0.001; 2* = 0.0056; 3* = 0.0508; 4* = 0.0510; 5* = 0.0014; 6* = 0.0352.
*$P < 0.05$ after multiple comparison correction. The reference group is Class 4.
[a] The models were additionally adjusted for the condition of interest in 2014.

Table 4
Results of multivariable logistic regression.

Variables	Class 1	Class 2	Class 3	Class 4 (reference)
In 2014				
Hypertension	1.44 (1.10, 1.88)[1]*	1.00 (0.81, 1.24)	0.97 (0.77, 1.22)	1.00
Obesity	1.48 (1.16, 1.89)[2]*	0.85 (0.70, 1.04)[5]*	1.09 (0.89, 1.33)	1.00
Hyperglycemia	1.04 (0.84, 1.30)	0.88 (0.74, 1.03)[6]*	1.08 (0.92, 1.28)	1.00
Dyslipidemia	2.41 (1.28, 4.52)[3]*	1.36 (0.73, 2.52)	1.50 (0.82, 2.77)	1.00
In 2019[a]				
Hypertension	2.48 (1.28, 4.84)[4]*	1.27 (0.77, 2.11)	0.87 (0.45, 1.71)	1.00
Obesity	1.45 (0.79, 2.67)	1.20 (0.81, 1.78)	1.18 (0.73, 1.91)	1.00
Dyslipidemia	1.12 (0.54, 2.33)	1.01 (0.64, 1.59)	0.67 (0.38, 1.19)	1.00
Hyperglycemia	3.33 (0.28, 39.28)	1.37 (0.19, 10.09)	2.26 (0.30, 16.98)	1.00

$P < 0.05$, 1 = 0.0036; 2* = 0.0003; 3* = 0.0194; 4* = 0.0060; 5* = 0.001; 6* = 0.0287.
Hypertension was adjusted for age, sex, breastfeeding, birth weight, gestational hypertension, house income, height, and physical activity.
Obesity was adjusted for age, sex, breastfeeding, birth weight, house income, and physical activity.
Hyperglycemia and dyslipidemia were adjusted for age, sex, breastfeeding, birth weight, house income, and physical activity.
[a] The models were additionally adjusted for the condition of interest in 2014.

we found has something in common with low-fat and low-carbohydrate diets mentioned earlier. MDS has been reported to be negatively associated with obesity prevalence, and it can reduce blood lipids that numerous observational studies confirmed this finding.[39–41] DASH has also been proven to reduce weight.[42,43] Although our research did not find this pattern alter lipid profile and hypertension in children. Our DP is based on the collection of long-term dietary data and is not a strictly designed low-energy diet, so there may not be significant changes in lipid profile.

Table 5
Relative risks of Poisson regression from 2019.

	Class 1	Class 2	Class 3	Class 4
In 2019				
Hypertension	2.67 (1.45, 4.92)[1]*	1.21 (0.74, 2.00)	0.82 (0.40, 1.70)	1.00
Dyslipidemia	1.09 (0.60, 1.99)	0.96 (0.65, 1.43)	0.83 (0.50, 1.38)	1.00
Obesity	1.84 (1.02, 3.31)[2]*	1.40 (0.91, 2.18)	1.53 (0.92, 2.56)	1.00

$P < 0.05$, 1 = 0.0017, 2* = 0.0422.
Model was adjusted for age, sex, breastfeeding, birth weight, house income, and physical activity.

The DP 'high-energy intake' was likely equal to an unhealthy pattern based on empirical data.[44] This DP was characterized by a high consumption of red meat, drinks, and fast food, which is similar to the Western DP. Studies have found that the Western diet may increase the risk of CVD.[45] Its mechanism of action may be related to trans fatty acids produced in fried food processing,[46] a fat diet–induced sensitization of angiotensin II,[47] and interfere with the regulation of appetite and cause a significant reduction in sensory-specific satiety, ultimately leading to increased BMI and insulin resistance.[48] Although the 'high-energy intake' pattern has not statistically significant impact, this pattern has a tendency of higher risk in hyperlipidemia and obesity. In Western pattern, researchers observed that the low-density lipoprotein cholesterol and triglyceride were associated with the Western pattern,[44] which was consistent with our findings.

This study had several strengths. First, this study explored the effects of DPs on CVD risk in children from both a cross-sectional and prospective aspects. Second, this study focuses on pre-adolescents who received less attention in lifestyle care than younger children or older adolescents. Finally, we found a

relationship between DPs and CVD risks in children from urban–rural areas that could represent the Southwest of China. Our study also had several potential limitations. First, dietary data were self-reported, and recall bias was existed. In response to this, a telephone follow-up was used to verify the dietary information. Second, four DPs were discussed; in Chongqing, people like spicy food, and this characteristic was not reflected in this article, which might reflect that most children did not like spicy food.

Conclusions

The relationship between four major DPs and cardiovascular risks was identified in children both from a cross-sectional and a prospective aspects. Compared with the regular diet pattern, the low intake of nuts and algae pattern was associated with an increased risk of higher hyperglycemia and obesity, whereas low-energy intake pattern was associated with a decreased risk of obesity from a cross-sectional aspect. Children with low intake of nuts and algae pattern at baseline may have a higher hypertension risk in adolescent from a cohort aspect. Importantly, this study found that low nuts and algae intake is associated with the CVD risks in children, suggesting recommendation of dietary rich in nuts and algae for children in Southwest China will have a cardiovascular protective effect.

Author statements

Acknowledgments

The authors acknowledge the effort of the study participants to fill out daily surveys and thank them for their participation. The authors thank the s Children's Hospital of Chongqing Medical University for their support.

Ethical approval

The studies involving human participants were reviewed and approved by the institutional review board at the Children's Hospital of Chongqing Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Funding

This work was supported by Key Development Project of Big Health of Chongqing Science and Technology Bureau (No. CSTC2021jscx-gksb-N0001), Program for Youth Innovation in Future Medicine from Chongqing Medical University (No. W0088), the Basic Research Project of Key Laboratory of Ministry of Education of China in 2021 (No. GBRP-202106), the Joint Medical Research Project of Chongqing Municipal Health Commission and Chongqing Science and Technology Bureau (No. 2020MSXM062), the Technology Foresight and Institutional Innovation Project of Chongqing Science and Technology Bureau (No. cstc2020jsyj-zzysbAX0016), the Natural Science Foundation of Youth Project (81502826), the Education Commission of Chongqing Municipality (No. KJQN201900443), the China Postdoctoral Science Foundation (No. 2014M562289), and Chongqing Postdoctoral Research Funded Projects (No. Xm2014129).

Competing interests

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.018.

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Public Health 220 (2023) 112–119

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Antenatal and postnatal factors associated with neonatal death in the Indian subcontinent: a multilevel analysis

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ARTICLE INFO

Article history:
Received 12 October 2022
Received in revised form
14 April 2023
Accepted 5 May 2023

Keywords:
Antenatal care
Postnatal care
Infant
Neonatal death
Indian subcontinent

ABSTRACT

Objectives: This study aimed to identify significant antenatal and postnatal factors associated with neonatal death at 2–7 days and at 2–28 days in the Indian subcontinent. Results from this study may help guide strategies to improve antenatal and postnatal care services and reduce neonatal mortality.
Study design: Nationally representative recent Demographic and Health Survey data sets from five countries, including Bangladesh, India, Pakistan, Maldives and Nepal, were used.
Methods: Survey-weighted univariate distributions were used for study population characteristics and bivariate distributions, along with the chi-squared test for unadjusted associations. Finally, multilevel logistic regression models were performed to determine the association of antenatal care (ANC) and postnatal care (PNC) factors with neonatal deaths.
Results: Among 200,499 live births, the highest neonatal death rate was observed in Pakistan, followed by Bangladesh, whereas the lowest rate was in Nepal. After adjusting for sociodemographic and maternal control variables, the multilevel analysis showed a significantly lower likelihood of neonatal death at 2–7 days and 2–28 days with ANC visits <12 weeks' gestation, at least four ANC visits during pregnancy, PNC visits within the first week after birth and breastfeeding. Delivery at home by a skilled birth attendant compared to unskilled birth attendant was significantly associated with lower neonatal death at 2–7 days. Multifoetal gestation was significantly associated with higher neonatal death at 2–7 days and at 2–28 days.
Conclusions: The findings suggest that strengthening ANC and PNC services will improve newborn health in the Indian subcontinent and decrease neonatal mortality.

Introduction

Neonatal mortality remains a persistent public health concern worldwide. In 2020, it was estimated that there were 2.4 million neonatal deaths globally, which demonstrates the vulnerability of the neonatal period (i.e. the first 28 days of life).[1] Although global neonatal mortality decreased by 54% between 1990 and 2020 (from 37 to 17 deaths per 1000 live births),[1] substantial regional and national variations exist. In 2020, South Asia had the second highest neonatal mortality rate, with 24 deaths per 1000 live births; only Sub-Saharan Africa had a higher neonatal mortality rate.[1] Compared with high-income countries, a child born in South Asia is nine times more likely to die in the first month of life.[1] Current neonatal death rates per 1000 live births in the South Asian countries included in this study are 40 in Pakistan, 20 in India, 18 in Bangladesh, 17 in Nepal and four in the Maldives.[2]

Antenatal care (ANC) plays a significant role in reducing neonatal mortality rates all over the world.[3,4] To reduce perinatal mortality and enhance women's experiences with care, the World Health Organisation (WHO) recommends at least four ANC visits and four postnatal care (PNC) contacts.[5] One study showed a 34% reduction in the likelihood of neonatal death among infants born to mothers who received appropriate ANC.[6]

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https://doi.org/10.1016/j.puhe.2023.05.004
0033-3506/

PNC is another important service, and proper management can help to reduce early neonatal mortality.[7–9] Most maternal deaths and many neonatal deaths occur during this time, making it a crucial period for both the mother and the infant. Pneumonia case management and referral, breastfeeding promotion, hypothermia prevention and management, and kangaroo care (for low-birth-weight babies) are some of the early PNC interventions that can be given to newborns.[10] PNC does not directly address intrapartum-related birth asphyxia, which is a complication that must be managed during labour, delivery and the immediate postpartum period. However, follow-up care for these infants is vital, especially if they have long-term problems, and PNC can help caregivers connect to available services. According to the WHO guidelines, if delivery takes place in a healthcare facility, the first PNC check-up should occur within the first hour of life; if the delivery takes place at home, the first PNC visit should be within 24 h of birth.[11] After that, follow-up PNC visits should be conducted within 2–3 days, 6–7 days and at 6 weeks.[12,13] Based on the existing literature, this study hypothesised that ANC and PNC would be associated with reduced neonatal mortality.

The patterns of association between ANC and PNC and neonatal death may help guide strategies to improve these services and ultimately reduce neonatal mortality. However, to date, there are no studies that investigate these associations based on data from the Indian subcontinent. One study based on multicountry pooled data in South Asia and Sub-Saharan Africa reported that prenatal asphyxia and severe neonatal infections were the leading causes of neonatal deaths, followed by preterm birth; however, the study did not focus on the impact of ANC and PNC.[14] According to a study conducted in Nepal, sepsis was the most common cause of neonatal death, followed by birth asphyxia, preterm birth and low birth-weight. The risk of death from birth asphyxia relative to sepsis was higher among nulligravida mothers who had <4 ANC visits and had multiple births.[15] Other studies have shown the effectiveness of traditional birth attendant (TBA) training, where small increases in the use of ANC lead to reduced perinatal and neonatal mortality.[16]

This study aimed to identify significant antenatal and postnatal factors associated with neonatal death at 2–7 days and 2–28 days in the Indian subcontinent based on country-pooled data from Bangladesh, India, the Maldives, Nepal and Pakistan.

Methods

Study design and participants

The recent Demographic and Health Survey (DHS) data from five countries within the Indian subcontinent (Bangladesh, India, Pakistan, Nepal and the Maldives) were used. These countries were considered because they have the most recent data available (Bangladesh: 2017–18; India: 2016; Maldives: 2017–18; Nepal: 2016; Pakistan: 2017–18). Each of the DHSs was nationally representative and collected data on demographic characteristics, marital and sexual activity information, reproduction and contraception, pregnancy and PNC, and maternal and child health via in-person interviews using multiple survey questionnaires. In each country investigated in this study, the survey was cross-sectional and based on a stratified two-stage cluster sampling design. All DHSs were approved by the Institutional Review Board (IRB) of ICF International, Rockville, MD, USA, and were funded by the United States Agency for International Development (USAID).

To analyse recent neonatal mortality, only women whose infants survived their first day of life were included in the research. Women whose children died during the first day of life were excluded from this study because it was not possible to determine whether these infants had received PNC; DHSs do not record whether neonates who died on their first day of life did so shortly after birth (i.e. before they would have been eligible for a PNC check-up) or after an hour when they may have qualified if they had been delivered in a healthcare facility. In addition, women who had not given birth in the 5 years before the survey were excluded from the analysis. The sample included 200,499 women from five countries.

Outcome variables

Neonatal death at 2–7 days (yes/no) and neonatal death at 2–28 days (yes/no) were the two outcome variables.

Key independent variables

The first PNC checks on the first day of life and the first PNC check within the first week of life were the PNC independent variables. Therefore, these two variables were included in separate regression analyses because they were not mutually exclusive. The categories for each of these independent variables were as follows: (1) None, not checked; (2) Yes, checked by an unskilled birth attendant, such as a TBA or community health worker; and (3) Yes, checked by a skilled birth attendant or medically trained provider (including a qualified doctor, nurse, midwife, paramedic, family welfare visitor or community skilled birth attendant). Newborn breastfeeding status was also included.

This study examined available maternal health variables in addition to the PNC variables. These were as follows: (1) ANC visit <12 weeks' gestation (yes/no); (2) ≥4 ANC visits during pregnancy (yes/no); (3) received all the basic ANC components (including weight and blood pressure measurements, urine and blood tests, and information on signs of possible complications) at least once (yes/no); (4) the skill of the birth attendant and location of delivery (unskilled at home, unskilled in a healthcare facility, skilled at home or skilled in a healthcare facility); and (5) multifoetal gestation.

Control variables

The sociodemographic control variables were maternal age (15–19, 20–24, 25–34, 35–49 years), parity (one, two to three and four or more), education (none, primary and secondary or more), place of residence (urban or rural) and wealth quintile (poorest, poorer, middle, richer, richest). Based on the literature, the independent sociodemographic variables were selected and added to the regression models as control variables.

Statistical analyses

The frequency distribution along with the percentage of the weighted sample by country was constructed. A table showing the distribution of the weighted sample by all the sociodemographic, antenatal and postnatal characteristics was included. To show the association between antenatal and postnatal factors and the outcome variables (i.e. neonatal death at 2–7 days and 2–28 days), a bivariate table was constructed to report the death rate by the antenatal and postnatal factors along with chi-squared test statistics and the corresponding *P*-values. Additionally, a bar diagram was created to show the number of neonatal deaths by country.

Conventional logistic regression assumes that respondents are independent across countries and have equal variation across countries. However, because the data were clustered within countries, these assumptions were violated. As a result of the clustered nature of the data, multilevel logistic regression models were used with the country as a level to identify the significant

antenatal and postnatal factors associated with neonatal death at 2–7 days and at 2–28 days.

Four key models were fitted, two for each outcome variable. A PNC variable was measured in two different ways: PNC visit on the first day and PNC visit within the first week; thus, two separate models were fitted for each outcome variable. The other key variables included ANC visits <12 weeks' gestation, total ANC visits, ANC components, type of delivery, multifoetal gestation and ever breastfed. To control for possible confounding effects, the following characteristics were used in all four models: mother's age at birth, mother's education, residence, wealth quintile, parity, preceding birth interval <24 months, sex of the child and ever had a terminated pregnancy.

This study also fitted eight additional models to see the effect of PNC visits measured as two separate variables within the first day and the first week using the definition (i) unskilled vs skilled birth attendant and (ii) none vs unskilled and skilled birth attendant.

To validate the model, log-likelihood, Akaike Information Criteria (AIC) and Likelihood Ratio (LR) tests were performed for all models. Stata SE version 17 was used to estimate all statistical analyses, and DHS-specific sampling weights were utilised for each country.

Results

Table 1 represents the distribution of study participants by country. Most study participants were from India (91.05%), while Pakistan, Bangladesh, Nepal and the Maldives only accounted for 3.30%, 2.49%, 1.98% and 1.17% of the total participants, respectively.

Table 2 shows that most respondents were in the 20–24 years (42%) and 25–34 years (41.61%) age groups, had completed secondary education (58%) and lived in rural areas (70%). About 23% of study participants were from the poorest wealth quintile. Over 83% did not have a birth interval of <24 months between the children, and 83.57% had never had a terminated pregnancy. The majority of participants (52%) had at least four ANC visits during pregnancy, and approximately 62% received all the ANC components at least once. Approximately 78% of participants gave birth at a healthcare facility with skilled health professionals present, and the history of multifoetal gestation was <1%. However, 75% of neonates did not receive PNC services on the first day, and only 22% received PNC services from skilled health professionals. Within the first week, 71% of neonates did not receive PNC services, and only 24% received PNC services from skilled health professionals. More than 95% of women breastfed their children.

A total of 2138 women were excluded from the analysis because their children died on or before the first day of life. This cohort of women showed differences in some sociodemographic characteristics compared to the sample included in the present study (see Table S1 in the supplementary material). For example, the proportion of mothers aged 35–49 years at the time of birth in the excluded population showed was 5% higher (9.49% vs 4.79%). This cohort also had more uneducated mothers (40.10% vs 27.39%), more

Table 1
Distribution of the weighted sample by country (n = 200,499).

Country	Frequency (n)	Percentage (%)
Bangladesh	4999	2.49
India	182,564	91.05
Maldives	2339	1.17
Nepal	3975	1.98
Pakistan	6623	3.30

Table 2
Sample characteristics: survey-weighted percentages (n = 200,499).

Characteristic	Frequency (n)	Percentage (%)
Sociodemographic		
Mother's age at birth in years		
15–19	23,051	11.50
20–24	84,401	42.10
25–34	83,434	41.61
35–49	9613	4.79
Mother's education		
None	54,911	27.39
Primary	28,111	14.02
Secondary+	117,477	58.59
Residence		
Urban	61,035	30.44
Rural	139,464	69.56
Wealth quintile		
Poorest	46,185	23.04
Poorer	42,165	21.03
Middle	40,021	19.96
Richer	38,391	19.15
Richest	33,737	16.83
Parity		
1	67,539	33.69
2–3	101,211	50.48
4+	31,749	15.83
Preceding birth interval <24 months		
No	167,839	83.71
Yes	32,660	16.29
Sex of child		
Male	108,618	54.17
Female	91,882	45.83
Ever had a terminated pregnancy		
No	167,556	83.57
Yes	32,943	16.43
Antenatal care		
ANC visit at <12 weeks' gestation		
No	150,805	75.21
Yes	49,694	24.79
Total ANC visits		
< 4	94,293	47.03
≥ 4	106,206	52.97
ANC components[a]		
No	75,260	37.54
Yes	125,239	62.46
Delivery[b]		
Type of delivery		
Unskilled at home	31,938	15.93
Unskilled at facility	3863	1.93
Skilled at home	7962	3.97
Skilled at facility	156,736	78.17
Multifoetal gestation		
No	198,731	99.12
Yes	1768	0.88
Postnatal care		
PNC visit on first day[b]		
None	151,052	75.34
Unskilled	6242	3.11
Skilled	43,205	21.55
PNC visit within first week[b]		
None	142,202	70.92
Unskilled	9301	4.64
Skilled	48,996	24.44
Ever breastfed		
No	8876	4.43
Yes	191,623	95.57

ANC, antenatal care; PNC, postnatal care.
[a] ANC components: receives all of the basic components of ANC (weight and blood pressure measurements, urine and blood tests, and information on signs of possible complications) at least once.
[b] Skilled refers to the presence of a medically trained provider, including qualified doctor, nurse, midwife, paramedic, family welfare visitor, community skilled birth attendant (doctor, nurse or midwife) and sub-assistant community medical officer; Unskilled refers to the presence of a traditional birth attendant or community health worker.

in the poorest quantile (33.76% vs 23.04%), higher parity for four or more children (24.14% vs 15.83%) and a higher percentage of mothers with a preceding birth interval <24 months (22.95% vs 16.43%). As it was beyond the scope of the study's objectives, this cohort of women were not included for further study in association with ANC and PNC characteristics.

The distribution of all these characteristics was also assessed by country and is presented in Table S2 in the supplementary material. Bangladesh had the highest percentage (29.04%) of teenage mothers (aged 15–19 years), while Pakistan had the highest percentage (12.71%) of mothers aged between 35 and 49 years. About half (47.88%) of the mothers from Pakistan did not receive any formal education. In contrast, 80.71% of mothers from the Maldives completed at least 6 years of education. Pakistan had the highest percentage (41.29%) of women with four or more previous births. Pakistan also had the highest percentage (32.1%) of women who had terminated a pregnancy, whereas India experienced the lowest rate (15.71%). The Maldives had the highest percentage of women who attended ANC visits at <12 weeks' gestation and had at least four ANC visits during pregnancy (88.34% and 97.29%, respectively), while Bangladesh had the lowest percentages (16.82% and 47.04%, respectively). Almost all (99.07%) women in the Maldives had delivery at health facilities with skilled birth attendants. In India, 23.16% of women received PNC visits on the first day from skilled providers, while in Pakistan, only 3.48% of women received such visits. The Maldives had the highest percentage (39.1%) of women who received PNC visits within the first week, whereas Bangladesh had the lowest percentage (6.82%).

Fig. 1 indicates that neonatal mortality was highest in Pakistan, with neonatal death rates of 13.40 and 24.80 per 1000 live births at 2–7 days and at 2–28 days, respectively. The second highest neonatal mortality rate was observed in Bangladesh (10.70/1000 live births) at 2–28 days and (5.80/1000 live births) at 2–7 days. However, the Maldives experienced the lowest neonatal mortality rate at both time frames; 2–7 days (0.30/1000 live births) and 2–28 days (3.20/1000 live births).

Table 3 demonstrates the significant association (unadjusted) between the factors, including ANC visits <12 weeks' gestation, total ANC visits, ANC components, multifoetal gestation, PNC visit on the first day, PNC visits in the first week, breastfeeding status and each of the outcome variables. Type of delivery was only associated with neonatal death at 2–28 days but not at 2–7 days. Significantly higher neonatal death rates (2–7 days and 2–28 days) were evident among pregnant women with no ANC visits <12 weeks' gestation, less than four total ANC visits and no basic ANC components. A similar pattern of higher neonatal death rates with no PNC visits either on the first day or within the first week was also evident. Moreover, PNC visits with skilled compared with unskilled healthcare workers lowered the chance of neonatal death. Having multifoetal gestation increased the likelihood of neonatal death within 28 days by more than 8-fold and within the first week by more than 7-fold. Delivery at home by an unskilled birth attendant also showed an increased likelihood of neonatal mortality compared to other delivery options.

The distribution of ANC and PNC characteristics by country is summarised in Table S3 (Supplementary Materials). ANC visits <12 weeks' gestation and total ANC visits were significantly associated with both forms of neonatal death in India and the Maldives, while ANC components and delivery facilities were associated with neonatal mortality only in India. In Bangladesh, multifoetal gestation was associated with neonatal death at 2–28 days; in India, multifoetal gestation was associated with neonatal death at both 2–7 days and 2–28 days. With the exception of the Maldives and Nepal, PNC visits within the first day or the first week were significantly associated with neonatal death. Never breastfeeding was significantly associated with neonatal mortality in all countries.

The results of the multilevel logistic modelling for the two outcomes are displayed in Table 4. The significance of the random effect suggested countrywide variation in the regression model's intercepts. After adjusting for other factors, unskilled PNC within the first week was linked to a 50% reduction (adjusted odds ratio [AOR]: 0.50; 95% confidence interval [CI]: 0.34, 0.73) in the probability of neonatal death at 2–7 days and a 33% reduction (AOR: 0.67; 95% CI: 0.53, 0.86) in the probability of dying at 2–28 days compared with neonates who received no PNC within the first week. Furthermore, skilled PNC within the first week was associated with a 17% decrease (AOR: 0.83; 95% CI: 0.71, 0.98) in the probability of death at 2–7 days compared with neonates who received no PNC within the first week. Moreover, there was a significant protective effect for ANC visits at <12 weeks' gestation and at least four ANC visits in all models. Multifoetal gestation and ever

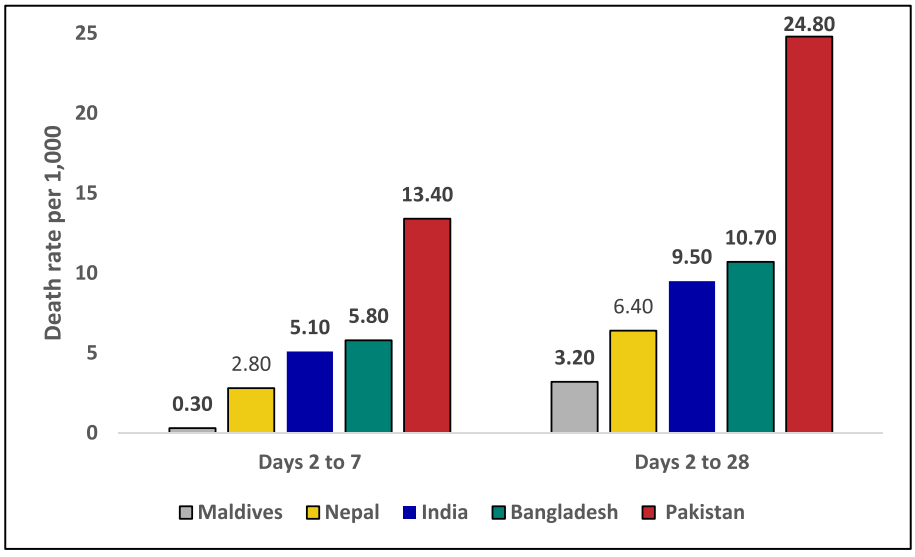

Fig. 1. Survey-weighted neonatal death (per 1000) by country.

Table 3
Survey-weighted neonatal death (per 1000 live births) by antenatal and postnatal factors.

Factors	Mortality rate per 1000 live births					
	Days 2–7	χ^2 value	*P*-value	Days 2–28	χ^2 value	*P*-value
ANC visit at <12 weeks' gestation						
No	5.80	16.14	<0.001	10.90	31.13	<0.001
Yes	3.70			6.90		
Total ANC Visits						
<4	6.70	30.54	<0.001	12.80	80.29	<0.001
≥4	4.00			7.40		
ANC components[a]						
No	6.80	14.67	<0.001	13.70	69.99	<0.001
Yes	4.40			7.70		
Type of delivery[b]						
Unskilled at home	6.70			14.10		
Unskilled at facility	4.30			8.50		
Skilled at home	4.10	4.96	0.175	11.10	30.27	<0.001
Skilled at facility	5.10			9.10		
Multifoetal gestation						
No	5.00	376.09	<0.001	9.30	924.98	<0.001
Yes	36.30			84.30		
PNC visit on the first day[b]						
None	5.70			10.60		
Unskilled	4.60	7.09	0.029	10.10	8.94	0.011
Skilled	4.00			7.80		
PNC visit within the first week[b]						
None	5.90			10.90		
Unskilled	3.20	23.29	<0.001	8.30	21.80	<0.001
Skilled	3.90			7.60		
Ever breastfed						
No	55.20	4400	<0.001	76.70	4000	<0.001
Yes	3.00			6.80		

ANC, antenatal care; PNC, postnatal care.
[a] ANC components: receives all of the basic components of ANC (weight and blood pressure measurements, urine and blood tests, and information on signs of possible complications) at least once.
[b] Skilled refers to the presence of a medically trained provider, including qualified doctor, nurse, midwife, paramedic, family welfare visitor, community skilled birth attendant (doctor, nurse or midwife) and sub-assistant community medical officer; Unskilled refers to the presence of a traditional birth attendant or community health worker.

having breastfed were strongly associated with increased and decreased probability of neonatal mortality, respectively, at 2–7 days and 2–28 days in all the models.

To evaluate the effect of the type of PNC provided (unskilled vs skilled and none vs unskilled and skilled) within the first day and the first week, eight additional multilevel logistic regression models were fitted, and the results are summarised in Tables S4 and S5.

The findings (Table S4) revealed that skilled PNC visits within the first day of birth were significantly associated with a higher likelihood of neonatal death at 2–7 days (AOR: 1.86; 95% CI: 1.00, 3.42) but not at 2–28 days. Skilled PNC visits within the first week were significantly associated with higher neonatal death at 2–7 days (AOR: 2.14; 95% CI: 1.29, 3.53) and at 2–28 days (AOR: 1.45; 95% CI: 1.05, 2.01).

Compared with none vs unskilled and skilled PNC visits within the first day of birth, the lower likelihood of neonatal deaths at 2–7 days (AOR: 0.88; 95% CI: 0.75, 1.03) and at 2–28 days (AOR: 0.93; 95% CI: 0.23, 1.05) was evident but not statistically significant. However, PNC visits (skilled and unskilled) within the first week was significantly associated with a lower probability of neonatal death at 2–7 days (AOR: 0.76; 95% CI: 0.66, 0.89) and at 2–28 days (AOR: 0.85; 95% CI: 0.77, 0.95).

Discussion

This study aimed to determine whether antenatal and postnatal factors influence newborn mortality in the Indian subcontinent. Nationally representative data sets from five countries, including Bangladesh, India, Pakistan, Nepal and the Maldives, were used. Results suggest that ANC visits at <12 weeks' gestation, four or more ANC visits during pregnancy and unskilled and skilled PNC within the first week were significantly associated with lower neonatal deaths. Evidence from other studies shows that improved access to quality antenatal, intrapartum and postnatal interventions has resulted in a decline in maternal and neonatal mortality in recent decades.[17] In addition, breastfeeding, delivery at a healthcare facility and delivery by skilled health professionals significantly reduced neonatal mortality.

The majority of participants (52%) attended ANC, and 78% gave birth in a healthcare facility with skilled healthcare professionals present. However, PNC services were not satisfactory among study participants. Only 22% of neonates received PNC services from a skilled health professional on the first day, compared with approximately one-third (75%) who did not receive PNC services on the first day. Similarly, 71% of neonates did not receive PNC services within the first week of life. Only 24% of neonates were given PNC in the first week of life by a skilled health professional. Compared with the current findings, the prevalence of maternal and health services, including ANC and PNC, was low in Sub-Saharan African countries.[18]

It has been estimated that nearly 1 million babies die each year on their first day of life, indicating this to be a vulnerable day for infants around the globe.[13,19,20] Most newborn deaths occur in developing countries, with Sub-Saharan Africa having the highest rate, followed by South Asia.[20] Compared with other Indian subcontinent countries in this study, Pakistan had the highest neonatal mortality rate (24.80/1000 live births). Distributions by countries showed that Pakistan had the second lowest percentage of women who attended four or more ANC visits, with only 52.08% receiving this level of care. Additionally, only 68.64% of women in Pakistan had a skilled delivery at a facility, which was the third lowest among countries in this study. Furthermore, Pakistan had the lowest

Table 4
Estimated adjusted odds ratio (AOR) and 95% confidence interval (CI) for multilevel weighted logistic regression models of death at 2–7 days and death at 2–28 days by antenatal and postnatal factors, and sociodemographic controls[a] (n = 200,499).

Explanatory variables	Deaths in the first week		Deaths in the first month	
	Model I AOR (95% CI)	Model II AOR (95% CI)	Model III AOR (95% CI)	Model IV AOR (95% CI)
Fixed effects				
Antenatal care				
ANC visit in <12 weeks				
No	1.00	1.00	1.00	1.00
Yes	0.82 (0.69, 0.97)*	0.82 (0.69, 0.97)*	0.82 (0.72, 0.93)**	0.82 (0.72, 0.93)**
Total ANC visits				
< 4	1.00	1.00	1.00	1.00
≥4	0.84 (0.72, 0.98)*	0.85 (0.73, 0.99)*	0.86 (0.77, 0.96)**	0.86 (0.77, 0.97)*
ANC components[d]				
No	1.00	1.00	1.00	1.00
Yes	1.05 (0.9, 1.23)	1.06 (0.91, 1.25)	0.89 (0.79, 1.01)	0.9 (0.8, 1.01)
Delivery characteristics				
Type of delivery[e]				
Unskilled at home	1.00	1.00	1.00	1.00
Unskilled at facility	0.76 (0.46, 1.27)	0.75 (0.45, 1.25)	0.73 (0.5, 1.05)	0.72 (0.5, 1.04)
Skilled at home	0.67 (0.46, 0.98)*	0.67 (0.46, 0.97)*	0.9 (0.71, 1.13)	0.89 (0.71, 1.13)
Skilled at facility	1.05 (0.88, 1.25)	1.03 (0.86, 1.22)	0.92 (0.81, 1.04)	0.91 (0.8, 1.03)
Multifoetal gestation				
No	1.00	1.00	1.00	1.00
Yes	5.37 (4.05, 7.12)***	5.33 (4.02, 7.08)***	8.57 (7.08, 10.37)***	8.56 (7.07, 10.37)***
Postnatal care				
PNC visit on first day[e]				
None	1.00		1.00	
Unskilled	0.71 (0.48, 1.07)		0.79 (0.6, 1.04)	
Skilled	0.91 (0.77, 1.08)		0.96 (0.85, 1.09)	
PNC visit within first week[e]				
None		1.00		1.00
Unskilled		0.5 (0.34, 0.73)***		0.67 (0.53, 0.86)**
Skilled		0.83 (0.71, 0.98)*		0.9 (0.8, 1.02)
Ever breastfed				
No	1.00	1.00	1.00	1.00
Yes	0.05 (0.04, 0.06)***	0.05 (0.04, 0.06)***	0.08 (0.08, 0.09)***	0.08 (0.08, 0.09)***
Random effects				
Country-level variance (SE)[b]	0.54 (0.08, 3.56)	0.57 (0.09, 3.64)	0.20 (0.04, 0.93)	0.21 (0.04, 0.94)
Log-likelihood	−5529.47	−5522.08	−9777.85	−9772.90
AIC	11112.95	11098.16	19609.70	19599.81
LR test (Chi-square)[c]	43.84***	46.42***	56.48***	58.05***

Parameters for predictors (fixed effects) are reported as odds ratio; for random effects, the parameter is the variance.
ANC, antenatal care; PNC, postnatal care.
*P < 0.05; **P < 0.01; ***P < 0.001.
PNC visit was measured as: (i) PNC visit on the first day and (ii) PNC visit within the first week. Models I and III used the PNC variable defined in (i), and models II and IV used the other definition. All other variables used in models I-IV were the same.

[a] Full model including all demographic control variables: mother's age at birth, mother's education, residence, wealth quintile, parity, preceding birth interval <24 months, sex of child, ever had a terminated pregnancy.

[b] Significance of random effects evaluated by comparing model with a similar one in which random effects have been constrained to be zero.

[c] Compared to null model with no covariate.

[d] ANC components: receives all of the basic components of ANC (weight and blood pressure measurements, urine and blood tests, and information on signs of possible complications) at least once.

[e] Skilled refers to the presence of a medically trained provider, including qualified doctor, nurse, midwife, paramedic, family welfare visitor, community skilled birth attendant (doctor, nurse or midwife) and sub-assistant community medical officer; Unskilled refers to the presence of a traditional birth attendant or community health worker.

percentage of skilled PNC visits for newborns within the first day (3.48%), and the second lowest percentage of skilled PNC visits for a newborn within the first week (9.68%). These ANC and PNC factors may be associated with Pakistan's high rate of neonatal deaths.

The lowest neonatal mortality rate in Sub-Saharan Africa was in Rwanda (15/1000 live births).[21] In Burkina Faso, neonatal mortality declined from 27.8/1000 live births in 2016 to 25.3/1000 in 2021.[22] While in Ethiopia, neonatal mortality ranged from 29 per 1000 live births in 2016 to 33 per 1000 live births in 2019.[23] Ethiopia's neonatal mortality rate increased over this period due to several factors, the most important being the lack of ANC and PNC services. Neonatal mortality remains high despite the satisfactory use of ANC in the present study. This might be due to the low utilisation of neonatal PNC services.

According to this study, neonatal mortality rates were low for women who received ANC at least four times during pregnancy and at least once within the first 12 weeks of pregnancy. Multilevel logistic modelling also showed the protective effect of ANC visits during pregnancy on reducing neonatal mortality. A similar observation was made in a systematic review and meta-analysis.[24,25] For example, a study using data from Indonesia's DHS showed that women who received <4 ANC visits during pregnancy had a 2.4 times greater risk of neonatal death compared with those who received ≥4 ANC visits.[26] A study in Kenya also found that women with a history of few ANC visits had a high risk of infant mortality.[27] Furthermore, another meta-analysis and systematic review showed that delivery at a healthcare facility reduces neonatal mortality by 29%.[28] However, the meta-analysis and

systematic review study areas included only one country from the Indian subcontinent (Pakistan). Conflicting results have been reported from countries in the Indian subcontinent. Studies showed an increased likelihood of facility delivery with neonatal death in India[29] and Nepal,[30] whereas there was no association in Bangladesh[31] and Pakistan.[32] For the Maldives, no evidence for such an association was found in the literature. These findings from individual countries justified the current results based on the pooled data.

Improving child health cannot be achieved merely by promoting ANC and skilled attendance at birth. PNC is also essential[33] to reduce neonatal and maternal mortality.[13] In line with this, the present study findings were also conclusive. WHO and UNICEF recommend that neonates receive two postnatal visits from a health professional within the first hour and 24 h of birth,[11] and researchers have found that receiving a PNC within 2 days of delivery can reduce neonatal mortality by 30–60%.[34–36] The current results suggested that PNC visits within the first week significantly reduce (17%–50%) the chance of neonatal death. The results in the supplementary material show that PNC provided by skilled or unskilled health workers also significantly reduces neonatal death compared to no PNC. However, a higher likelihood of neonatal death was evident in association with skilled PNC compared to unskilled PNC, which is an unexpected result. However, in low- and middle-income regions, such as the Indian subcontinent, women with more complications during pregnancy, delivery or after delivery may be more likely to require and receive PNC from skilled providers. This may result in increased neonatal death among women receiving skilled PNC compared to unskilled PNC. Two studies from India[37] and Bangladesh[38] also found unskilled PNC to be more effective in reducing neonatal death compared to no PNC. Another multilevel study in Sub-Saharan Africa also reported similar findings regarding PNC.[39]

It is estimated that 20% of newborn deaths and 13% of under-five deaths can be avoided if breastfeeding starts early and continues exclusively during the first 6 months of a child's life.[40] Additionally, breastfeeding can reduce neonatal infection mortality due to sepsis, pneumonia, tetanus and diarrhoea.[41] This study lacked data on breastfeeding initiation time or delayed initiation of breastfeeding; however, the ever breastfeeding variable was considered. Women who did not breastfeed experienced a higher neonatal mortality rate than those who did. In multilevel logistic modelling, breastfeeding significantly reduced the probability of death in all four models. A study from India found that breastfeeding improves the survival of infants in the first 28 days of life, irrespective of the cause of death.[42] Studies conducted in Ethiopia and Malaysia identified factors associated with breastfeeding, including maternal education, having a supportive husband, unemployment status and lower family income. In the present study, the effect of breastfeeding in neonatal mortality could be a proxy for some other factors, and further investigation is necessary for specific recommendations in this regard.[43–45]

There are some limitations to the present study. As cross-sectional data sets were used, the results show associations rather than cause-and-effect relationships. For causation, longitudinal data sets from each country are required. Although the present study considered most of the potential confounders found in similar studies,[37,39,46] some other factors, such as the mother's physical health status, preterm status, birthweight, complications during pregnancy and birth, medical care access and health insurance affordability, could impact the relationship between ANC and PNC characteristics and neonatal mortality. As the data sets used in this study did not have information on these variables, it was not possible to control for their effects. Some studies have shown a significant association between neonatal deaths and other factors, including birthweight, gestational age, malformations, complications during pregnancy and birth maternal–foetal and obstetrical morbidity.[47,48]

In conclusion, reduced neonatal mortality at 2–7 and 2–28 days were substantially correlated with ANC and PNC characteristics, such as ANC visits <12 weeks' gestation, four or more ANC visits during pregnancy, home birth with skilled birth attendant and unskilled and skilled PNC visits for infants within the first week. Furthermore, multifoetal gestation was associated with the highest risk of neonatal mortality, whereas breastfeeding was associated with the lowest risk of neonatal mortality. Overall, the study results indicate that strengthening ANC and PNC will improve newborn health in the Indian subcontinent and decrease neonatal fatalities. The prevalence of PNC services was lower than that of ANC services. This study advocates for increased early PNC for newborns, which may reduce neonatal deaths in the Indian subcontinent.

Due to the lack of healthcare facilities in the Indian subcontinent, multifaceted approaches may be beneficial in reducing neonatal death. Strategies may include increasing community engagement, more skilled healthcare providers, rebuilding and improving existing healthcare systems, implementing incentives and proper referral systems, addressing social norms and digitisation of the systems. Government agencies, non-government organisations (NGOs) and other stakeholders must work together to facilitate these service improvements.

Author statements

Acknowledgements

The authors are grateful to ICF International, Rockville, Maryland, USA, for granting access to the DHS data sets used in this study.

Ethical approval

This study was based on the secondary DHS data sets approved by ICF International. Each of the DHS protocols was reviewed and approved by the Institutional Review Board (IRB) of ICF International. IRB procedures for DHS public-use data sets do not allow respondents, households or sample communities to be identified.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Competing interests

The authors have no conflicts of interest to declare.

Author contributions

D.P. Dasgupta and M.T.F. Khan contributed to conceptualisation, resources, software, supervision and validation; D.P. Dasgupta, M.T.F. Khan, N. Sultana, S.M. Suman and K. Fatema contributed to data curation, formal analysis, investigation, visualisation, writing – original draft and writing – review editing; the final version of the manuscript has been read and approved by all authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.05.004.

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Public Health 220 (2023) 88–95

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Assessing the construction of a Healthy City in China: a conceptual framework and evaluation index system

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ARTICLE INFO

Article history:
Received 7 December 2022
Received in revised form
5 April 2023
Accepted 21 April 2023

Keywords:
Healthy city
Conceptual framework
Evaluation
Optimization and regulation

ABSTRACT

Objectives: COVID-19 has brought challenges to the health of all mankind. It is particularly important to promote the construction of a 'Healthy China' and build a 'healthy community'. The aims of this study were to construct a reasonable conceptual framework for the Healthy City concept and to assess Healthy City construction in China.

Study design: This study combined qualitative and quantitative research.

Methods: This study proposes the concept model of 'nature–human body–Healthy City' and accordingly constructs an evaluation index system for the construction of a Healthy City that integrates five dimensions, namely, the medical level, economic basis, cultural development, social services, and ecological environment to explore the spatial and temporal heterogeneity of Healthy City construction in China. Finally, the influencing factors of Healthy City construction patterns are explored using GeoDetector.

Results: (1) The pace of Healthy City construction is generally on the rise; (2) the construction of Healthy Cities exhibits significant global spatial autocorrelation and gradually increasing agglomeration. The spatial distribution of cold hotspot areas was relatively stable; (3) medical and health progress is an important factor; the level of economic development is the leading support; the endowment of resources and environment is the basic condition; public service support provides important support; and scientific and technological innovation capabilities provide technical support for the construction of a Healthy City.

Conclusions: The spatial heterogeneity of Healthy City construction in China is evident, and the state of spatial distribution is relatively stable. The spatial pattern of Healthy City construction is shaped by a combination of factors. Our research will provide a scientific basis for promoting the construction of Healthy Cities and helping to implement the Health China Strategy.

Introduction

Although global urbanization brings convenience and opportunities, it also poses great threats and challenges. Living standards and production practices have increased along with various health risks due to environmental pollution, the global spread of infectious diseases, and aging populations. In particular, the outbreak of COVID-19 at the end of 2019 put the safety of the people and the country's stability at risk.[1] Building Healthy Cities to manage social and environmental factors is the best way to address urban health challenges. The 'Healthy City' was first introduced in 1984 in Toronto, Canada. In 1988, Dual and Hancock proposed that a healthy city is a city that enables the creation and improvement of the natural and social environment and the expansion of social resources to enable people to support each other, perform all the functions of life, and achieve the most desirable state of health. A Healthy City was defined by the World Health Organization (WHO) in 1995 as "a place that provides services to people and the planet; where the natural, ecological, and social environments develop steadily; where people's well-being increases; and where a dynamic cycle of health is achieved."[2] The Healthy City movement is gaining popularity worldwide, with many cities in Asia, Europe, and the United States building distinctive Healthy City models.[3–5] A Healthy City, as currently identified by the WHO, puts health, social well-being, equity, and sustainable development at the center of local policies, strategies, and programs based on the core values of

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https://doi.org/10.1016/j.puhe.2023.04.020

the right to health and well-being, peace, social justice, gender equality, solidarity, social inclusion, and sustainable development. The guiding principles of Healthy Cities are health for all, universal health coverage, intersectoral governance for health, health-in-all-policies, community participation, social cohesion, and innovation. A healthy city, as currently identified by the WHO, is one that puts health, social well-being, equity and sustainable development at the center of local policies, strategies, and programs based on core values of the right to health and well-being, peace, social justice, gender equality, solidarity, social inclusion and sustainable development and guided by the principles of health for all, universal health coverage, intersectoral governance for health, health-in-all-policies, community participation, social cohesion, and innovation.[6] The WHO also approaches Healthy Cities as a process that enables the possibility of health in people instead of an end state.[7] Monitoring and evaluation are important safeguards for the sustainability of Healthy City.[8] In 1996, the WHO arranged for experts and scholars to identify a total of 32 indicators in four dimensions, population, services, environment, and economy, to constitute a system of indicators for evaluating the health of a city.[9] Later, politics,[10] transportation planning,[11] information,[12] and other categories were also added to the evaluation indicator system, emphasizing the role of public,[13] government,[14] non-profit organizations,[15] and private sector.[16] The basis for the development of indicators was the 11 objectives of a healthy city according to the WHO.[17] Strengthening the governance of different urban sectors is key to healthier cities,[18] emphasizing that health cuts across all policies through inter sectoral synergies.[19] Most scholars have focused on the transformation of cities into healthier ones by improving health systems and urban infrastructure and promoting the equalization of public services.[20–22] Building a healthy city is the key to improving urban livability,[23,24] improving the habitats by strengthening environmental pollution control,[25,26] improving the human environment,[27,28] and enhancing the vitality and metabolism of a city is also the focus and direction of Healthy City construction.[29] Urban planning is a tool for healthy urban development,[30,31] and urban planners have long emphasized the need for urban planning to be 'people centered,' with health promotion as a goal. Urban planning also includes the need for better public education, dissemination, and mental health support in the context of public mental health emergencies[32] in an effort to improve the health literacy of residents. The introduction of policies such as new urbanisation[33], high-quality development[34], smart cities[35], and shared cities[36] also provides a good opportunity to Healthy City. Since its launch, the Healthy City campaign has provided models for other regions through strict management systems, policies, financial investments, and pilot projects.[37]

Academic enquiry into the 'Healthy City' has moved from qualitative theoretical research to quantitative research. Research themes have been updated over time, whereas research directions have intersected with more disciplines. Therefore, the indicators of Healthy City need to be updated according to the research objectives. In addition, there is a lack of investigation into the spatial and temporal evolution and influencing factors Healthy City construction. This study explores the spatial and temporal patterns of Healthy City construction in 341 Chinese cities. It also analyzes the factors affecting spatial and temporal patterns of Healthy City construction in China, discusses the regulation paths and key construction directions for Healthy City construction, and provides theoretical guidance.

Methods

Research framework

Healthy City construction research is a comprehensive system composed of connotation generalization, spatial–temporal pattern evolution, construction paths, and other systems. The exploration and deepening the connotation of Healthy City form the basis of research on Healthy City construction. A five-dimensional model for measuring the construction of Healthy City was developed, starting from five subsystems (medical level, economic foundation, cultural development, social services, and ecological environment) and analyzing the comprehensive construction level of Healthy City among cities, provinces, and districts. The spatial evolution of the construction of Healthy City is discussed from the perspective of

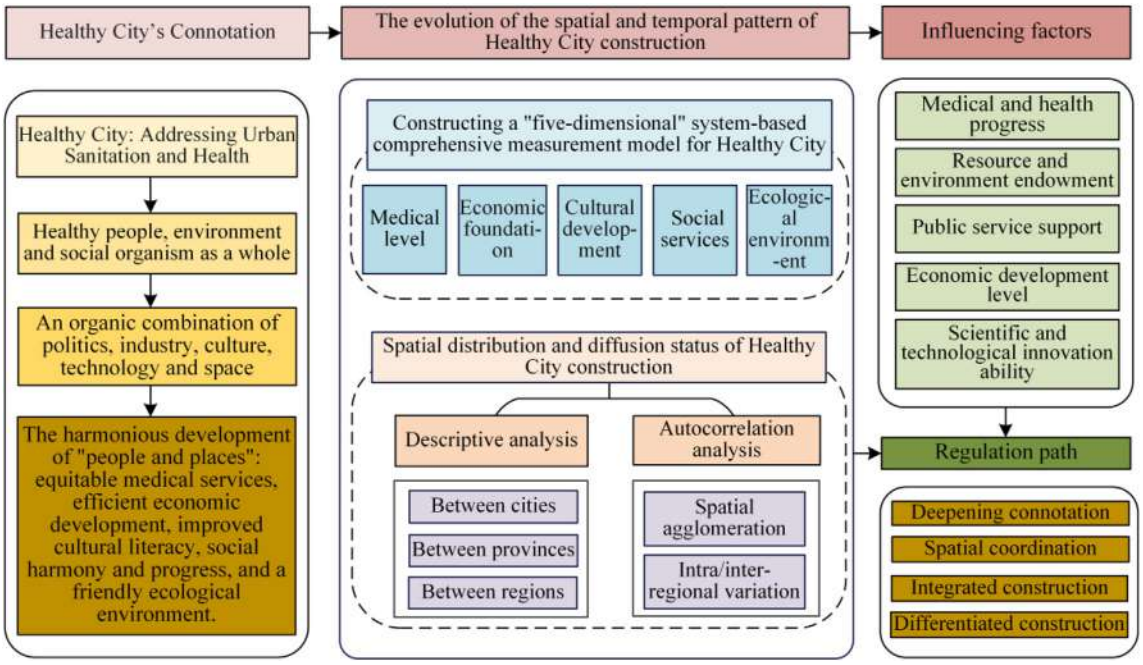

Fig. 1. Theoretical framework of Healthy City construction in China.

spatial analysis, and the formation mechanism and regulation strategies affecting the construction of Healthy City are discussed from five aspects: medical and health progress, resource and environmental endowment, public service support, economic development level, and scientific and technological innovation capacity (Fig. 1).

Connotation and developmental changes of Healthy City

Healthy City is a global movement proposed by the WHO in 1980. It has been widely applied as an academic concept in many fields of research. This research summarizes Healthy City as follows: under the guidance of the harmonious symbiotic relationship between man and the land system, a healthy city adheres to a people-oriented concept and rationalizes the mechanism of action among various elements by solving the relationship of 'population-society-economy-space-ecology'. A virtuous cycle system of all elements is thereby constructed, with a sound ecological environment as the basis, medical and health care as the key, economic development as the support, public services as the guarantor, and scientific and technological innovation as guidance. Finally, a new city construction pattern is formed, including healthy and coordinated development of 'man-land', and characterized by fair medical services, economic and efficient development, cultural quality improvement, social harmony and progress, and a supportive ecology and environment.

Yi's philosophical theory states that all things are interconnected and interact with each other. All things in the world are in a kind of correlation, whether celestial phenomena, objective substances, or earthly, human, or imaginary phenomena. Nature is a large system composed of five basic substances: gold, wood, water, fire, and earth, each of which is mutually exclusive to achieve the harmony and unity in nature. In traditional Chinese medical theory, it is customary to draw on the theory of generation and restriction among five elements to analyze the phase of the heart, liver, spleen, lung, and kidney in the human body and to establish a one-to-one correspondence between the five elements and the five organs from the perspective of the human–earth relationship. What a healthy city pursues is not only the health of people but also the overall health with the external environment. 'Wood' and 'Liver' correspond to the medical level, and both have the function of detoxification and elimination of diseases, which is the key to the construction of Healthy City. 'Fire' and 'Heart' correspond to the cultural development, and these three represent the spiritual civilization in their respective systems, which is the innovation and direction of Healthy City construction. 'Spleen' and 'Earth' correspond to the social services, and they are functionally the guarantors of the functioning of the system and the cornerstone of the development of a healthy city. 'Gold' and 'Lung' correspond to the economic foundation and are both functionally supportive and important pillars of the construction of Healthy City. 'Water' and 'kidney' correspond to the ecological environment, and all three of them have the function of purification and elimination in their respective systems; ecological health is the environmental foundation for the construction of Healthy City. The five dimensions of Healthy City construction complement each other in promoting the development of the city toward wellness.

Research methods

After standardizing the original data, the principal component analysis method[38] was used to determine the index weight using the orthogonal transformation of N-dimensional factors. Then, the comprehensive measure model of Healthy City construction was used to calculate the Healthy City construction level in each period in the study area. ArcGIS and global spatial autocorrelation tools were used to determine the distribution status of Healthy City construction.[39] After this, the spatial agglomeration patterns were analyzed using Getis-Ord Gi* through local spatial autocorrelation analysis,[40] and the spatial and temporal distribution patterns of Healthy City construction were quantitatively analyzed. Finally, a factor detector of GeoDetector[41] was used to analyze the spatial differentiation mechanism of Healthy City construction (the parameter descriptions of the specific research methods are presented in Table 1).

Index system and data sources

Evaluation of Healthy City construction

The current evaluation of a healthy city refers to the evaluation index system provided by WHO. This study combined the current strategic outline of Healthy China with the evaluation indicators of Healthy City in China (2018) to develop Healthy City construction evaluation index system (Table 2), consisting of 25 specific indicators from five aspects: medical level, economic foundation, cultural development, social services, and the ecological environment. A total of 341 cities in China were used as research subjects. Primary data were obtained from the Statistical Yearbook (2011 and 2021), the National Economic and Social Development Statistical Bulletin, and the official Web sites of local governments. The national intangible cultural heritage list was obtained from the China Intangible Cultural Heritage Web site. Energy data were obtained from energy consumption bulletin for each province and city. Missing data were supplemented by extrapolating from the trends in adjacent years. The administrative map of China is a standard

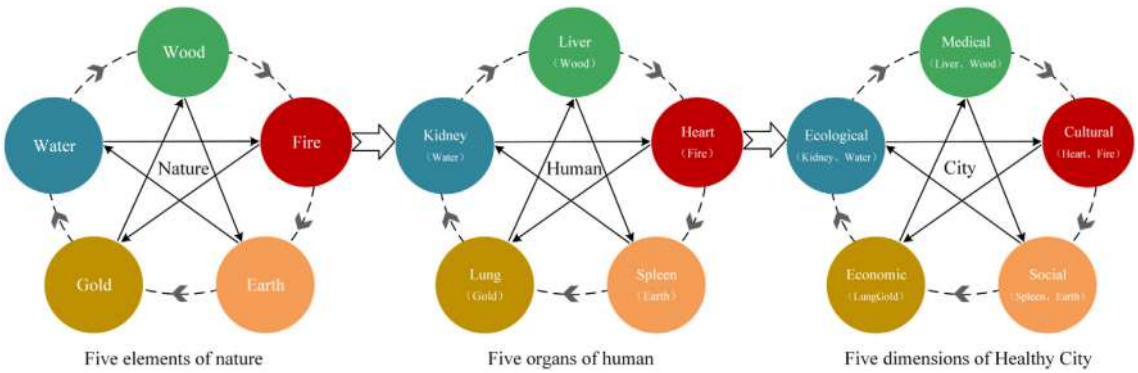

Fig. 2. Healthy City composition based on human–land system synergy.

Table 1
Description of research methods.

Research methods	Equation		Method description
Comprehensive measurement model incorporating the 'five dimensions' system	$I_k = \frac{\sum Y_{ij} W_j}{\sum W_j}$	(2.1)	I_K represents the composite score of each subsystem, where k is the ordinal number of primary indicators, M_K (medical level health index), EC_K (economic foundation health index), C_K (cultural development health index), S_K (social services health index), EV_K(ecological environment health index). (Notes: i: municipalities; j: measure indicators; Y_{ij}: standardized data; W_j: weight of each measure indicator).
	$HC = M_K W_j + EC_K W_j + C_K W_j + S_K W_j + EV_K W_j$	(2.2)	
Analysis of spatial–temporal differences	$I = \frac{\sum_{k=1}^{n} \sum_{j=1}^{n} (X_k - \overline{X})(X_j - \overline{X})}{S^2 \sum_{k=1}^{n} \sum_{j=1}^{n} W_{kj}}$	(2.3)	Moran's I lies between [−1,1]; when the value tends to 1/−1, it indicates the presence of spatial positive/negative correlation and spatially clustered/dispersed distribution; equal to 0 indicates no spatial autocorrelation and spatially random distribution. When there are clustering or dispersion characteristics, if Z ($G_i \times [d]$) is positive and significant, it indicates that location I and its adjacent spaces is a high-value spatial clustering, that is, a hotspot area; conversely, it is a cold spot area, so as to analyze the spatial and temporal distribution pattern of Healthy City construction. (Notes: X_k and X_j denote the attribute values of cell k, j, $\overline{X}$ represents series mean, W_{kj} denotes the weighting matrix, S^2 denotes the variance of sample, E(I) represents expected value, var(I) is the coefficient of variation, $E(G_i^*(d))$ and $Var(G_i^*(d))$ denote the mathematical expectations and variance of $G_i^*(d)$).
	$Z(I) = \frac{1 - E(I)}{\sqrt{\mathrm{var}(I)}}$	(2.4)	
	$G_i{}^*(d) = \frac{\sum_{k=1}^{n} \sum_{j=1}^{n} W_{kj}(d) X_j}{\sum_{j=1}^{n} X_j}$	(2.5)	
	$Z(G_i{}^*(d)) = \frac{G_i{}^*(d) - E(G_i{}^*(d))}{\sqrt{\mathrm{var}(G_i{}^*(d))}}$	(2.6)	
Analysis of the mechanism of spatial differentiation	$q = 1 - \frac{\Sigma_{h=1}^{L} N h \sigma_h^2}{N \sigma^2} = 1 - \frac{SSW}{SST}$	(2.7)	q-value between [0,1], with larger q-value, indicating more pronounced spatial heterogeneity; the larger value of q indicates a stronger explanatory power of the independent variable X on Healthy City construction and vice versa. (Notes: h = 1, …, L represent the stratification of Y or X, that is partitioning; N_h, N are the number of cells in stratum h and the whole region; σ_h^2, σ^2 are the variance of variable Y in stratum h and the whole region; SSW and SST denote the sum of variance within stratum and the total variance of the whole region).

SSW, within sum of squares; SST, total sum of squares.

map with review number GS (2019)1822, downloaded from the standard map service Web site of the Ministry of Natural Resources of China.

Selection of influencing factors

Combined with the specific situation of Healthy City construction in China, 10 driving factors were selected from five dimensions, medical and health progress, resource and environment endowment, public service support, economic development level, and scientific and technological innovation capacity to explore the degree of impact of different factors and mechanism on Healthy Cities.

Results

Overall differentiation pattern of Healthy City construction

The Jenks natural breaks method was used to classify the construction levels of a healthy city in 341 prefecture-level cities in

Table 2
Evaluation index system of Healthy City construction.

Target layer	Index layer	Unit	Weight
Medical level	Life expectancy	Years of age	0.0485
	Natural population growth rate	%	0.0372
	Ten thousand people have the number of doctors	Person/ten thousand person	0.0481
	Coverage rate of basic medical insurance for urban and rural residents	%	0.0562
	The proportion of healthcare expenditure in general public finance expenditure	%	0.0419
Economic foundation	Proportion of output of secondary and tertiary industries in GDP	%	0.0563
	Average salary of employees in employment	yuan	0.0366
	Percentage of employees in the tertiary industry	%	0.0164
	Per capita general budgetary income of local finance	yuan	0.0412
	Reduction rate of energy consumption per unit GDP	%	0.0443
Cultural development	Number of university students per 10,000 people	Person/ten thousand person	0.0429
	10,000 people have the number of books in public libraries	Volume/ten thousand person	0.0408
	Patent ownership per 10,000 people	Piece/ten thousand person	0.0360
	R&D spending as a percentage of GDP	%	0.0319
	Number of national intangible cultural heritage protection catalogs	Piece	0.0357
Social services	Urbanization rate	%	0.0400
	Unemployment insurance participation rate	%	0.0254
	Internet penetration rate	%	0.0444
	Number of buses per 10,000 people	Unit/ten thousand person	0.0434
	Per capita sports field area	Square meters per person	0.0347
Ecological environment	Days of air quality (API) at or above level	Number of days	0.0251
	Centralized treatment rate of urban domestic sewage	%	0.0351
	Green coverage rate of built-up area	%	0.0508
	Harmless disposal rate of domestic garbage	%	0.0461
	Comprehensive utilization rate of industrial solid waste	%	0.0408

GDP, gross domestic product.

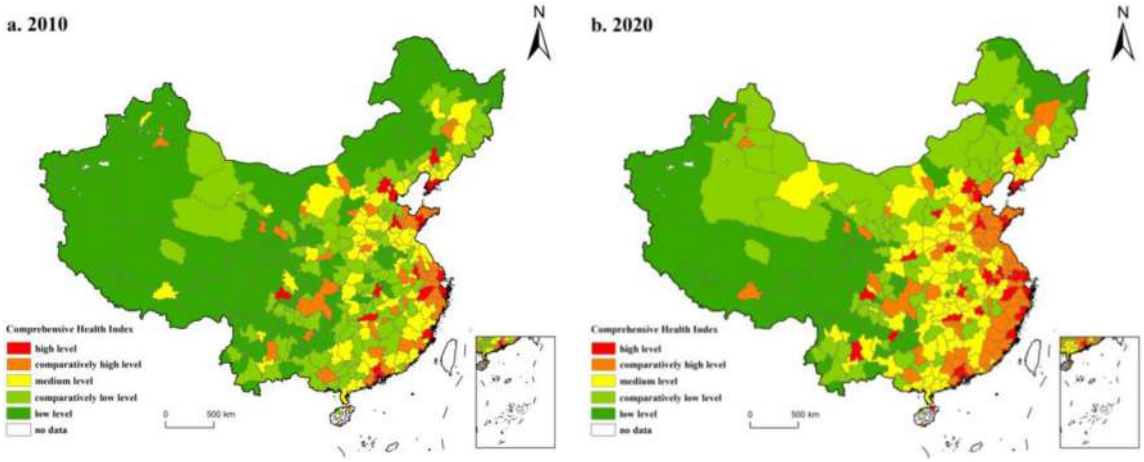

Fig. 3. Comprehensive assessment results of Healthy City construction in 2010 and 2020.

China in 2010 and 2020 into five levels: low level, comparatively low level, medium level, comparatively high level, and high level (Fig. 3), and the construction of Healthy Cities in China showed noticeable regional differences in both years, with a long-term structural layout of 'coastal high and inland low levels, eastern high and western low levels'.

From these two periods, the average comprehensive health index of Chinese cities increased from 0.367 in 2010 to 0.438 in 2020. The number of cities at a high level in 2010 was 12, and it reached 33 by 2020, mainly in developed cities in the eastern region of China, such as Beijing and Shanghai, as well as individual provincial capitals in the inland region, showing a sporadic distribution pattern, also in the Yangtze River Delta region, there is already an evident agglomeration feature, and the spatial agglomeration increased by 2020. In 2010, there were 41 comparatively high-level cities, and by 2020, there were 92, mainly in the Yangtze River Delta city cluster, Shandong Peninsula city cluster, and the Pearl River Delta city cluster, showing a cluster-like agglomeration distribution around the higher level cities and a trend of extending to the inland areas, with the number of comparatively high-level cities in the central and northeastern regions increasing significantly. In 2010, there were 74 medium-level cities, and by 2020, there were 139, mainly in the central cities of China, showing concentrated and contiguous growth. By 2020, most medium-level cities were concentrated in northern, central, and southern China, as well as in the western regions of Xinjiang and Gansu Province, with more significant clustering characteristics. Notably, 119 cities at comparatively low level in 2010 shrank to 58 by 2020, with concentrated distribution in the western and northeastern border areas of China, especially in the southwest, northwest, and northeast regions where a large number of cities will be upgraded from low level to comparatively low level, with greater changes in spatial distribution patterns. Ninety-five cities at low level in 2010 shrank to 19 by 2020, mainly in the Qinghai-Tibet Plateau region and the western part of the Yunnan-Guizhou Plateau, and the distribution range was greatly reduced.

Spatial distribution correlation analysis

As presented in Table 3, Moran's I index was greater than 0 in 2010 and 2020, with Z-statistic values greater than 2.58 and p-statistics values of 0. This indicates that Healthy City construction of the 341 prefecture-level city units in China is not homogeneous in its spatial distribution and that there is a significant spatial correlation. The spatial agglomeration of Healthy City construction between prefecture-level administrative units has increased significantly, and the differences in the spatial distribution of Healthy City construction between regions have gradually increased.

Table 3
Estimation of Global Moran's I for Healthy City construction in 2010 and 2020.

Year	Moran's I	Z (I)	*P*-values
2010	0.278	19.27	0
2020	0.295	21.12	0

The Getis' G index was calculated for Healthy City construction in 2010 and 2020 after classifying them into five types: hot spots, sub-hot spots, transitions, sub-cold spots, and cold spots areas (Fig. 4). From 2010 to 2020, the geospatial distribution of each district type was relatively stable, and cold and hot spot cities showed dynamic changes within a specific range. In 2010, there were 27 cities in the hot spot area, with a relatively scattered spatial distribution, mainly in the Beijing-Tianjin-Hebei region, Shandong Peninsula region, Yangtze River Delta region, and the Pearl River Delta region, forming local hot spot areas in cities, such as Beijing, Tianjin, Yantai, Weifang, Shanghai, Hangzhou, Guangzhou, and Shenzhen. By 2020, the number of cities in hot spot areas reached 40 in the Shandong Peninsula city cluster and the Yangtze River Delta. The hot spot areas in the urban agglomerations have a tendency to spread to the periphery, expanding the radiation range and showing cluster characteristics. The sub-hot spot areas mainly show a tendency to spread from the hot spot areas at the core, showing a certain hierarchy, and expanded significantly by 2020, especially the Shandong Peninsula urban agglomeration, the West Coast urban agglomeration, the Pearl River Delta urban agglomeration, and the Beijing-Tianjin-Hebei urban agglomeration. The cold spots are mainly located in the Tibet Autonomous Region, Qinghai Province, Xinjiang Uygur Autonomous Region, and the northern part of Heilongjiang Province in the western interior of China. In addition, because of the national policy of revitalizing the old industrial bases in the northeast, the extent of the cold spot areas in the northeast has also been further reduced. From 2010 to 2020, the transition areas and sub-cold spot areas are the most widely distributed in the country, indicating that the overall level of Healthy City construction in China is not high and still needs to be

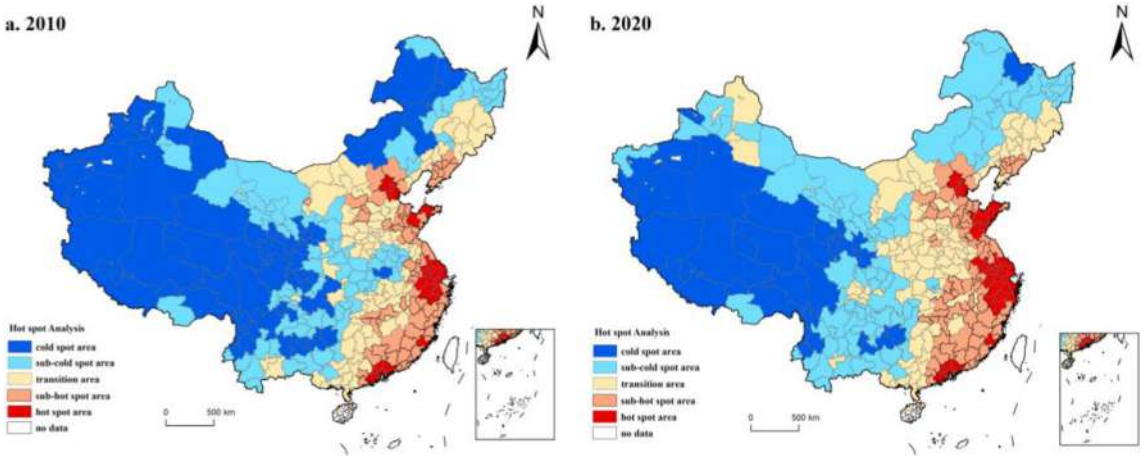

Fig. 4. Hot spot analysis of Healthy City construction in 2010 and 2020.

further developed. Further strengthening of construction efforts is therefore needed.

Analysis of influencing factors of spatial–temporal pattern of Healthy City construction

The magnitude of the influence of each factor on the level of Healthy City construction in China was using GeoDecter (Table 4). The results show that all 10 driving factors from 2010 to 2020 were significant at the 0.01 level, with q-values ranging from 0.174 to 0.578, indicating that all indicators help to explain the characteristics of the current spatial–temporal pattern of Healthy City construction (Fig. 5).

Discussion

Previous studies on Healthy City construction have focused mainly on different perspectives such as sociology, sports, and national policies. In addition, much research has been conducted on the evaluation of Healthy Cities from the perspectives of society, population, and environment, thereby providing suitable reference and guidance. However, the research lacks a targeted evaluation of any specific city, and there is little research on the improvement measures and implementation suggestions for the construction of Healthy Cities. In the present research, we calculated the Healthy City construction level and analyzed the spatial and temporal distribution patterns and factors influencing of Healthy City construction. The spatial heterogeneity of Healthy City construction in China is evident. With per capita disposable income and a per capita GDP q-value greater than 0.395, strengthening the economy will lead to the flourishing of modern technologies in many enterprises, forming a sustainable development model and a healthy economic structure. Therefore, 'health promotion and health first' should be integrated into economic construction to promote a sustainable development model and a healthy economic structure. A balance between the environmental and human systems is the premise of Healthy City construction. The results show a steady increase in the influence of the combined air quality index and forest cover, especially the q-value of the combined air quality index is more significant among the driving factors reaching 0.578, indicating the increasing maintenance and response to the ecological environment in the construction of a healthy city. We should insist on following the concept of green development, strictly protecting the ecological environment, and striving to improve the greening of national space to lay a firm foundation for the survival and health of human beings. The influence of the healthcare progress factor rose significantly from 2010 to 2020, and the influence of the indicator of the number of tertiary hospitals on the level of Healthy City construction in 2020 reached a q-value of 0.466, emphasizing the key role of health care in the construction of Healthy City. Taking the COVID-19 as an example, as the diversity of medical services increases, the public's awareness of health will be enhanced in several ways, good living habits will be developed, and life expectancy per capita will increase. How to coordinate the better use of existing medical resources so that people can enjoy life while giving full play to their potential is a question worthy of in-depth

Table 4
Detection results of influencing factors of Healthy City construction.

Target layer	Index layer	*q-value* (2010)	*q*-value (2020)
Medical and health progress	X_1 Number of tertiary and above hospitals	0.444	0.466
	X_2 Index of aging	0.326	0.348
Resource and environment endowment	X_3 Forest coverage rate	0.507	0.516
	X_4 Comprehensive index of air quality	0.551	0.578
Public service support	X_5 Ratio of per capita disposable income between urban and rural	0.174	0.207
	X_6 Proportion of expenditure on basic public services in general public budget expenditure	0.195	0.231
Economic development level	X_7 Per capita disposable income	0.395	0.457
	X_8 Per capital GDP	0.406	0.431
Scientific and technological innovation capacity	X_9 Proportion of expenditure on science education in total fiscal expenditure	0.252	0.315
	X_{10} Contribution of scientific and technological progress	0.237	0.260

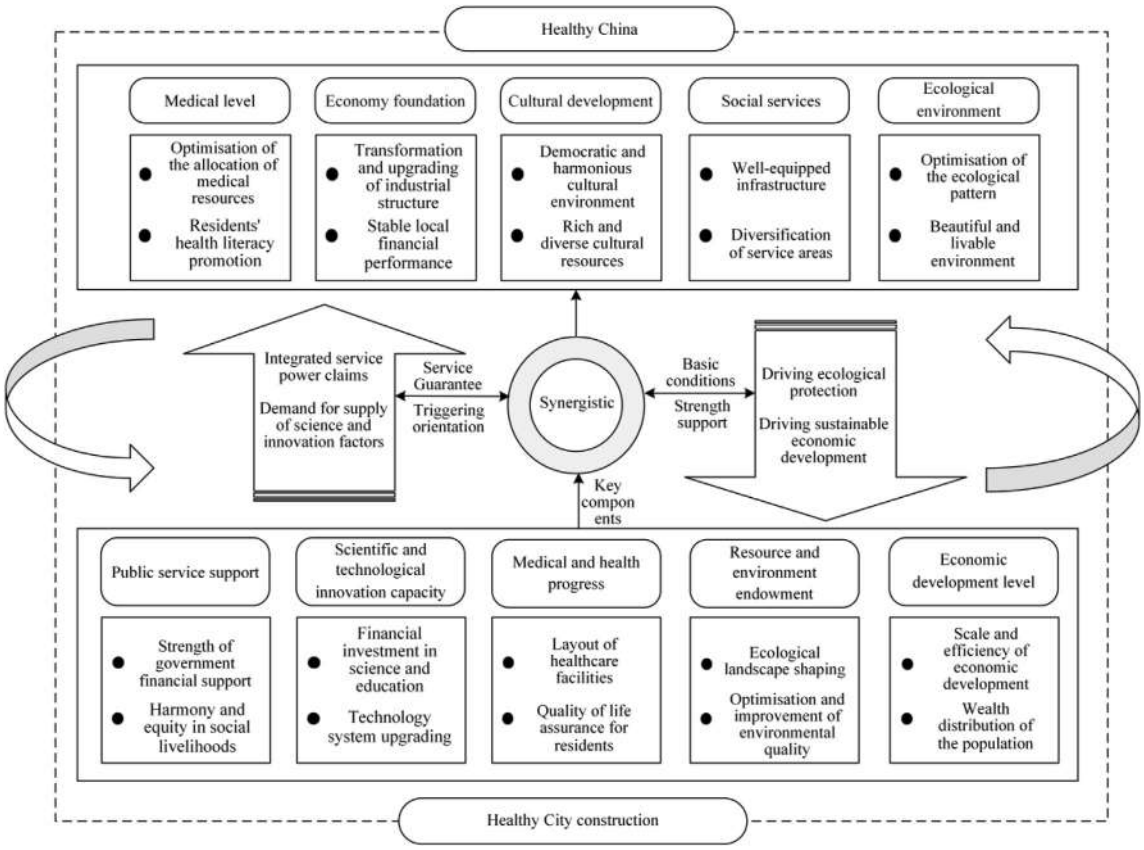

Fig. 5. Driving mechanism of Healthy City construction.

consideration. From 2010 to 2020, the q-value of "scientific and technological innovation capacity" is smaller compared to other influencing factors, indicating that the role of "scientific and technological innovation capacity" in promoting the construction of a healthy city is weak but increasing. Building Healthy City and realizing the national strategy of building a 'Healthy China' must be supported by technology. It is important to promote the integration of cultural and technological innovation with the health industry and the modernization of health governance. The supporting capacity of public services plays an important role in guaranteeing the construction of a healthy city, and with the implementation of the new urbanization strategy, the state has gradually developed policy and increased financial support for urban and rural development and increased expenditure on health care, education, sports, and social security. This shows that public services provide important support for Healthy City, and it is necessary to strengthen the status and management role of the government in the construction of a healthy city. We must explore innovation and strive to provide quality and efficient health services.

Administrative divisions and the hierarchy of cities exacerbate the unevenness of urban health development. To promote Healthy City construction, it is necessary to adhere to local conditions. Each region and city should be selected based on their levels of economic and social development and work foundations. They should explore distinctive experience models and gradually develop effective patterns of integrated development.

Healthy City construction in China adheres to government leadership. The global COVID-19 pandemic suggests that the construction of Healthy City should involve all aspects of production and life and that there is an urgent need to consider how to deepen the development of Healthy City and the specific implementation paths to promote them. It is necessary to continue to deepen the coordinated development of various complex systems such as 'population-society-economy-space-ecology'. Socio-economic development and practical experience should be promoted to increase the number of Healthy City, taking into account the characteristics of the time and region.

Conclusion

The construction rate of Healthy City in China is on increasing, and the spatial distribution pattern shows a clear positive global spatial correlation and a gradual increase in spatial agglomeration. The local spatial autocorrelation results show that the cold and hot spot areas of Healthy City construction in China from 2010 to 2020 showed dynamic changes within a certain range, and the spatial distribution was relatively stable. Healthy City construction is a complex system formed by the combined effects of several factors. The level of economic development, resource and environmental endowment, medical and healthcare progress, scientific and technological innovation capacity, and public service support are the driving factors affecting the spatial pattern of the construction of Healthy City. Health care, economic development levels, environmental resources, the support of public services, and the orientation of scientific and technological capabilities play a role in advancing Healthy City construction. This research put forward the concept model of 'nature—human body—Healthy City' and accordingly constructs an evaluation index system for the construction of a Healthy City that integrates five dimensions of

'medical level, economic foundation, cultural development, social services, and ecological environment', which provides a theoretical reference and guidance for other countries or regions to assess the construction of Healthy Cities and countries.

Author statements

Ethical approval

This research was ethically approved by Ludong University.

Funding

This research was supported by the grant from the National Social Science Foundation of China (Grant Number:19CGL070) and Shandong Higher Education 'Youth Innovation Science and Technology Support Program'(Grant Number:2021RW042) and Yantai School-Land Integration Development Project (Grant Number: 2021XDRHXMQT31).

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

M.Z. contributed to conceptualization, data curation, formal analysis, visualization, and writing the original article. W.Q. contributed to data curation, review and editing the article, formal analysis, visualization, resources, supervision, methodology, and funding acquisition. S.Z. contributed to conceptualization, data curation, and visualization. F.Q. contributed to data curation and writing, reviewing, and editing the article. X.L. contributed to visualization and review and editing the article. X.L. contributed to data curation and review and editing the article.

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Public Health 220 (2023) 80–87

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Childhood social adversity and clustering of health risk behaviours during early adolescence in a population-based birth cohort

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ARTICLE INFO

Article history:
Received 25 October 2022
Received in revised form
29 March 2023
Accepted 3 May 2023

Keywords:
Adverse childhood experiences
Socio-economic circumstances
Latent class analysis
Prospective study

ABSTRACT

Objectives: This study aimed to prospectively explore the association between early lifetime exposure to psychosocial adversity and engagement in health risk behaviours (HRBs) during early adolescence.
Study design: This was a prospective study.
Methods: This study used data from the baseline (2005–2006), third (2016–2017) and fourth waves (2018–2020) of the Generation XXI birth cohort. Socio-economic circumstances (SECs) at baseline, adverse childhood experiences (ACEs; e.g. abuse, neglect, household dysfunction) at age 10 years and HRBs (i.e. alcohol consumption, smoking, physical exercise level, sedentary behaviours, sleep duration and eating behaviours) at age 13 years were measured. Patterns of HRBs were obtained using latent class analysis. Latent class regression analysis was used to estimate the likelihood of being engaged in HRBs according to the extent of exposure to ACEs (i.e. 0 ACEs, 1–3 ACEs, 4–5 ACEs and ≥6 ACEs) and negative family SECs.
Results: Adolescents whose mothers had a low level of education (adjusted odds ratio [aOR] = 2.72 [95% confidence interval {CI}, 2.33–3.18]), low occupational status (aOR = 3.21 [95% CI, 2.68–3.85]) and low income (aOR = 2.70 [95% CI, 2.23–3.28]) were more likely to be engaged in HRBs than their peers with higher SECs. Adolescents who experienced more ACEs were at a significantly increased risk of involvement in HRBs (aOR = 1.86 [95% CI, 1.33–2.63] for 4–5 ACEs vs aOR 2.41 [95% CI, 1.72–3.43] for ≥6 ACEs). No significant gender differences were observed.
Conclusions: Adolescents from families with low SECs were more likely than their more affluent counterparts to be engaged in HRBs. Furthermore, more ACEs contributed to widening health inequalities.

Introduction

Health risk behaviours (HRBs; e.g. smoking, alcohol and drug use, poor eating habits, physical inactivity, early sexual activity, violent or suicidal behaviours) are mainly established during adolescence and extend into adulthood.[1] These behaviours do not occur in isolation but cluster in somewhat predictable ways.[2–4] Involvement in one type of HRB increases the likelihood of becoming involved in other risky behaviours. HRBs are socially patterned among adults and partially explain the high morbidity and mortality among the most disadvantaged population groups.[5,6]

Emerging evidence suggests that the possible mechanisms linking social adversity to long-term consequences for health lie in the following three interrelated pathways: (1) directly via alterations in the balance and responsiveness of neurobiological stress–response systems and brain structure; (2) indirectly via socio-economic or psychosocial factors; and (3) via the adoption of HRBs.[7–9] HRBs, such as smoking, drinking, and consuming high-sugar and saturated fats foods, provide short-term ameliorative effects and may help the individual to cope with adversity-induced stress.[10] The social gradient in health in early childhood and adulthood is a well-established finding.[11,12] However, adolescents are generally regarded as a 'healthy' population group, making it challenging to detect socio-economic differences in health. Current evidence on the relationship between socio-economic circumstances (SECs) and HRBs among adolescents is not always consistent. West et al.[13,14] suggested that the transition from childhood to youth involves a certain level of equalisation, whereby the defining

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https://doi.org/10.1016/j.puhe.2023.05.001

features of adolescence (i.e. school, peers, youth culture) cut across traditional class boundaries, resulting in a homogenising effect (from health inequality to relative equality). However, some studies[15,16] hypothesised that even if there is no consistent social gradient in adolescents' health, socio-economic differences in involvement in HRBs during this period of life (termed latent differences) may be seen as potential predictors of socio-economic health differences in adulthood.

Psychosocial stress is likely to affect individuals differently depending on their position in the social structure across their life course.[17] In addition to the contribution of negative SECs, adverse childhood experiences (ACEs) have also been linked to an increased likelihood of engaging in HRBs.[18–20]

The contribution of psychosocial adversity, including SECs in which adolescents grow up and the additional role of other stressful life events, on HRBs should be assessed in individuals from birth to adolescence. The data generated from such studies can guide policies to prevent HRBs and programmes aimed at improving health across the lifespan. Therefore, this study aimed to prospectively explore the association between early lifetime exposure to psychosocial adversity (i.e. low family SECs and early exposure to ACEs) and engagement in HRBs (i.e. alcohol consumption, cigarette smoking, physical exercise level, sedentary behaviours, sleep duration and eating behaviours) during early adolescence using data from the Generation XXI birth cohort.

Methods

Study design and participants

This study used data from the Generation XXI study, a population-based birth cohort from Porto, Portugal. The background and design of the Generation XXI study have been previously described in detail.[21] Briefly, of the invited mothers, 91.4% agreed to participate in the study, and their 8647 infants born from 2005 to 2006 in the public maternity wards of the Porto Metropolitan Area in Northern Portugal were enrolled in the cohort. Since then, the entire cohort has been invited to attend the first, second, third and fourth follow-up assessments when children were aged 4, 7, 10 and 13 years (86.3%, 79.6%, 73.9% and 54.0% participation rate, respectively). The 13-year follow-up assessment was initiated in August 2018 and planned to end in late 2020; however, it was suspended due to COVID-19 pandemic in March 2020, which resulted in unusually low participation in this wave (n = 4640; participation rate, 54.0%). The current analysis was limited to 4452 adolescents at the fourth follow-up assessment (at age 13 years; 2161 girls and 2291 boys) who had complete information for all the variables that were considered in the class definition (i.e. alcohol consumption, cigarette smoking, physical activity level, sedentary behaviours, sleep duration and eating behaviours). Comparisons of selected baseline characteristics between non-participants (n = 4195) and participants (n = 4452) revealed that the study participants were frequently born to families with more advantageous SECs (see Table S1 in the supplementary material).

Measures

Early socio-economic circumstances

Information on sociodemographic characteristics was collected from mothers in face-to-face interviews conducted by trained interviewers at baseline using structured questionnaires.

Maternal education, which was measured as the number of educational years completed in formal schooling, was classified according to the International Standard Classification of Education 2011 classes as low (≤9 years of education), intermediate (10–12 years of education) and high (>12 years of education).[22] Maternal occupation was classified by major professional groups according to the National Classification of Occupations as low (blue collar), intermediate (lower white collar) and high (upper white collar).[23] Maternal employment was classified as employed or unemployed based on respondents' self-reported employment status before the childbirth. Monthly disposable household income, defined as salaries and other sources of income, was classified as low (≤1000€ per month), intermediate (1001€–2000€ per month) and high (>2000€ per month).[24]

Adverse childhood experiences

At the follow-up evaluation for children aged 10 years, trained interviewers assessed lifetime exposure to a range of ACEs (e.g. exposure to abuse, neglect and household dysfunction) using 15 questions adapted from the Adverse Childhood Experiences Study.[25] The questionnaire was self-reported, with adolescents replying in a private setting but had access to a trained interviewer if they needed any assistance. Cumulative exposure to childhood adversity was calculated by summing the occurrences among the adversities assessed, each classified as binary (0/1). Subsequently, total childhood adversity was categorised into 0 ACEs, 1–3 ACEs, 4–5 ACEs and ≥6 ACEs, as previously described.[26]

Health risk behaviours

The low- and high-risk health behaviours variable was computed using latent class analysis (LCA). This variable was defined using indicators such as alcohol consumption, cigarette smoking, sedentary behaviours, physical exercise level, sleep duration and eating behaviours collected at the follow-up evaluation for participants at age 13 years.

Adolescents were classified regarding their alcohol consumption ('Do you drink or have you ever tried alcoholic beverages [e.g., wine, beer, liqueurs]?') and cigarette smoking ('Do you smoke or have you ever smoked?') as never users (if they had never tried alcoholic beverages or if they had never initiated smoking) and experimenters (if they had ever tried alcoholic drinks or had ever smoked cigarettes in their lifetime).

Sedentary behaviours were defined as the total time spent on recreational screen time (i.e. television watching, use of computer and mobile devices, video gaming and reading, studying or doing homework [not including school hours]), including both weekdays and weekends. Sedentary behaviours were recoded as ≤240 min/d, 241–330 min/d and ≥331 min/d.[27] Physical activity was assessed by asking adolescents whether they practiced any type of regular physical or sports activity outside of school. If the answer was affirmative, the adolescents were asked to report the frequency of practicing sports per week. Physical exercise was coded as none, <3 times per week and ≥3 times per week based on the recommendations of the World Health Organisation (WHO) for physical activity and sedentary behaviour for children and adolescents.[28]

Adolescents were also asked to report usual weekday bedtimes ('During weekdays, at what time do you go to bed?') and wake-up times ('During weekdays, at what time do you get up?'). Sleep duration was estimated by the difference between self-reported bedtimes and wake-up times and was recoded based on the American Academy of Sleep Medicine guideline recommendations as <8 h, 8–10 h (recommended) and >10 h.[29]

Adolescents' eating behaviours were evaluated through a Food Frequency Questionnaire, previously tested in a subsample of the Generation XXI cohort.[30] A healthy eating index, based on the WHO dietary recommendations, previously developed to evaluate the diet quality of Generation XXI participants, was adapted to this study.[31–33]

Covariates. Information on adolescents' sex (girls/boys), age (in months), body mass index (BMI), depressive symptoms, and history of injuries in the last 12 months and any pain in the last 3 months were included in the analysis. Adolescents' ages were categorised as ≤158 months, 159–160 months and >160 months. According to standard procedures, a team of trained examiners performed objective measurements of adolescents' heights and weights. Age- and sex-specific BMI standard *z* scores (zBMI) were calculated and classified based on WHO recommendations as underweight/normal weight, overweight and obesity.[34] Depressive symptoms were reported by adolescents at 13 years of age and measured using the Portuguese validated version of Beck Inventory-II, which measures the severity of depressive symptoms among adults and adolescents aged ≥13 years. A score cutoff value of 13 (ranging from 0 to 51) was used to define the presence of relevant depressive symptoms.[35] Adolescents were also asked about whether they had been injured and had to be treated by a physician or nurse in the last 12 months (classified as 'yes' or 'no') and whether they had any pain in the last 3 months (classified as 'yes' or 'no').

Statistical analyses

To derive a classification scheme of HRBs among adolescents, LCA was used. LCA is a person-centred statistical model that assumes that within a population, there are homogeneous mutually exclusive groups of individuals who have similar response patterns to a given set of indicators.[36,37] In this study, this set of indicators included alcohol consumption, cigarette smoking, physical exercise level, sedentary behaviours, sleep duration and eating behaviours.

A series of LCA models were explored, specifying between two and four classes, to determine the number of classes that best represented the patterns of HRBs in this study population. Of these four competing models, the two-class solution was considered the best fitting model based on the Akaike Information Criterion and Bayesian Information Criterion,[38] where lower values indicate better model fit (see Table S2 in the supplementary material). Participants were placed in their respective latent classes based on their posterior probabilities of belonging to a particular latent class. For each class, the proportion of HRBs and other covariates was computed, and differences across classes were tested using Chi-squared tests.[39] Odds ratios (ORs) and their respective 95% confidence intervals (CIs) were computed using logistic regression models to evaluate the association between (1) early SECs and engagement in HRBs and (2) ACEs and involvement in HRBs. Both models were adjusted for adolescents' sex and age (in months). A significant level of alpha=0.05, as well as independence between observations, was assumed. All statistical analyses were performed using R (version 4.2.3).[40] The poLCA software package for R (version 1.4.1) was used to estimate latent class regression models for polytomous outcome variables.[41]

Results

Study population characteristics

In the study population of 4452 adolescents (48.5% girls), the most prevalent HRBs were alcohol consumption (49.8%), followed by not participating in exercise or sports activities (41.3%) and having a predominantly sedentary lifestyle (37.4%). In total, 27.7% of participants reported consuming an unhealthy diet, approximately 13.0% reported sleeping more and/or fewer hours than recommended, and only 3.3% reported experimenting with smoking. Half of the participants reported being exposed to ≥4 ACEs (Table 1). Most adolescents were born to mothers who were employed at the time of interview (76.8%), had an intermediate occupational status (45.6%), had an intermediate household income (42.5%) and had a low educational level (32.2%; Table 1).

Table 1
Descriptive statistics of generation XXI participants ($N = 4452$).

Adolescents' characteristics		*n* (%)
Sex	Girls	2161 (48.5)
	Boys	2291 (51.5)
Age	≤158 mo	15539 (35.5)
	159–160 mo	1747 (40.3)
	>160 mo	1053 (24.3)
Body mass index[a]	Underweight and normal	2974 (66.8)
	Overweight	1047 (23.5)
	Obese	430 (9.7)
	Missing data	1 (0.0)
Depressive symptoms (BDI-II)	BDI-II ≤13	3749 (84.2)
	BDI-II >13	524 (11.8)
	Missing data	179 (4.0)
Any pain in past 3 mo	No	978 (22.0)
	Yes	1614 (36.3)
	Missing data	1860 (41.8)
Injuries in past 12 mo	No	3368 (75.7)
	Yes	1081 (24.3)
	Missing data	30 (0.1)
Alcohol consumption	Never	2236 (50.2)
	Experimenter	2216 (49.8)
Cigarette smoking	Never	4303 (96.7)
	Experimenter	149 (3.3)
Sedentary behaviours	≤240 min/d	1433 (32.2)
	241–330 min/d	1355 (30.4)
	>331 min/d	1664 (37.4)
Physical exercise	None	1839 (41.3)
	<3 times/wk	1287 (28.9)
	≥3 times/wk	1326 (29.8)
Sleep duration	<8 h/d	209 (4.7)
	8–10 h/d	3876 (87.1)
	>10 h/d	367 (8.2)
Eating behaviours[b]	1st tertile	1233 (27.7)
	2nd tertile	1396 (31.4)
	3rd tertile	1823 (40.9)
Adverse childhood experiences	0	172 (3.9)
	1–3	1715 (38.5)
	4–5	1158 (26.0)
	≥6	1082 (24.3)
	Missing data	325 (7.3)
Maternal characteristics		
Maternal educational level[c]	Low	1434 (32.2)
	Intermediate	1292 (29.0)
	High	1356 (30.5)
	Missing data	370 (8.3)
Maternal occupational status[d]	Low	862 (19.4)
	Intermediate	2030 (45.6)
	High	1321 (29.7)
	Missing data	239 (5.4)
Maternal employment status[e]	Unemployed	665 (14.9)
	Employed	3417 (76.8)
	Missing data	370 (8.3)
Disposable household income[f]	Low	1286 (28.9)
	Intermediate	1892 (42.5)
	High	739 (16.6)
	Missing data	535 (12.0)

BDI-II, Beck Depression Inventory, Second Edition.
[a] Age- and sex-specific body mass index standard *z* scores were calculated and classified based on the World Health Organization recommendations as underweight/normal weight (≤1 SD), overweight (>1 SD to <2 SD) and obesity (≥2 SD).
[b] Lower tertiles reflect the worst dietary habit.
[c] Maternal education is recoded as low (≤9 years of education), intermediate (10–12 years of education) and high (>12 years of education).
[d] Maternal occupation is recoded as low (blue collar), intermediate (lower white collar) and high (upper white collar).
[e] Maternal employment is recoded as employed or unemployed.
[f] Monthly disposable household income is recoded as low (≤1000€ per month), intermediate (1001€–2000€ per month) and high (>2000€ per month).

LCA of HRBs

The low-risk HRB group (which accounted for 54.5% of the study population) had the highest probability of never drinkers (62.1%) and never smokers (99.6%). Participants in this group were more likely to report fewer sedentary behaviours (44.2%), more frequent exercise (38.8%), adhering to recommendations for sleep (90.8%) and consuming less unhealthy foods (68.6%) compared with their counterparts (Table 2). The high-risk HRB group (which accounted for 45.5% of the study population) consisted of adolescents who had the highest probability of alcohol use (64.0%), cigarette smoking (6.9%), more sedentary time (54.3%), not engaging in any physical exercise (62.2%), not adhering to sleep recommendations (17.4%) and higher consumption of unhealthy foods (56.4%). Significant differences were found in behavioural characteristics across the two classes (i.e. the low- and high-risk groups; Table 2).

The two classes differed significantly in some characteristics; adolescents in the high-risk group reported a higher proportion of obesity (10.8%), depressive symptoms (15.4%) and exposure to ≥4 ACEs (61.1%) compared with the low-risk group (Table 3).

Associations of psychosocial adversity and HRBs

To examine the association between early SECs and engagement in HRBs, logistic regression analyses were conducted, with the low-risk group specified as the reference class. The results suggested that adolescents from less advantaged SECs have a higher likelihood of being engaged in HRBs than adolescents from higher SECs. In particular, adolescents whose mothers had lower educational attainment (adjusted OR [aOR], 1.93 [95% CI, 1.65–2.26] for intermediate vs 2.72 [95% CI, 2.33–3.18] for low educational attainment), lower occupational status (aOR, 2.17 [95% CI, 1.87–2.52] for intermediate vs 3.21 [95% CI, 2.68–3.85] for low occupational status), lower monthly disposable household income (aOR, 1.82 [95% CI, 1.52–2.19] for intermediate vs 2.70 [95% CI, 2.23–3.28] for low household income) and being unemployed (aOR, 1.58 [95% CI, 1.34–1.87]) were more likely to be involved in HRBs than their peers from higher SECs (Fig. 1).

The association between exposure to ACEs and involvement in HRBs was statistically significant for adolescents who had been exposed to ≥4 ACEs (aOR, 1.86 [95% CI, 1.33–2.63] for 4–5 ACEs vs 2.41 [95% CI, 1.72–3.43] for ≥6 ACEs) even after controlling for adolescents' sex and age (Fig. 1). Adolescents who were born to mothers with a higher educational level had significantly higher odds of being involved in HRBs if they were exposed to ≥4 ACEs (aOR, 2.13 [95% CI, 1.36–3.44] for 4–5 ACEs vs 2.73 [95% CI, 1.73–4.41] for ≥6 ACEs) even after controlling for adolescents' sex and age (Table 4).

Discussion

This study identified two distinct behavioural patterns (low risk and high risk) using LCA with six HRBs (alcohol consumption, cigarette smoking, physical exercise level, sedentary behaviours, sleep duration and eating behaviours) among 13-year-old Portuguese adolescents. The high-risk class was characterised by a higher prevalence of all risk behaviours.

In this cohort, adolescents from families of low SECs were more likely than their more affluent counterparts to be engaged in HRBs. These results confirm the existence of latent differences in HRBs within the study population, indicating that involvement in HRBs is socially patterned by the age of adolescence. Existing evidence about the relationship between SECs and engagement in HRBs in adolescence is often inconsistent and contradictory. Several studies have shown that adolescents from families with low SECs are more likely to engage in HRBs, such as cigarette smoking,[42,43] alcohol consumption,[43] lack of physical exercise[15] and unhealthy diets.[44] However, other studies found no or only slight socio-economic differences for these behavioural outcomes.[15,16,43,45] Richter et al.[43] reported that HRBs that begin to develop in adolescence (e.g. cigarette smoking and alcohol use) are less strongly influenced by parental socio-economic status than behaviours that are established early in childhood (e.g. fruit and vegetable consumption and television viewing).

The present study findings also suggest that all SEC components (measured by maternal education, occupation status, employment and household income) are strongly linked to the involvement in HRBs among adolescents. Previous studies reported that different dimensions of SECs may represent different processes and implications for health. For example, Tuinstra et al.[15]

Table 2
Probability of latent class membership and item-response probabilities within each of the latent classes ($N = 4452$).

Health risk behaviours	Class 1: low risk ($n = 2427$), n (%)	Class 2: high risk (n = 2025), n (%)	P value
Alcohol consumption			<0.001
Never	1506 (62.1)	730 (36.0)	
Experimented	921 (37.9)	1295 (64.0)	
Cigarette smoking			<0.001
Never	2417 (99.6)	1886 (93.1)	
Experimented	10 (0.4)	139 (6.9)	
Sedentary behaviours			<0.001
≤240 min/d	1073 (44.2)	360 (17.8)	
241–330 min/d	789 (32.5)	566 (28.0)	
>331 min/d	565 (23.3)	1099 (54.3)	
Physical exercise level			<0.001
None	579 (23.9)	1260 (62.2)	
<3 times/wk	907 (37.4)	380 (18.8)	
≥3 times/wk	941 (38.8)	385 (19.0)	
Sleep duration			<0.001
<8 h/d	11 (0.5)	198 (9.8)	
8–10 h/d	2203 (90.8)	1673 (82.6)	
>10 h/d	213 (8.8)	154 (7.6)	
Eating behaviours[a]			<0.001
1st tertile	75 (3.1)	1143 (56.4)	
2nd tertile	688 (28.3)	712 (35.2)	
3rd tertile	1664 (68.6)	170 (8.4)	

[a] Lower tertiles reflect the worst dietary habit.

Table 3
Probability of selected covariates within each of the latent classes ($n = 4452$).

Characteristic	Class 1: low risk ($n = 2427$), *n* (%)	Class 2: high risk (n = 2025), *n* (%)	*P* value
Sex			>0.99
Girls	1178 (48.5)	983 (48.5)	
Boys	1249 (51.5)	1042 (51.5)	
Age			<0.001
≤158 mo	848 (35.7)	691 (35.2)	
159–160 mo	1010 (42.5)	737 (37.6)	
>160 mo	519 (21.8)	534 (27.2)	
BMI[a]			
Underweight and normal weight	1679 (69.2)	1295 (64.0)	0.001
Overweight	537 (22.1)	510 (25.2)	
Obese	211 (8.7)	219 (10.8)	
Depressive symptoms (BDI-II score)[b]			<0.001
≤13	2100 (90.4)	1649 (84.6)	
>13	223 (9.6)	301 (15.4)	
Any pain in past 3 mo			0.74
No	523 (38.1)	455 (37.4)	
Yes	851 (61.9)	763 (62.6)	
Injuries in past 12 mo			0.61
No	1828 (75.4)	1540 (76.1)	
Yes	597 (24.6)	484 (23.9)	
Adverse childhood experiences			<0.001
0	116 (5.1)	56 (3.0)	
1–3	1052 (46.2)	663 (35.9)	
4–5	607 (26.6)	551 (29.8)	
≥6	504 (22.1)	578 (31.3)	
Maternal education level[c]			<0.001
Low	635 (28.2)	799 (43.6)	
Intermediate	684 (30.4)	608 (33.2)	
High	930 (41.4)	426 (23.2)	
Maternal occupational status[d]			<0.001
Low	919 (39.6)	402 (21.2)	
Intermediate	1042 (44.9)	988 (52.2)	
High	360 (15.5)	502 (26.5)	
Maternal employment[e]			<0.001
Employed	302 (13.4)	363 (19.8)	
Unemployed	1948 (86.6)	1469 (80.2)	
Disposable household income[f]			<0.001
Low	1047 (48.8)	845 (47.7)	
Intermediate	511 (23.8)	228 (12.9)	
High	587 (27.4)	699 (39.4)	

BDI-II, Beck Depression Inventory, Second Edition.
[a] Age- and sex-specific body mass index standard *z* scores were calculated and classified based on the World Health Organization recommendations as underweight/normal weight (≤1 SD); overweight (>1 SD to <2 SD), and obesity (≥2 SD).
[b] Lower tertiles reflect the worst dietary habit.
[c] Maternal education is recoded as low (≤9 years of education), intermediate (10–12 years of education) and high (>12 years of education).
[d] Maternal occupation is recoded as low (blue collar), intermediate (lower white collar) and high (upper white collar).
[e] Maternal employment is recoded as employed or unemployed.
[f] Monthly disposable household income is recoded as low (≤1000€ per month), intermediate (1001€–2000€ per month) and high (>2000€ per month).

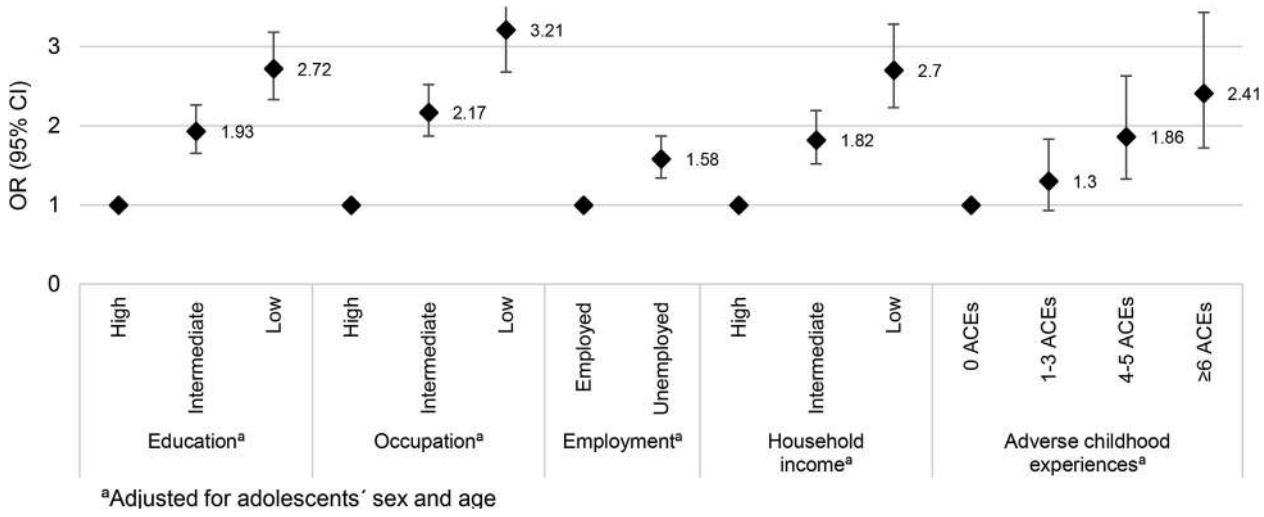

Fig. 1. Logistic regression models to test the associations between early socio-economic circumstances (at baseline), exposure to adverse childhood experiences (AECs) at 10 years of age and engagement in health risk behaviours (at 13 years of age). Odds ratios (ORs) with 95% confidence intervals (CIs) are shown ($N = 4452$).

Table 4
Logistic regression models to test the association between adverse childhood experiences (at 10 years of age) and engagement in health risk behaviours (at 13 years of age)[a].

Adverse childhood experiences	High risk, odds ratio (95% CI)			
	Low maternal education level[b]		High maternal education level[b]	
	Crude	Adjusted[c]	Crude	Adjusted[c]
0	1	1	1	1
1–3	1.05 (0.60–1.84)	1.08 (0.62–1.89)	1.54 (0.99–2.47)	1.55 (1.00–2.49)
4–5	1.54 (0.87–2.73)	1.58 (0.89–2.80)	2.13 (1.36–3.42)	2.13 (1.36–3.44)
≥6	1.93 (1.09–3.43)	1.99 (1.12–3.55)	2.69 (1.71–4.33)	2.73 (1.73–4.41)

CI, confidence interval.
[a] Odds ratios (95% CIs) adjusted for adolescents' sex, by maternal education ($N = 4452$).
[b] Maternal education is recoded as low (≤9 years) and high (10–12 years and >12 years).
[c] Adjusted for adolescents' sex and age.

showed that a linear relationship was found between SECs (measured by parental education and occupation) and sports, with adolescents from families of low SECs engaging in sports less often. Richter et al.[43] observed significant differences between lower SECs (measured by parental occupation and family affluence) and higher levels of excessive television viewing and lower levels of daily vegetable consumption among adolescents across 28 European countries. Piko and Fitzpatrick[16] reported significant associations between families of lower SECs (measured by parental occupation, education and family structure) and low levels of sports activity among adolescents; a significant and inverse association was also found between adolescent alcohol use and education level of the mother.

Consistent with the current findings, some studies[44–46] also reported a positive association between the number of ACEs adolescents had been exposed to and their engagement in HRBs. Furthermore, the results of the present study show that adolescents with exposure to ≥4 ACEs were more likely to be involved in HRBs if they were born to mothers with higher educational levels compared with those who were born to mothers with lower educational levels. Perhaps, for those adolescents who grow up in more disadvantaged circumstances (such as material deprivation), ACEs (as other adverse risk factors) do not amplify the negative effect of socio-economic deprivation as strong as for those adolescents who were born into more favourable circumstances.

The current findings also indicate that there were no significant gender differences in the patterning of HRBs. These results suggest that engagement in HRBs tends to reduce sex differences between girls and boys, which is a concerning trend considering that engagement in HRBs may become a long-term risk factor for chronic health conditions in adulthood, contributing to the leading causes of mortality and morbidity.[5,6]

Strengths and limitations

The use of data from the well-established population-based birth cohort Generation XXI is one of the main strengths of this study. The follow-up periods allowed this study to prospectively examine a potential causal relationship between the exposures (i.e. SECs and ACEs) and the outcome (i.e. HRBs) during early adolescence. Because this is a population-based study where children were chosen independently of their exposure to adversity or involvement in HRBs, the behavioural patterns and adversity variability observed in the study population are likely to represent the general population of 13-year-old adolescents. The results from this study are an essential contribution to the field of research.

This study also has some limitations. The COVID-19 pandemic and attrition of participants over time resulted in the inclusion of a more socio-economically advantaged study population. Similar socio-economic patterning of loss to follow-up has been observed in other studies.[46,47] Howe et al.[48] suggested that loss to follow-up may have no impact on estimates of inequalities when there is no direct causality between the outcome (i.e. engagement in HRBs) and participation in the study. In this situation, the current study would expect to see similar estimates of socio-economic inequalities in the full cohort and analyses, and the already observed socio-economic disparities would widen. In addition, the cumulative effect of ACEs was examined in this study, but there was no account for the severity of different types of adverse events, which could possibly be captured by other weighting schemes. However, when more than two adverse events occur, regardless of which ACEs, child health appears to deteriorate.

Conclusions

This study showed a strong graded relationship between family SECs, exposure to ACEs and engagement in HRBs during early adolescence, suggesting that involvement in HRBs is socially patterned. Interventions targeting barriers to higher education, increasing minimum wage and guaranteeing income are central to helping parents find the resources needed to adequately support healthy adolescent development and prevent health risks.

Author statements

Acknowledgements

The authors thank the families enrolled in Generation XXI for their kindness, the members of the research team for their enthusiasm and perseverance and the participating hospital staff for their help and support.

Ethical approval

The study protocol complied with the ethical principles outlined in the Declaration of Helsinki and was approved by the joint ethics committee of the São João Hospital and University Centre and the University of Porto Medical School (CES-01/2017). The study is registered with the Portuguese Authority of Data Protection (authorisation No. 5833/2011). Written informed consent was obtained from all parents or legal guardians and oral assent was obtained from children at each evaluation.

Funding

This work was supported by the European Regional Development Fund through the Operational Programme Competitiveness and Internationalization and national funding from the Foundation for Science and Technology (FCT), Portuguese Ministry of Science, Technology, and Higher Education under the projects “HIneC:

When do health inequalities start? Understanding the impact of childhood social adversity on health trajectories from birth to early adolescence" (POCI-01-0145-FEDER-029567; reference: PTDC/SAU-PUB/29567/2017). It is also supported by Unidade de Investigação em Epidemiologia-Instituto de Saúde Pública da Universidade do Porto (EPIUnit) (UIDB/04750/2020), Laboratório para a Investigação Integrativa e Translacional (ITR), Porto, Portugal (LA/P/0064/2020), PhD grant SFRH/BD/144503/2019 (to A.A.) funded by FCT through Fundo Social Europeu, and FCT Investigator contract CEECIND/01516/2017 (to S.F.).

Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.05.001.

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Public Health 220 (2023) 142–147

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Could it be monkeypox? Use of an AI-based epidemic early warning system to monitor rash and fever illness

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ARTICLE INFO

Article history:
Received 21 December 2022
Received in revised form
3 May 2023
Accepted 10 May 2023

Keywords:
Mpox
Communicable diseases
Emerging
Artificial intelligence
Public health surveillance
Orthopoxvirus

ABSTRACT

Objectives: The EPIWATCH artificial intelligence (AI) system scans open-source data using automated technology and can be used to detect early warnings of infectious disease outbreaks. In May 2022, a multicountry outbreak of Mpox in non-endemic countries was confirmed by the World Health Organization. This study aimed to identify signals of fever and rash-like illness using EPIWATCH and, if detected, determine if they represented potential Mpox outbreaks.

Study design: The EPIWATCH AI system was used to detect global signals for syndromes of rash and fever that may have represented a missed diagnosis of Mpox from 1 month prior to the initial case confirmation in the United Kingdom (7 May 2022) to 2 months following.

Methods: Articles were extracted from EPIWATCH and underwent review. A descriptive epidemiologic analysis was conducted to identify reports pertaining to each rash-like illness, locations of each outbreak and report publication dates for the entries from 2022, with 2021 as a control surveillance period.

Results: Reports of rash-like illnesses in 2022 between 1 April and 11 July (n = 656 reports) were higher than in the same period in 2021 (n = 75 reports). The data showed an increase in reports from July 2021 to July 2022, and the Mann–Kendall trend test showed a significant upward trend ($P = 0.015$). The most frequently reported illness was hand-foot-and-mouth disease, and the country with the most reports was India.

Conclusions: Vast open-source data can be parsed using AI in systems such as EPIWATCH to assist in the early detection of disease outbreaks and monitor global trends.

Introduction

Techniques such as social media mining and news media scanning using open-source data have been utilized in public health surveillance for the early detection of new or emerging infectious disease outbreaks.[1,2] This can be useful in countries with low diagnostic capacity or where censorship (for political reasons, cultural stigma or for fear of impacting tourism) may result in a lack of formal reporting.[1,2] The EPIWATCH system uses artificial intelligence (AI) to harness open-source data, such as media reports, press releases, official reports and social media, for early epidemic signals and can provide an early warning for emerging infectious disease outbreaks.[1–3] It scans vast, open-source data for diseases and clinical syndromes using two AI subsystems.[4]

On 7 May 2022, a case of Mpox was confirmed in England by the United Kingdom Health Security Agency (UKHSA) in a person with recent travel history to Nigeria.[5] On 21 May 2022, the World Health Organization confirmed a multicountry outbreak of Mpox in 12 non-endemic countries, mostly in Europe, with no established travel links to endemic areas in the African continent, suggesting local transmission.[5] As of 29 November 2022, there were more than 81,000 cases with 56 deaths globally in this outbreak, peaking in June 2022, with the majority of cases reported from Europe and the United States (USA).[6] As of 29 November 2022, Mpox had spread to 110 countries, of which 103 had not previously reported Mpox.[6]

Human Mpox was first detected in 1970 in the Democratic Republic of the Congo (DRC), and there have been subsequent epidemics in Central and West Africa, with a significant resurgence of

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https://doi.org/10.1016/j.puhe.2023.05.010
0033-3506/

cases in Nigeria and the DRC since 2017.[7] The increasing number of infections in previously endemic and non-endemic countries has in part been attributed to the growing number of people without orthopoxvirus immunity due to both the accumulation of unvaccinated people since the smallpox vaccination ceased following eradication in 1980 and waning of immunity from smallpox vaccines, which protect against Mpox.[8,9]

In the 2022 outbreak, the epidemiological situation was further complicated by the atypical presentation of Mpox symptoms compared with previous outbreaks.[10] The main feature of Mpox is a vesicular-pustular rash characterized by multiple lesions on the face, hands and feet.[9] In a study of more than 500 cases in the current epidemic, while a rash was reported in 97% of cases, 64% of cases had less than 10 lesions, with 10% having only a single lesion.[10] The most common sites of the rash were the anogenital region, followed by the trunk, extremities and face.[9,10] Other presenting features of Mpox include a prodrome of fever, lethargy, headache and lymphadenopathy, which can differentiate Mpox from chickenpox.[9,10] These clinical features are shared with more common viruses such as varicella, measles, herpes simplex, secondary syphilis and hand-foot-and-mouth disease.[11]

Many physicians in non-endemic countries have minimal or no experience with Mpox and may misdiagnose it as another rash and fever illness. In a 2022 study of Italian medical professionals, it was shown that there were significant knowledge gaps on all aspects of Mpox infections, including systemic complications, rash distribution and use of vaccination as a preventative measure.[12] Another study of university medical students reported that of 11 Mpox knowledge items, only three were correctly identified by more than 70% of respondents and only 26.2% knew that vaccination against Mpox was available.[13] Clinical diagnostic errors may also cause misdiagnosis of Mpox cases for other rash-like diseases such as varicella. In Central Africa, Mpox was misdiagnosed as varicella in up to 50% of the confirmed cases.[14] Reasons identified for the misdiagnoses include clinician difficulty differentiating between Mpox and other rash-like illnesses, poor laboratory testing capacities especially in low-resource settings, low rates of health seeking behaviour, and test refusal due to social stigma in certain communities.[15–17]

International case definitions have primarily focused on people who identify as gay, bisexual or men who have sex with men (MSM), collectively GBMSM, or has had one or more sexual partners in the preceding 21 days.[18] Mpox infection can occur in anyone following close physical contact with a person with Mpox, or even clothing and bedding items that have been in contact with lesions.[9,18] In the 2022 epidemic, there were documented cases in women and children, with at least 83 cases in children recorded in the USA as of 24 September 2022, including 28 children aged 0–12 years.[18–20] Restrictive case definitions may lead to restricted testing and, therefore, under-ascertainment of the extent of the early stages of the 2022 epidemic.[18,21]

Due to the possibility that Mpox may be misdiagnosed as other illnesses with rash and fever and that countries with weak surveillance systems may not have complete ascertainment of Mpox, in this study we aimed to monitor trends in rash-like illnesses using EPIWATCH during the time period prior to, and coinciding with, the MPX outbreak.

Methods

This study involves three parts 1) search of the EPIWATCH early warning system, 2) data extraction and screening and 3) descriptive analysis and time series analysis of the rash-like illnesses reported prior to and during the 2022 Mpox epidemic, which began on 7 May 2022.

The EPIWATCH system

EPIWATCH is a curated open-source, AI-based outbreak observatory that searches vast quantities of media reports, press releases, official reports and social media for early detection of outbreaks of infectious diseases.[4] The collected data undergoes human review, with a trained analyst screening the article for outbreak information including disease, syndrome or symptoms of human or zoonotic disease, case numbers, location and date.[1,2] If outbreak information is validated, a 'report' is entered onto the EPIWATCH database.[1,2] This removes irrelevant articles. EPIWATCH can be used to detect early reports of potential outbreaks through publicly available sources in settings with inadequate or absent disease surveillance.[1–3] The system has been used to collect outbreak data since 2016 and has been further enhanced by AI and machine learning.[1,2,4] Searches can be tailored for specific languages or regions as well as for specific infectious disease syndromes. The EPIWATCH observatory was developed at University of New South Wales Sydney (UNSW) and is managed by staff at the Biosecurity Program, The Kirby Institute, UNSW.[4]

Search strategy

In consultation with the EPIWATCH team, we considered potential candidates for misdiagnosis of Mpox, namely diseases and syndromes with clinical features of rash-like illness, and used the EPIWATCH system to identify possible trends in the month leading to the first case identified in the United Kingdom and during the ongoing outbreak. Symptom-related terms such as 'acute fever and rash', 'fever of unknown origin' and a list of differential diagnosis for Mpox inclusive of 'hand, food and mouth disease (HFMD)', 'varicella', 'herpes simplex', 'measles', 'syphilis', and 'tomato flu/fever' were searched. 'Tomato Flu/Fever', a term used in India for a rash and fever illness, was also included in this analysis due to lack of case definition at the time and the characteristics of mucocutaneous blisters.[22] Table S1 presents the list of the illnesses and their characteristics in the supplementary material. The searches were conducted for the period of 1 April 2022 to 11 July 2022, to capture the period 1 month prior to and 2 months following the first identified case in the United Kingdom of this outbreak.

Data were collected for comparison to the same period in the previous year (1 April 2021 to 11 July 2021) as a comparator. Monthly total reports for rash-like illnesses from the EPIWATCH system were collected for the 43 months from January 2019 to July 2022 for a time-series analysis.

Data extraction and screening process

All articles in non-English languages are autotranslated to English in the EPIWATCH system. These were extracted into a Microsoft Excel spreadsheet and reviewed. There were a total of 2187 reports in the initial search for the 2019–2022 surveillance period. From title screening for relevance, 57 duplicate entries were removed. Articles related to diseases not in the search list were also removed (n = 73).

Data analysis

A descriptive epidemiologic analysis was conducted using Microsoft Excel to identify the number of reports pertaining to each rash-like illness, the locations of each outbreak and time of publication of the reports for the entries from the 2021 (n = 75) and 2022 (n = 656) surveillance periods. The locations were ranked according to the number of associated reports in 2022, and the top eight were selected for further analysis. If the information was

available, additional information such as Mpox case numbers, diagnostic capabilities and smallpox vaccination coverage was also included and is presented in Table S2 in the supplementary material.

The percentage increase in the number of reports across the years 2021 and 2022 was compared. A time-series analysis using the Mann–Kendall test using XLSTAT software[23] was used to detect the changes in trend from reports of rash-like illnesses from January 2019 to July 2022. IBM SPSS Statistics, Version 22, was used,[24] and to identify if the change was significant, a *P*-value of 0.05 was applied.

Results

There were 656 reports of rash and fever illness made between the dates 1 April 2022 and 11 July 2022, which were included in the analysis. Results from the surveillance period are shown in Fig. 1a, with Fig. 1b comparing the total number of reports with the previous year (2021) over the same time period for comparison (n = 75).

For each search term, the number of reports were as follows: HFMD (n = 191), varicella (n = 84), herpes simplex (n = 0), measles (n = 175), syphilis (n = 56), acute rash and fever (n = 8), fever of unknown origin (n = 47) and tomato flu/fever (n = 96).

The number of reports per country for the 2022 surveillance period and per search term for the 2021 and 2022 surveillance period are included in Tables S3–5 in the supplementary material. The geographical distribution of reports made during the surveillance period is demonstrated in Fig. 2. Table 1 summarises information related to the Mpox outbreak status of the top eight countries ranked by report.

Reports were analysed from the EPIWATCH system from January 2019 to July 2022. Fig. 3 presents the variation in reports per month for rash-like illnesses over this time period. The data showed an increase in reports from July 2021 to July 2022, and the Mann–Kendall trend test showed a significant upward trend ($P = 0.015$).

Discussion

The number of reports about rash-like illnesses in 2022 between 1 April and 11 July (n = 656 reports) was much higher (775% increase) than the same time period in 2021 (n = 75 reports). The observed peak in reports of rash-like illnesses in 2022 occurred between 6 May and 13 May 2022 coinciding with the early reports of cases of Mpox in the United Kingdom in the current outbreak. HFMD was the most frequently reported diagnosis, of which there were multiple ongoing outbreaks in Malaysia at the time, with 32 times more cases reported compared to the same period the previous year.[25] India had the most reports, ranging from 'tomato flu/fever', a colloquial term for the rash associated with dengue, HFMD or other illnesses with fever and rash,[22] a varicella outbreak, and

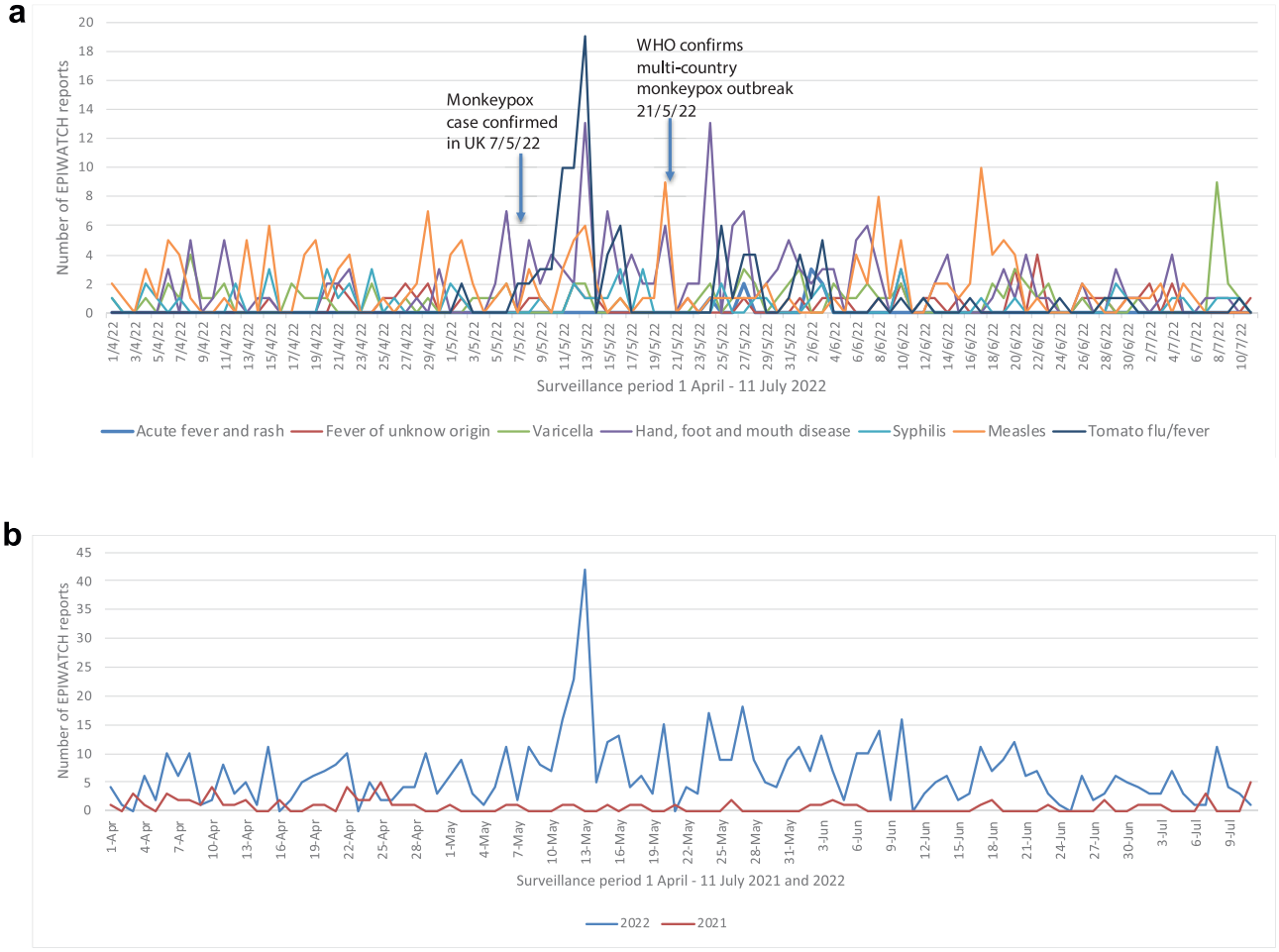

Fig. 1. a. Global reports of a rash-like illness over the 2022 surveillance time period (1 April to 11 July 2022). b. Comparison of global reports of a rash-like illnesses over the surveillance time period (1 April to 11 July 2022 and 2021).

Fig. 2. Geographical distribution of reports during the surveillance period (1 April to 11 July 2022). Note – circles denote regional clusters, blue pins are single locations/cases. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article).

Table 1
Top eight countries (by number of EPIWATCH reports collected during surveillance period) and confirmed Mpox cases as of 30 November 2022.

Country	EPIWATCH reports 1/4–11/7/22	MPX confirmed cases 30/11
India	181	17
Malaysia	135	0
USA	31	29,325
Japan	30	7
Brazil	26	9905
Afghanistan	23	0
Indonesia	16	1
Ukraine	16	5

reports of 'fever of unknown origin'. The majority of reports collected in the EPIWATCH system for rash-like illnesses were in Asia (India = 181, Malaysia = 135), and not in the countries of Europe and North America (USA = 31) where there was documented widespread transmission of Mpox. Subsequent reporting of Mpox cases in India total 17 as 29 November 2022.[6] However, diagnostic capability is higher in the USA and Europe, and it is possible in low- and middle-income countries that Mpox was misdiagnosed.

Inadequate diagnostic capability in low resource settings has been identified as a factor which may lead to underreporting or misdiagnosis,[21,26] and testing capacity was low in several of the countries in our analysis (see Table S3). However, there has also been a lack of testing in high-income countries, potentially due to restricted case definitions, lack of knowledge by primary health care providers leading to misdiagnosis, and stigma around the disease.[26] The majority of Mpox cases in the current outbreak have been identified in MSM.[18,21] International case definitions have defined a probable Mpox case as anyone with an unexplained rash or lesion(s) and has either a recent epidemiological link to a probable case of Mpox, or identifies as a MSM, or has had one or more new sexual partners in the 21 days before symptom onset.[18,27] This case definition may exclude women and children

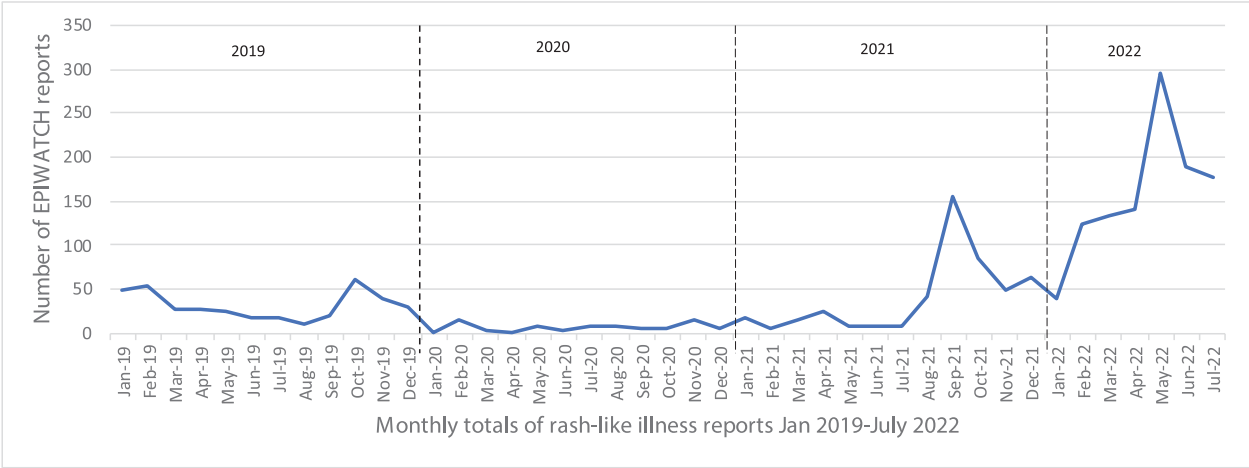

Fig. 3. A time series analysis of total monthly reports for rash-like illness extracted from the EPIWATCH system January 2019–July 2022.

who had no travel history or contact with confirmed infection, and may lead to misdiagnosis.[18,19]

The 2022 Mpox epidemic peaked in the middle of 2022 and has since waned.

While the signals for rash-like illnesses did not correspond to the countries experiencing the highest burden of the Mpox epidemic, we were looking for signals in low-income countries where surveillance may not be as complete and timely as in the high-income countries that were affected by Mpox in 2022. Clinicians may be unfamiliar with symptoms of orthopoxvirus infections; therefore, the signal we demonstrated can be used to prompt a formal investigation for Mpox and other rash and fever illnesses.

Advances in synthetic biology make it possible that orthopoxviruses could be used as bioweapons.[28,29] A system like EPIWATCH can be used to monitor for a sudden increase in rash and fever presentations, or any other clinical syndrome, as an early warning of an outbreak and a trigger for timely investigation.

This study includes several limitations. The EPIWATCH system is designed to observe an early-warning signal of a potential infectious disease outbreak through the use of syndromic surveillance; therefore, the data that are collected do not represent case numbers or an epidemic curve but report about a syndrome or disease. There is almost certainly reporting bias due to increasing media awareness leading to increased reports rather than actual increase in disease occurrence. Open-source data are not validated and are not intended to replace traditional diagnostics or surveillance but to be a trigger for more timely investigation of potential epidemics. Early identification of epidemics results in a more feasible prospect of containment. A strength of our methodology is that open-source intelligence can overcome weak surveillance systems. The EPIWATCH system uses AI to scan vast quantities of open-source data continuously for diseases and syndromes in 52 languages, which could not be processed manually due to the volume of data. Outbreak signals are reviewed and collated in a weekly digest by a group of trained analysts. The online dashboard is publicly available and updated in real time.

Conclusion

Considering the overlapping clinical characteristics within the case definitions of Mpox, hand-foot-and-mouth disease and varicella, it is possible that Mpox and other orthopoxviruses may be misdiagnosed as another viral illness, particularly in countries with low diagnostic capacities in poor resource settings. Open-source intelligence can be used to monitor for outbreaks of fever and rash-like illnesses, especially in countries without widespread testing capacity. The utility of open-source data from syndromic surveillance systems such as EPIWATCH could be used in early warning of emerging outbreaks and to inform international public health responses, such as increasing testing capacities and directing resources and investigations to resource-poor settings to curb the spread of infectious diseases with epidemic potential.

Author statements

Ethical approval

Not applicable.

Funding

The study was supported by the Balvi Filantropic Fund. C. Raina MacIntyre is supported by a NHMRC Principal Research Fellowship, grant no. 1137582.

Competing interests

All authors declare that they have no conflicts of interest.

Author contributions

Danielle Hutchinson: writing – original draft, review & editing, conceptualization, methodology and formal analysis. Mohana Kunasekaran: methodology, formal analysis and writing - review & editing. Ashley Quigley: methodology and writing - review & editing. Aye Moa: formal analysis and writing - review & editing. C. Raina MacIntyre: supervision, writing - review & editing and conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.05.010.

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Public Health 220 (2023) 10–17

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Review Paper

COVID-19 pandemic and neonatal birth weight: a systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 29 November 2022
Received in revised form
16 February 2023
Accepted 18 April 2023
Available online 21 April 2023

Keywords:
COVID-19 pandemic
Birth outcomes
Birth weight
Meta-analysis

ABSTRACT

Objectives: Lockdown was implemented in many countries during the pandemic, which led to myriad changes in pregnant women's lives. However, the potential impacts of the COVID-19 pandemic on neonatal outcomes remain unclear. We aimed to evaluate the association between the pandemic and neonatal birth weight.
Study design: This was a systematic review and meta-analysis of the previous literature.
Methods: We searched the MEDLINE and Embase databases up to May 2022 and extracted 36 eligible studies that compared neonatal birth weight between the pandemic and the prepandemic period. The following outcomes were included: mean birth weight, low birth weight (LBW), very low birth weight (VLBW), macrosomia, small for gestational age (SGA), very small for gestational age (VSGA), and large for gestational age (LGA). Statistical heterogeneity among studies was assessed to determine whether a random effects model or fixed effects model was conducted.
Results: Of the 4514 studies identified, 36 articles were eligible for inclusion. A total of 1,883,936 neonates during the pandemic and 4,667,133 neonates during the prepandemic were reported. We identified a significant increase in mean birth weight (pooled mean difference [95% confidence interval (CI)] = 15.06 [10.36, 19.76], I^2 = 0.0%, 12 studies) and a reduction in VLBW (pooled OR [95% CI] = 0.86 [0.77, 0.97], I^2 = 55.4%, 12 studies). No overall effect was identified for other outcomes: LBW, macrosomia, SGA, VSGA, and LGA. There was publication bias for mean birth weight with a borderline significance (Egger's P = 0.050).
Conclusion: Pooled results showed the pandemic was significantly associated with an increase in mean birth weight and a reduction in VLBW, but not for other outcomes. This review provided clues about the indirect effects of the pandemic on neonatal birth weight and more healthcare measures needed to improve neonatal long-term health.

Introduction

The outbreak of COVID-19 has profound effects on the global economy, social structures, and health services systems.[1,2] Then, many governments implemented national or regional blockades and restrictions on free activities, which led to myriad changes in how pregnant women live their lives.[3,4] Pregnant women are vulnerable to not only the direct effects of infection with COVID-19 but also the indirect effects of disruption of essential healthcare services and restrictions on social interaction. However, the indirect impact of the pandemic on pregnancy outcomes, including neonatal birth weight, remains unclear.

Birth weight, a sensitive indicator of intrauterine growth, is well documented that stress during pregnancy, prenatal care, and change in social life may result in adverse infant birth weight.[5,6] As the important predictive indicator of neonatal health, the changes of low birth weight (LBW), very low birth weight (VLBW), small for gestational age (SGA), very small for gestational age (VSGA), and other adverse outcomes during the pandemic have drawn more attention, but it is mainly regarded as the secondary outcome in

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https://doi.org/10.1016/j.puhe.2023.04.009
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previous studies and with inconsistent results. A large sample study showed a significant increase of 13 g in mean birth weight during the pandemic compared with before the pandemic,[7] but there were no differences in other studies.[8,9] For LBW, there were no significant differences in some countries, such as Ireland,[10] China,[11,12] and Australia,[13] whereas the studies from Spain[14] and Turkey[15] observed a significant increase in the pandemic period. Moreover, the recent two large sample sizes and nationwide studies reported a significant reduction in the rate of SGA during the pandemic (the United States[16] and England[17]), but not for other studies.[13,18,19] The COVID-19 lockdown and population response measures, as well as risk factors for adverse birth outcomes, vary from region to region, which may partly explain the differences between studies.[20]

Inconsistency among results from previous reports and a lack of evidence prompted us to conduct further exploration of neonatal birth weight changes during the pandemic. We aimed to assess the indirect effects on birth outcomes of the global COVID-19 pandemic.

Methods

We did a meta-analysis of studies on the effects of the pandemic on neonatal birth weight. This review was reported according to the Preferred Reporting Items in Systematic Reviews and Meta-analyses guidelines.[21] The study protocol was registered with PROSPERO (No. CRD42022337886).

Search strategy and selection criteria

We searched the MEDLINE and Embase databases and reference lists of included studies up to May 2022 for relevant articles. The keywords used in this study were 'COVID-19' or '2019-nCoV' or 'SARS-COV-2' or 'n-COV' or 'coronavirus' and combined them with terms related to outcomes, such as 'birth outcome,' 'neonates,' 'bw,' 'birth weight,' 'LBW,' 'VLBW,' 'macrosomia,' 'SGA,' 'VSGA,' and 'LGA' (Table S1). The search strategy was appropriately translated for the database. Studies were included if (1) the following outcomes were compared: mean birth weight, LBW, VLBW, macrosomia, SGA, VSGA, or large for gestational age (LGA) between the pandemic and the prepandemic period; (2) effect size (odds ratios [ORs] or risk ratios or β) with 95% confidence interval (CI) or mean with standard deviation were provided or could be calculated; (3) published in English. We excluded studies that were case reports or not published as full reports, studies with data unextractable or inappropriate design, and studies of only SARS-COV-2–infected women. Two investigators (X.D.Y. and H.J.) independently reviewed all the articles, and disagreements were resolved after discussion with the third author (J.Q.M.).

Data extraction

The characteristics of included studies were extracted based on authors, year of publication, sample size, study population and location, pandemic period definition, prepandemic period definition, effect size with 95% CI or mean with standard deviation, and other related information.

Neonatal birth weight assessed were mean birth weight, LBW, VLBW, macrosomia, SGA, VSGA, and LGA. LBW was defined as <2500 g, VLBW was defined as <1500 g, and macrosomia was defined as >4000 g. SGA was defined as birth weight less than the 10th percentile, VSGA was defined as birth weight less than the 3rd percentile, and LGA was defined as birth weight greater than the 90th percentile by gestational week at birth.[22–24]

Quality assessment

Each study was scored according to the Newcastle–Ottawa Scale[25] independently by two assessors (X.D.Y. and H.J.). Quality assessment of these studies was based on three domains: selection, comparability, and outcomes. A study that scored 0–3 was considered to have a high risk of bias, 4–6 have a moderate risk of bias, and 7–9 have a low risk of bias. A lower risk of bias denotes higher quality.

Statistical analyses

For binary outcomes, if adjusted OR was not given, crude OR was used. For continuous outcomes, mean difference (MD) with 95% CI was calculated by pooling the mean with standard deviation. Statistical heterogeneity among studies was evaluated using the Chi-squared test, I^2 statistics, and P values. If the homogeneous test was not significant ($I^2 < 50\%$ and/or $P > 0.10$), a fixed effects model was used to obtain a summary OR or MD. Otherwise, a random effects model was used. Publication bias was evaluated by using funnel plots and Egger's test. Then, we conducted a subgroup analysis for factors that could potentially affect COVID-19 pandemic definition, lockdown measures, or neonatal birth weight: effect size (adjusted OR or crude OR), sample size (<10,000 or ≥10,000), study population (single center, multicenter, or regionwide/nationwide), country classification (low-/middle-income or high-income country according to World Bank classifications), 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 analyses 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; College Station, TX, USA).

Results

Of the 4514 studies identified, 36 articles were eligible for inclusion with further screening (Fig. 1).[4,5,7–20,26–45] Table S2 shows the characteristics of included studies in the quantitative synthesis. All the studies used a historical cohort design. Across the included studies, a total of 1,883,936 neonates during the COVID-19 pandemic and 4,667,133 neonates during the prepandemic were reported. Of the 36 primary studies, 12 reported mean birth weight, 23 reported adverse birth weight (LBW, VLBW, or macrosomia), and nine reported birth weight for gestational age (SGA, VSGA, or LGA). Twenty-two countries were represented, with substantial variation in pandemic mitigation measures among countries. There were 21 reports from single-center studies, four multicenter studies, and six regional reports, and the remaining five were national registries. Total sample sizes varied from 81 to 2,219,914 neonates. The duration of the 'pandemic period' studied varied from 1 month to 11 months, and the duration of the 'prepandemic period' studied varied from 2 months to 18 years. The scores of quality assessments of the studies ranged from 5 to 9 (Table S3). There were 21 articles with moderate risk of bias and 15 articles with low risk of bias.

There was an increase in mean birth weight during the pandemic compared with the prepandemic period (pooled MD [95% CI] = 15.06 [10.36, 19.76], $I^2 = 0.0\%$, 12 studies; Fig. 2). We only found a significant decrease in the rate of VLBW (pooled OR [95% CI] = 0.86 [0.77, 0.97], $I^2 = 55.4\%$, 12 studies), but there was no difference for LBW and macrosomia during the pandemic compared with the prepandemic period (LBW: pooled OR [95% CI] = 0.96 [0.90, 1.03], $I^2 = 69.2\%$, 20 studies; macrosomia: pooled

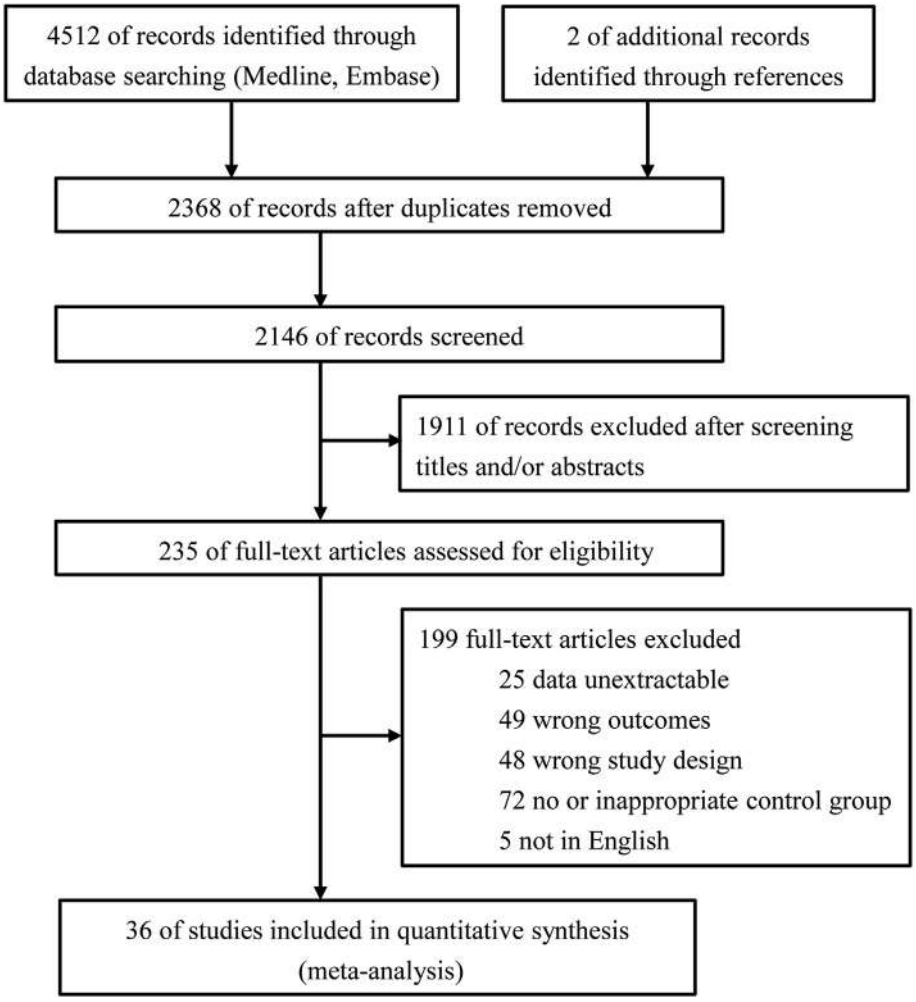

Fig. 1. Flowchart of study selection.

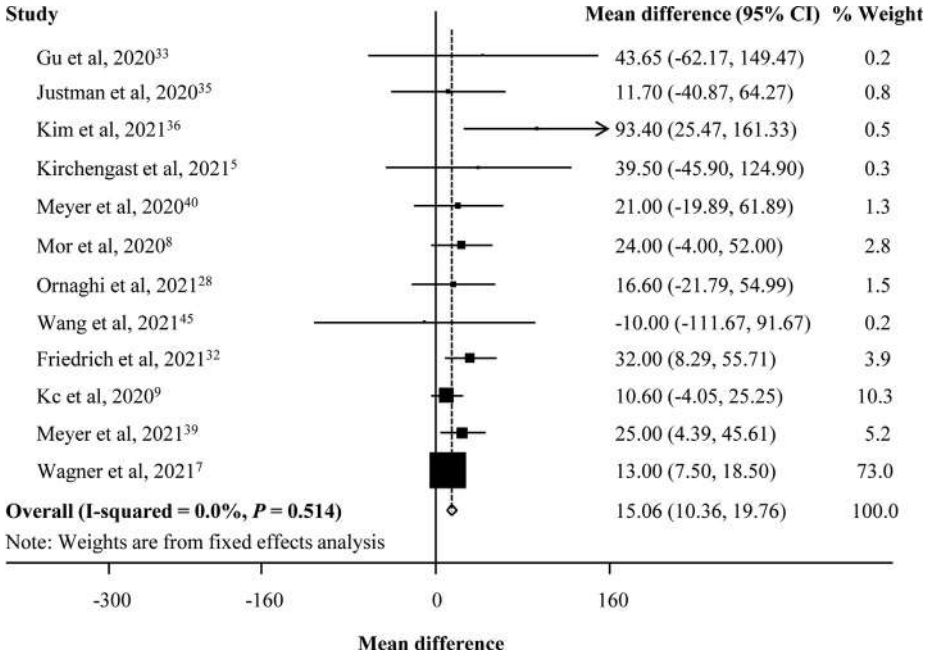

Fig. 2. Forest plot for mean birth weight.

OR [95% CI] = 0.70 [0.49, 1.02], I^2 = 87.7%, five studies; Fig. 3). Moreover, there was publication bias for mean birth weight with a borderline significance (Egger's $P = 0.050$) but not for LBW (Egger's $P = 0.681$) and VLBW (Egger's $P = 0.071$). Fig. 4 shows the funnel plots of the included studies for neonatal birth weight (≥10 studies). In studies with birth weight for gestational age, we found a reduction for SGA in the pandemic period with a borderline significance (SGA: pooled OR [95% CI] = 0.97 [0.94, 1.01], I^2 = 55.1%, nine studies), whereas there was no significant difference for VSGA and LGA (VSGA: pooled OR [95% CI] = 1.10 [0.95, 1.28], I^2 = 33.7%, three studies; LGA: pooled OR [95% CI] = 0.93 [0.76, 1.14], I^2 = 98.0%, two studies; Fig. 5).

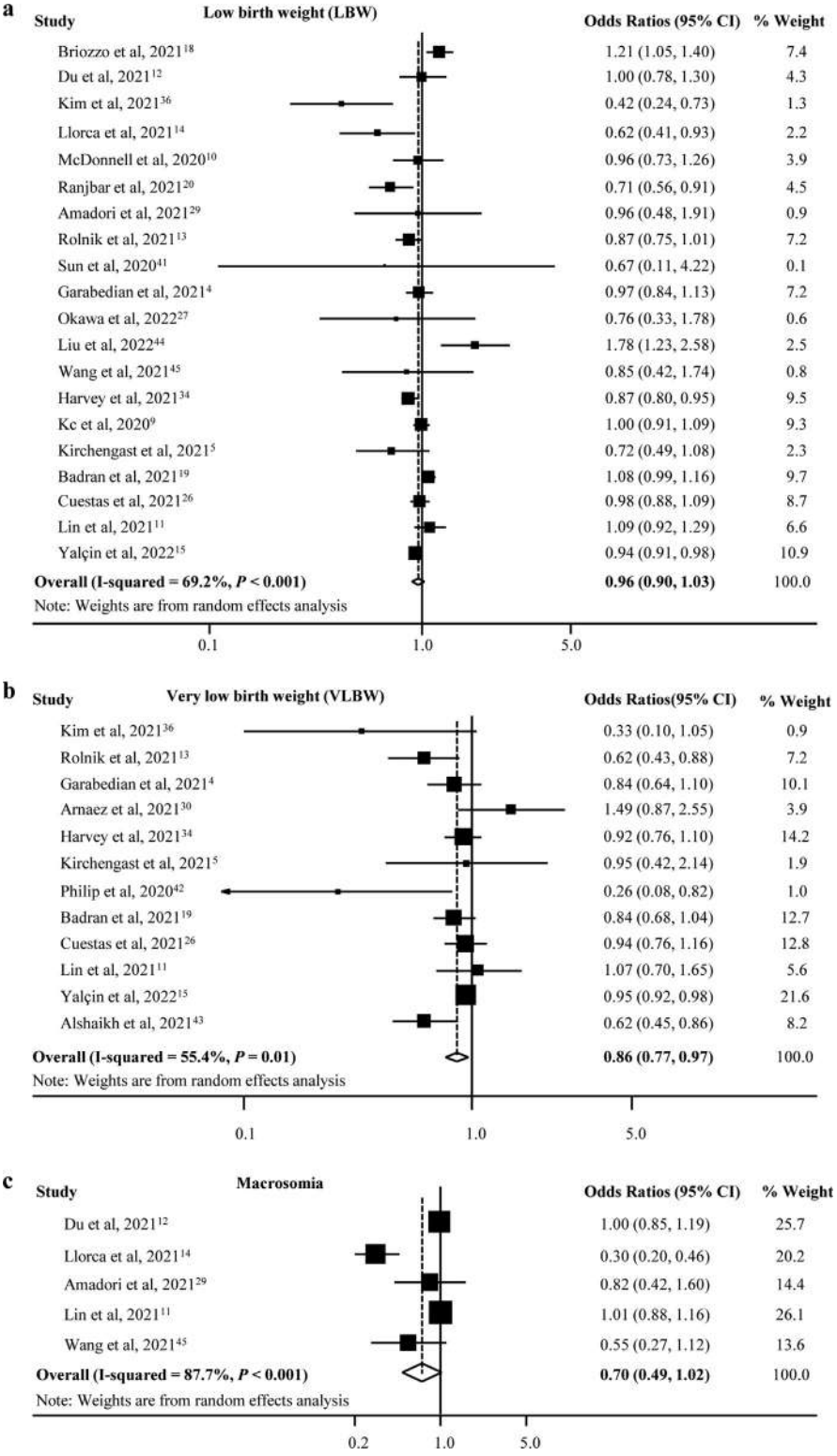

Fig. 3. Forest plot for odds of birth weight.

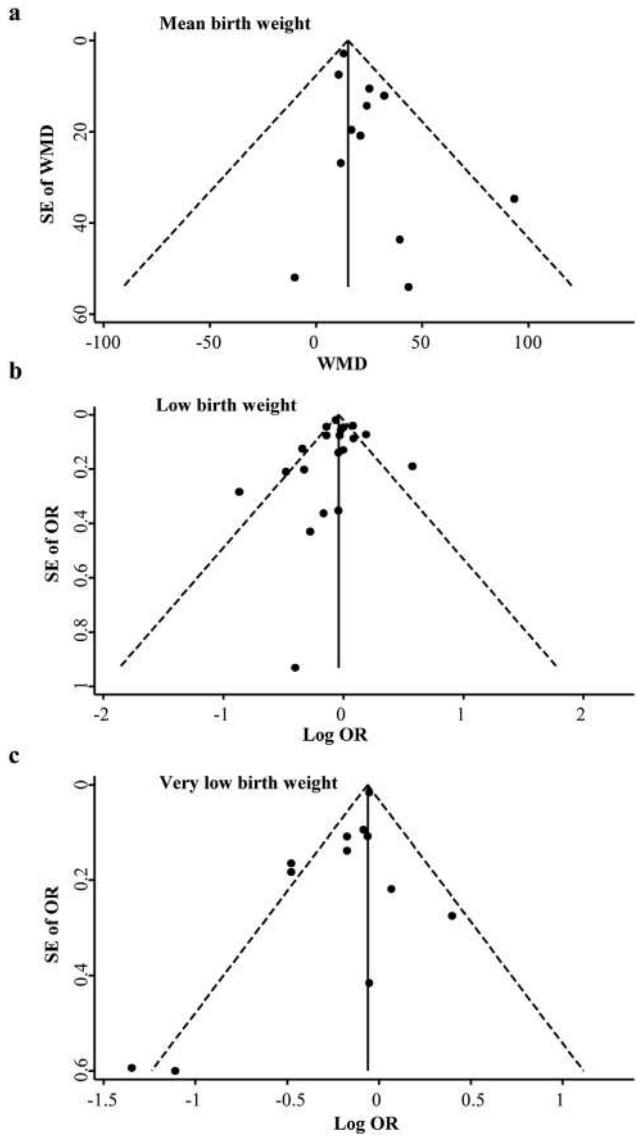

Fig. 4. Funnel plots for studies reporting on birth weight.

Further subgroup analyses were performed to assess the effect of potential confounders on the pooled results. For mean birth weight, there was a significant increase during the pandemic, which was supported by most study subgroups ($P < 0.01$), except for the data from low-/middle-income countries (Table S4). Although the pooled odds of LBW had no change during the pandemic, the subgroups analysis showed a significant decrease in the studies from regionwide/nationwide and high-income countries (studies from regionwide/nationwide: pooled OR [95% CI] = 0.92 [0.86, 0.97], $I^2 = 29.7\%$, three studies; studies from high-income countries: pooled OR [95% CI] = 0.85 [0.77, 0.95], $I^2 = 37.7\%$, nine studies; Table S5). Furthermore, we also found a significant reduction for VLBW in most subgroups, including the data from adjusted odds, low-/middle-income or high-income countries, and the studies with moderate risk of bias or total sample size <10,000, but not for other subgroups (Table S6). Different from summary odds of SGA, there was a significant reduction in specific subgroups: the studies from regionwide/nationwide or high-income countries, the studies with a low risk of bias or total sample size ≥10,000, and the prepandemic period defined as equivalent period in previous years ($P < 0.01$; Table S7).

In sensitivity analysis, most pooled estimates were not significantly different when a study was omitted, whereas the pooled estimate effect became significant for SGA when Briozzo et al.[18] or Badran et al.[19] were omitted ($P < 0.001$ and $P = 0.002$).

Discussion

We have provided quantitative estimates for the associations between the COVID-19 pandemic and neonatal birth weight through a systematic search and comprehensive meta-analysis. The results showed a significant increase of 15 g in mean birth weight in the pandemic period compared with before the pandemic period. We also identified a reduction in the rate of VLBW, but not for LBW and macrosomia. Besides, there was a reduction in the rate of SGA with a borderline significance but not for VSGA and LGA with a few studies included.

Recently, some reviews mainly reported the effects of COVID-19 infection on pregnancy outcomes[46–48] and the major birth outcomes, such as preterm birth and stillbirths.[49–51] This meta-analysis was designed to evaluate the indirect impacts of the COVID-19 pandemic on secondary birth outcomes and excluded studies that reported outcomes of maternal COVID-19 infection. In this review, pooled results showed that LBW did not significantly change during the COVID-19 pandemic, which was supported by the previous review.[50,51] However, we identified a significant decrease for LBW in the data from regionwide/nationwide and high-income countries. Yang et al.[49] found a reduction in LBW during the pandemic using regional/national data, but there was no overall difference in LBW and VLBW. In contrast, there was a significant decrease in the rate of VLBW during the pandemic compared with the prepandemic period in our study. Nevertheless, we also found substantial heterogeneity and discordant results among the subgroups. Inconsistency among conclusions from different studies possibly be attributed to variations in sample sizes, location of the population, socio-economic status, lengths or definition of the pandemic and prepandemic periods, and different blockade measures between countries.

The previous meta-analyses mainly reported the effects of the COVID-19 pandemic on preterm, stillbirths, maternal mortality, and LBW.[49–51] As a more sensitive indicator of neonatal health, SGA infants are more likely to have intensive care therapy, morbidity due to perinatal fetal distress and neonatal asphyxia, and perinatal mortality compared with appropriate for gestational age.[52] However, the effect of the pandemic on SGA has not received much attention in the previous review. To improve this deficiency, our study investigated the association between SGA and the pandemic. Although we found no difference in the rate of SGA during the pandemic compared with the prepandemic period, there was a significant decrease in the data from regionwide/nationwide, high-income countries, and the studies with low risk of bias. Besides, we found a significant change when Briozzo et al.[18] or Badran et al.[19] were omitted, and the studies were from single-center and low-/middle-income countries. Explanations for these results may be related to substantial variation in pandemic mitigation measures and population responses among countries.

The researchers have proposed that COVID-19–related lockdown may cause maternal behavioral modifications, potential reduction in work-related stresses, optimal opportunities for rest and sleep, reduced exposure to infections, and improved opportunities for nutritional support and exercise.[19,42] While the pandemic has caused disruption to healthcare systems, economic crises, and rising unemployment, people with high income and people in developed countries have experienced faster restructuring of healthcare systems and timely increased access to care through telehealth.[53] In addition, their family assets may ease the burden of unemployment

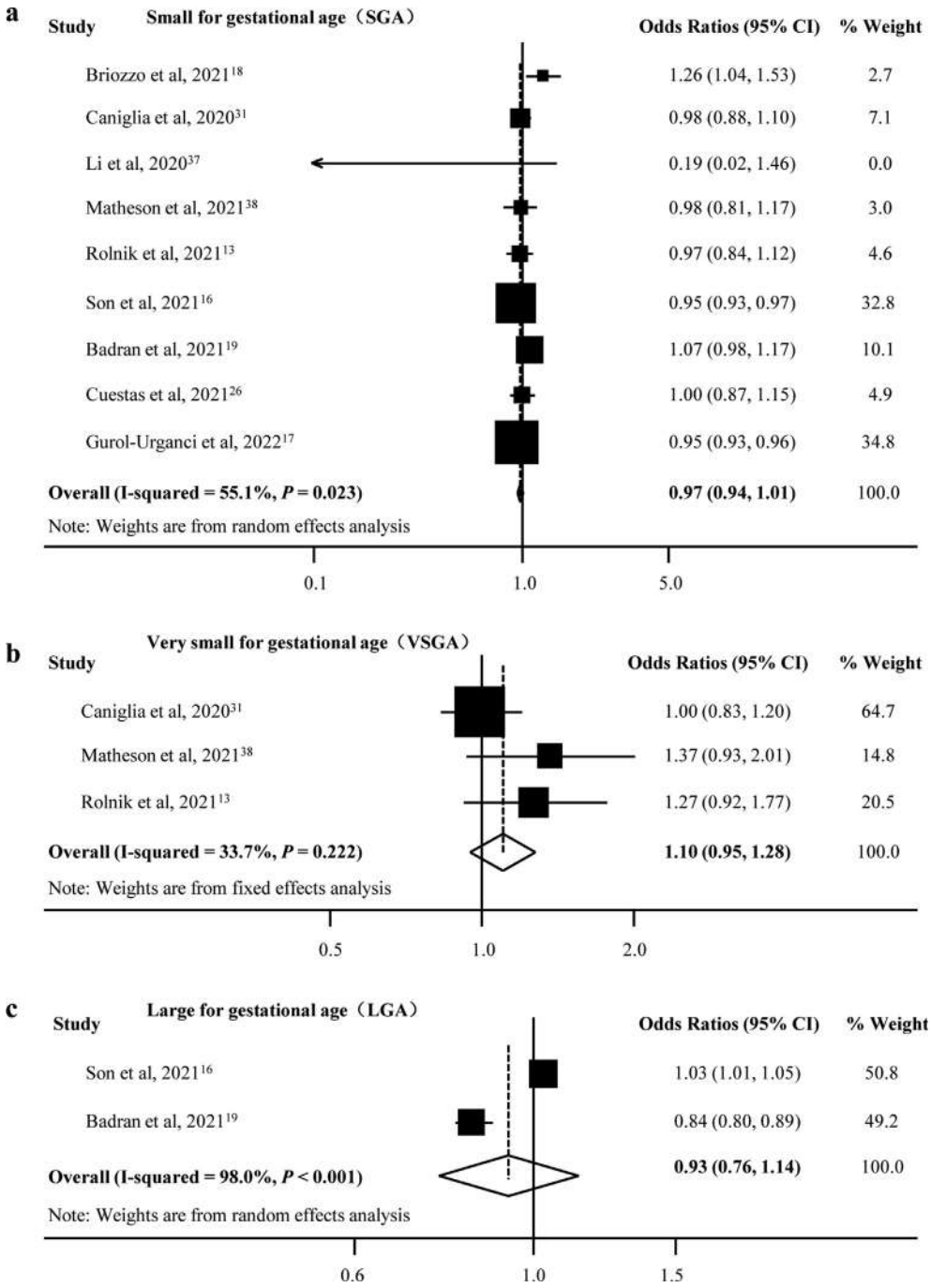

Fig. 5. Forest plot for odds of birth weight for gestational age.

and allow them to spend more time enjoying life. However, for low-income families, it may have exacerbated socio-economic inequalities in health, limitation of health services, family conflicts, perinatal anxiety, and depression.[26,54] In low-income countries, where remote consultations are less feasible, financial or employment issues are prominent, and maternity staff shortages exist, resulting in reduced access to preventive antenatal care and nutritional support for pregnant women.[55] As a result, pregnant women can suffer negative physical and mental health outcomes. Stress, worries, and anxieties during pregnancy are often associated with LBW.[56] Therefore, the effect of the pandemic on neonatal adverse birth weight is a double-edged sword. COVID-19 is not only a pandemic and global health crisis but also a psychosocial and economic disaster. The potential influence of a multitude of biological, physical, and environmental factors could cumulatively modify the birth outcomes of neonates.

The strength of this review was the inclusion of large populations from 22 countries and the synthesis of a broad range of articles. We mainly investigate the potential effects of the COVID-19 pandemic on secondary birth outcomes, and deep subgroup analysis was conducted to clarify the source of heterogeneity. Nevertheless, our study had some limitations. First, the included studies all used a retrospective design, and the heterogeneity of study countries, the definitions of comparable groups, and statistical

methodology all affected the comparability of results. Besides, we only reported the non–COVID-19 infection population, and more birth outcomes during the pandemic should be further assessed.

Conclusion

In this study, we found the COVID-19 pandemic was significantly associated with an increase in mean birth weight and a reduction in VLBW, but not for other outcomes. However, subgroup analysis showed that LBW and SGA had a significant reduction in specific subgroups. This review provided clues about the indirect effects of the pandemic on neonatal birth weight. Further studies should be conducted to clarify the underlying mechanisms of the findings, and more healthcare measures needed to improve neonatal long-term health.

Author statements

Author contributions

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

Ethical approval

None sought.

Funding

This work was supported by Jiangsu provincial key research and development program (BE2020626).

Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.009.

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Public Health 220 (2023) 127–134

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Effectiveness of China-PAR and Framingham risk score in assessment of 10-year cardiovascular disease risk in Chinese hypertensive patients

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ARTICLE INFO

Article history:
Received 31 August 2022
Received in revised form
21 March 2023
Accepted 10 May 2023

Keywords:
Cardiovascular diseases
Framingham risk score
China-PAR
Hypertension patients
Disease prevention

ABSTRACT

Objectives: Estimating the total risk of cardiovascular disease (CVD) using risk prediction models represents a huge improvement in identifying and treating each of the risk factors. The objective of this study was to evaluate the effectiveness of the China-PAR (Prediction of atherosclerotic CVD risk in China) and Framingham risk score (FRS) in predicting the 10-year risk of CVD in Chinese hypertensive patients. The results of the study can be used to design health promotion strategies.

Study design: A large cohort study was used to assess the validity of models by comparing model predictions with actual incidence rates.

Methods: In total, 10,498 hypertensive patients aged 30–70 years in Jiangsu Province, China, participated in the baseline survey that took place between January and December 2010 and were followed up to May 2020. China-PAR and FRS were used to calculate the predicted 10-year risk of CVD. The 10-year observed incidence of new cardiovascular events was adjusted by the Kaplan–Meier method. The ratio of the predicted risk to the actual incidence was calculated to evaluate the effectiveness of the model. The discrimination Harrell's C statistics and calibration Chi-square value were used to evaluate the predictive reliability of the models.

Results: Of the 10,498 participants, 4411 (42.02%) were male. During the mean follow-up of 8.30 ± 1.45 years, a total of 693 new cardiovascular events occurred. Both models overestimated the risk of morbidity to varying degrees, and the FRS overestimated to a greater extent. After adjustment for covariates, the results of Cox proportional hazards regression showed that the risk of CVD in the high-risk group was higher than in low-risk group. The degree of discrimination in both models was approximately 0.6, which showed that discrimination was not ideal in the models. In addition, Chi-square calibrations of the two models were <20 in males, which showed that calibration of the models was better for men than women.

Conclusions: The China-PAR and FRS models overestimated the risk of CVD for participants in this study. In addition, the degree of discrimination was not ideal, and both models performed better in males than in females in terms of calibration. The results of this study suggest that a more suitable risk prediction model should be established according to the characteristics of the hypertensive population in Jiangsu Province.

Introduction

Cardiovascular disease (CVD) generally refers to a group of circulatory system diseases mainly caused by heart and cerebrovascular abnormalities and is the primary cause of premature death and disability in the world, with 17 million people dying from it each year.[1,2] A century ago, <10% of all deaths were attributable to CVD; however, today, it accounts for 30% of worldwide deaths.[3] CVD risk is associated with factors such as smoking, hypertension

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https://doi.org/10.1016/j.puhe.2023.05.007

and dyslipidaemia, and lowering blood pressure, blood glucose and lipid-lowering therapies have been shown to reduce morbidity and mortality.[4] Timely identification of individuals who are at high risk of developing CVD events through risk assessment tools can effectively promote the primary prevention of CVD.

The China-PAR (Prediction of atherosclerotic CVD risk in China) is based on two prospective cohort studies with large sample populations in China, incorporating the north and south and urban and rural parameters with Chinese CVD epidemic characteristics. China-PAR provides an important theoretical and scientific basis for the prevention and control of CVD.[5] The Framingham risk score (FRS) is a refinement of the Framingham coronary heart disease (CHD) risk prediction model and consists of seven variables that estimate the risk of developing CVD.[6,7] FRS is usually used to study CVD risk or other disease risk factors associated with CVD.[8–10]

There are many studies on external validation of these two models, but most of the literature has concentrated on the general population, with limited data on the hypertensive population.[11,12] However, studies have shown that patients with hypertension have a much higher CVD risk than the general population;[13,14] therefore, it is necessary to carry out risk stratification using risk assessment tools to inform prevention and control measures for CVD in hypertensive populations. This study compared the difference between the China-PAR model and FRS for the predicted 10-year CVD risk and the actual CVD incidence in hypertensive patients in the Jiangsu Province of China. The results can provide a reference for the prevention and control of CVD and guide health promotion strategies.

Methods

Study design and participants

Participants in this study were recruited from the Follow-up Cohort Study of Hypertension (FCSH), which was established in 2010 in Jiangsu Province, China. According to the characteristics of regional economic development, population distribution and lifestyle, five representative counties or districts in Jiangsu Province were selected by multistage stratified random sampling. The total population in these five representative counties or districts was 4.99 million, which accounted for 6.35% of the total population of Jiangsu Province. Each area randomly selected three towns as project points, and each township randomly selected 8–10 administrative villages (or residents committees). In total, 148 villages (or residents committees) were selected to conduct the essential hypertension screening for all adults aged 18–70 years old, resulting in a total screening population of 60,512, with a response rate was 92.36%. A total of 11,000 hypertensive patients were ultimately included in the baseline survey that took place between January and December 2010, with strict inclusion and exclusion criteria. All participants signed the informed consent form, and the study protocol was approved by the ethical review committee of the Jiangsu Province Center for Disease Control and Prevention (SL2015-B004-01). Individual personal data (including any details, images, or videos) are not included in this article. The procedures were in accordance with the standards of the ethics committee of Jiangsu Provincial Center for Disease Control and Prevention and with the Declaration of Helsinki (1975, revised 2013).

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) adults aged between 18 and 70 years and (2) clearly diagnosed essential hypertension or those whose blood pressure was above the recommended ranges.

Patients were excluded if they met any of the following conditions: (1) in the acute phase of myocardial infarction and stroke in the last 3 months; (2) had secondary hypertension; (3) had serious complications and comorbidities (e.g. peripheral vascular disease, systemic inflammation disease and blood disease) in the previous 3 months; (4) had a life expectancy of <1 year; or (5) did not easily cooperate or were unwilling to sign the informed consent form.

A total of 375 patients were excluded because of a history of stroke; 41 patients were excluded because of a medical history of CHD; 31 patients were excluded because of missing baseline information, such as age, blood pressure and diabetes; and 65 patients were excluded because of loss to follow-up (43 patients were too ill or refused to follow-up; five patients died from other causes, such as accidents or tumours, and 17 patients were lost to follow-up due to a change of residence).

Finally, 10,498 participants aged 30–70 years were included in the final analysis.

Baseline data and measurements

Baseline data were collected through questionnaires, physical examinations and laboratory tests. Participants completed standard questionnaires to collect information on sociodemographic characteristics, medical history, family history of CVD and personal lifestyle.

Anthropometric measures included height, weight, waist circumference (WC) and body mass index (BMI). Blood pressure was measured in the left upper arm with the automated device (OMRON Model HEM-7200, Omron Co.). Participants were required not to do any exercise or consume any food or beverages (especially tea and coffee) 1 h before the blood pressure measurement; participants were also asked to stop smoking, relax and empty their bladder 30 min before measurement. When measuring, the cuff midpoint was required to be at the same level as the heart, and when the first measurement was completed, the participant took a 1-min break before the next measurement started. Each participant had their blood pressure measured three times, and the average of the three measurements was recorded as the final blood pressure.

Laboratory test indicators included fasting plasma glucose (FPG), fasting insulin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TGs). Participants were required to fast for at least 8 h before 4–5 mL of venous blood was collected. Blood samples were aliquoted within 2 h and frozen at −80°C, then transported in dry ice to the central laboratory in Jiangsu Province Center for Disease Control and Prevention, which was certificated by the National Laboratory Certification of China. The blood sugar and lipid levels were measured by automatic biochemical analyser (Abbott Laboratories, USA), and the whole process of laboratory testing was strictly controlled by professionals.

Follow-up and study outcomes

All participants were followed up once a year between June 2010 and May 2020. At each follow-up visit, indicators such as weight and blood pressure were measured, and data were collected on lifestyle factors, such as smoking, drinking and diseases (e.g. CVD, cerebrovascular diseases, cancer and diabetes).

The end point events in this study were the first diagnosed CVD events during the follow-up, including acute myocardial infarction, fatal CHD, and non-fatal or fatal stroke.[15] Stroke was confirmed by CT or MRI scans, and CHD was confirmed by electrocardiogram or serum enzyme diagnosis. All the outcomes were diagnosed by hospitals at or above the county level and reviewed by the Jiangsu Provincial Endpoint Event Review Committee. If a participant had

an end point event during the observation period, the investigator consulted the hospital medical records for confirmation.

Assessment of risk factors

Family history of CVD was defined as having at least one first-degree relative or at least two second-degree relatives with a history of CVD. Smoking was defined as having smoking behaviour within 30 days before the survey and smoking one or more cigarettes per day.[16] Alcohol consumption was defined as drinking behaviour within 30 days before the survey and drinking at least once a week.[17] Hypertension was defined as a mean systolic blood pressure (SBP) ≥140 mm Hg and/or a mean diastolic blood pressure (DBP) ≥90 mm Hg, or the subjects had a reported history of hypertension or were taking antihypertensive medication.[18] Hypertension treatment was defined as the regular use of antihypertensive drugs within the 2 weeks before the investigation. Diabetes was defined as FPG ≥7.0 mmol/L or respondents have a history of diabetes or taking hypoglycaemic drugs.[19] BMI was calculated by dividing the weight (kilogram) by the square of the height (square metre) and was categorised according to the Obesity Standards of China Working Group.[20]

CVD risk prediction models

Two models were used to assess CVD risk

The China-PAR model included sex, age, WC, SBP (treated or untreated), TC, HDL-C, current smoking (yes/no), diabetes (yes/no), geographic region (Northern China/Southern China), urbanisation (urban/rural) and family history of CVD (yes/no). Based on the cutoff points in Chinese guidelines, participants were divided into three categories (low risk [<5%], medium risk [5–9.9%] and high risk [≥10%]; in addition, a risk of ≥20% was classified as extremely high risk) according to the predicted 10-year CVD risk.

The FRS included sex, age, SBP, TC, HDL-C, smoking, diabetes and whether receiving hypertension treatment. Participants were divided into three categories (low risk [<5%], medium risk [5–9.9%] and high risk [≥10%]; in addition, a risk of ≥20% was classified as extremely high risk) according to the FRS predicted 10-year CVD risk.[21,22]

Statistical analyses

Data were analysed using Statistical Package for Social Sciences (IBM/SPSS) version 26.0 and R software (version 3.3.2). Continuous variables meeting the normal distribution were expressed using the mean and standard deviation, and comparisons between groups were performed using analysis of variance. Continuous variables that did not fit the normal distribution were represented using the median (interquartile spacing) and were compared between groups using the Kruskal–Wallis H test. Categorical variables were presented as numbers or percentages and analysed using the Chi-square test. A confidence interval (CI) of 95% was used in this study, and a *P*-value of <0.05 was considered as significant.

Multivariate Cox proportional hazards regression analysis, with the low-risk group as a reference and whether participants had a CVD event as the dependent variable, calculated the risk ratio and 95% CI in each group of the two prediction models, and further adjustment took place for other risk factors not included in the China-PAR model and FRS parameters. Because age was the most heavily weighted risk factor in the 10-year CVD risk prediction model,[23] the age variable remained as a covariate in the Cox model for adjustment.

For each participant, observed incidence rate was calculated and adjusted using the Kaplan–Meier method, and predicted CVD risk was calculated using FRS and China-PAR models for men and women. Within each category, the ratios of expected to observed events (EOR) were calculated, where >1.0 suggested overestimation and <1.0 indicated underestimation.[24]

Validation of the incidence risk prediction model included assessment of discrimination and calibration.[25] Discrimination reflected the risk score of the prediction model correctly identifying early-onset patients as high risk. Harrell's C statistics was used to evaluate the area under the curve of the participant's characteristic curve; a result above 0.7 is generally considered to be better. Calibration was used to measure the consistency of the fit between the predicted value of the absolute risk estimated by the prediction model and the observed actual situation. The Hosmer–Lemeshow test was used to evaluate the calibration of the prediction model; a χ^2 value < 20 indicated a good degree of calibration.[5] In addition, sensitivity analysis was used to analyse the confounding effects of loss to follow-up.

Results

Baseline characteristics

The mean follow-up time of 10,498 subjects was 8.30 years, with a cumulative period of 86,917 person-years. In total, 6087 (57.98%) participants were female, and the average age of males and females was 59.06 ± 7.79 and 57.77 ± 7.66 years, respectively. Table 1 shows the basic characteristics of the study participants. Men had higher rates of smoking and drinking and larger WCs than women; however, men also had lower BMI, TC, TG and LDL-C levels, a lower likelihood of family history of CVD and lower rates of treatment for hypertension. Sex differences were found in all the predictor variables except the proportion of diabetes and SBP levels. During follow-up, 693 participants (352 men and 341 women) were diagnosed with CVD, and the 10-year observed incidence of CVD was 7.98% in men and 5.60% in women.

Predicted risk distribution

Distribution of 10-year CVD risk class based on China-PAR and FRS is presented in Table 2. The proportion of participants in the low-risk, medium-risk and high-risk groups in the China-PAR model were 2.17%, 14.35% and 83.47% in males and 7.57%, 39.97% and 52.46% in females, respectively. In the FRS model, the low-risk, medium-risk and high-risk groups were 2.11%, 8.25% and 89.64% in males and 9.30%, 36.42% and 54.28% in females, respectively (Table 2). The difference in the distribution of risk class for both genders was statistically significant ($P < 0.05$).

Cox regression of different predicted risk groups

The results of the Cox proportional hazards regression analysis showed that in the China-PAR model, after adjustment for the age, BMI and drinking variables in model 2, predicted risk categories of 5-9.9% (medium risk), 10-19.9% (high risk) and ≥20.0% (extremely high risk) of CVD events were 2.38 times (95% CI, 1.10-5.18), 3.85 times (95% CI, 1.75-8.46), and 5.30 times (95% CI, 2.35-11.96) of the predicted risk at <5% (low risk), respectively (Fig. 1).

In the FRS model, the risk of CVD events at 5-9.9%, 10-19.9% and ≥20.0% predicted risk were 1.26 times (95% CI, 0.72-2.20), 1.80 times (95% CI, 1.03-3.15) and 2.06 times (95% CI, 1.15-3.68) of the predicted risk at <5% (low risk), respectively after adjusting for age, WC, BMI and drinking variables (Fig. 2).

These results indicate that individuals with a higher risk prediction score had a higher risk of CVD events than those with a low-risk prediction score.

Table 1
Baseline characteristics and CVD events of study participants.

Characteristics	Total (N = 10,498)	Male (n = 4411)	Female (n = 6087)	P-value
Age, mean (SD), years	58.31 (7.74)	59.06 (7.79)	57.77 (7.66)	<0.001
SBP, M (P_{25}–P_{75}), mm Hg	148.00 (142.00, 158.00)	148.00 (142.00, 158.00)	149.00 (142.00, 158.00)	0.941
DBP, M (P_{25}–P_{75}), mm Hg	92.00 (90.00, 98.25)	93.00 (90.00, 99.00)	92.00 (90.00, 98.00)	<0.001
WC, M (P_{25}–P_{75}), cm	89.20 (82.00, 96.00)	90.00 (84.00, 97.20)	88.00 (82.00, 95.20)	<0.001
TC, M (P_{25}–P_{75}), mmol/L	4.70 (4.17, 5.34)	4.60 (4.07, 5.24)	4.80 (4.24, 5.40)	<0.001
TG, M (P_{25}–P_{75}), mmol/L	1.50 (1.03, 2.20)	1.40 (0.95, 2.09)	1.60 (1.10, 2.29)	<0.001
HDL-C, M (P_{25}–P_{75}), mmol/L	1.57 (1.32, 1.88)	1.53 (1.27, 1.85)	1.60 (1.35, 1.91)	<0.001
LDL-C, M (P_{25}–P_{75}), mmol/L	2.59 (2.09, 3.19)	2.54 (2.04, 3.13)	2.62 (2.13, 3.23)	<0.001
BMI, M (P_{25}–P_{75}), kg/m^2	25.77 (23.50, 28.30)	25.58 (23.37, 28.04)	25.89 (23.58, 28.48)	<0.001
Urban, n (%)	1357 (12.93)	707 (16.03)	650 (10.68)	<0.001
Smoking, n (%)	2019 (19.23)	1862 (42.21)	157 (2.58)	<0.001
Drinking, n (%)	1713 (16.32)	1617 (36.66)	96 (1.58)	<0.001
Family history of CVD, n (%)	2226 (21.20)	886 (20.09)	1340 (22.01)	0.017
Diabetes, n (%)	1009 (9.61)	410 (9.29)	599 (9.84)	0.349
Antihypertensive treatment, n (%)	8581 (81.74)	3567 (80.87)	5014 (82.37)	0.049
Incident CVD events, n (%)	693 (6.60)	352 (7.98)	341 (5.60)	<0.001

BMI, body mass index; CVD, cardiovascular and cerebrovascular diseases; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; M, median; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

Table 2
10-year CVD risk prediction distribution.

Model and risk score grade	Male, n (%)	Female, n (%)	χ^2	P-value
China-PAR			1090.95	<0.001
Low	96 (2.17)	461 (7.57)		
Medium	633 (14.35)	2433 (39.97)		
High	3682 (83.47)	3193 (52.46)		
FRS			1498.68	<0.001
Low	93 (2.11)	566 (9.30)		
Medium	364 (8.25)	2217 (36.42)		
High	3954 (89.64)	3304 (54.28)		

FRS, Framingham risk score; Low, low-risk: predicted risk <5%; Medium, medium-risk: predicted risk 5–9.9%; High, high-risk: predicted risk ≥10%.

Comparison of models

The results comparing the 10-year predicted CVD risk based on the China-PAR model and FRS with the observed incidence are presented in Table 3.

The predicted risks from the China-PAR model were all higher than the observed CVD event rates for the low-, medium-, high- and extremely high-risk groups, at 2.60 times, 1.82 times, 1.75 times and 2.23 times, respectively.

Similarly, in the FRS, the predicted risks were 1.66 times, 1.87 times, 2.04 times and 3.64 times of the observed CVD event rates in the low-, medium-, high- and extremely high-risk groups, respectively. Furthermore, the ratio of predicted risk to actual incidence rate after Kaplan–Meier adjustment was greater, suggesting a more pronounced overestimation in the FRS model.

Discrimination and calibration of China-PAR and FRS

As presented in Table 4, the China-PAR and FRS performed modestly in the study cohort (C statistic for men: 0.584 [95% CI: 0.554–0.614] using China-PAR and 0.576 [95% CI: 0.546–0.606] using the FRS; the corresponding values for women were 0.619 [95% CI: 0.591–0.647] and 0.608 [95% CI: 0.580–0.635]), indicating the China-PAR and FRS may not have sufficient discriminatory ability (C statistics) to identify individuals at high risk of CVD this study cohort.

As also presented in Table 4,in contrast, this study found that the China-PAR and FRS performed better in males than in females in terms of calibration (χ^2 value: men, China-PAR: 15.959 [P = 0.043],

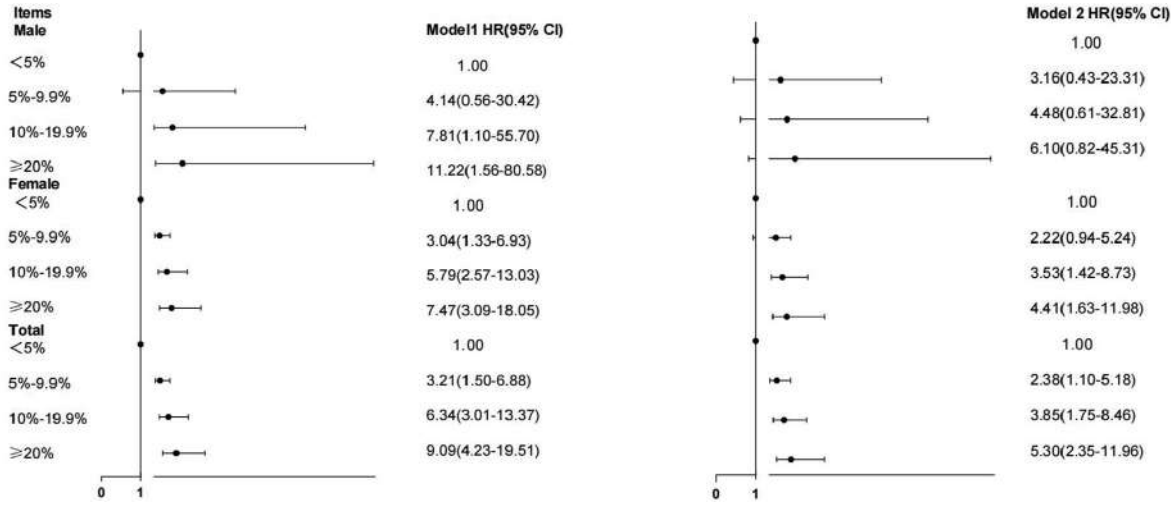

Fig. 1. Cox proportional risk regression analysis of the risk of CVD events in different predictive risk rating groups by China-PAR Model 1: unadjusted; Model 2: adjusted age, BMI and drinking. HR, hazard ratio; CI, confidence interval.

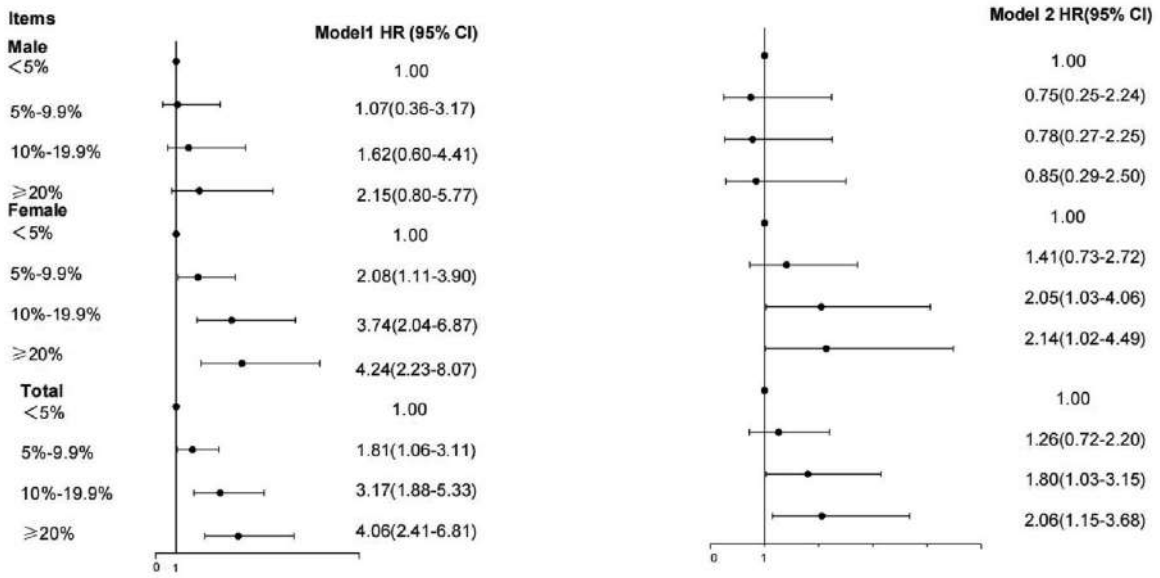

Fig. 2. Cox proportional risk regression analysis of the risk of CVD events in different predictive risk rating groups by FRS Model 1:unadjusted; Mode l2: adjusted age, WC, BMI and drinking. HR, hazard ratio; CI, confidence interval.

Table 3
External validation of 10-year CVD risk prediction by China-PAR and FRS.

Risk group	Observed rate (%)		Kaplan–Meier-adjusted rate (%)		Expected rate (%)		EOR		Adjusted EOR	
	China-PAR	FRS	China-PAR	FRS	China-PAR	FRS	China-PAR	FRS	China-PAR	FRS
Total										
Low (<5%)	1.26	2.28	0.74	1.26	3.28	3.79	2.60	1.66	4.43	3.01
Medium (5–9.9%)	4.01	4.11	2.15	2.20	7.31	7.69	1.82	1.87	3.40	3.50
High (10–19.9%)	7.72	7.03	4.17	3.80	13.54	14.32	1.75	2.04	3.25	3.77
Extremely high (≥20%)	10.86	8.89	6.03	4.85	24.27	32.38	2.23	3.64	4.02	6.68
Male										
Low (<5%)	1.04	4.30	0.36	1.23	3.04	3.65	2.92	0.85	8.44	2.97
Medium (5–9.9%)	4.42	4.67	2.39	2.70	7.55	7.95	1.71	1.70	3.16	2.94
High (10–19.9%)	8.10	6.92	4.19	3.65	14.21	15.39	1.75	2.22	3.39	4.22
Extremely high (≥20%)	11.54	9.14	6.07	4.88	24.35	33.89	2.11	3.71	4.01	6.94
Female										
Low (<5%)	1.30	1.94	0.80	1.28	3.33	3.82	2.56	1.97	4.16	2.98
Medium (5–9.9%)	3.90	4.01	2.08	2.11	7.25	7.65	1.86	1.91	3.49	3.63
High (10–19.9%)	7.34	7.090	4.15	3.88	12.85	13.75	1.75	1.94	3.10	3.54
Extremely high (≥20%)	9.24	7.99	5.89	4.72	24.06	27.10	2.60	3.39	4.08	5.74

Adjusted EOR, adjusted expected-observed ratio: Kaplan–Meier-adjusted rate/observed rate; EOR, expected-observed ratio, Expected Rate/Observed Rate; FRS, Framingham risk score.

FRS: 11.221 [$P = 0.189$]; women, China-PAR: 24.190 [$P = 0.002$], FRS: 33.361 [$P < 0.001$]).

Sensitivity analysis

Considering the possible bias of the results caused by the loss of follow-up or non-response, a sensitivity analysis was performed; similar results were observed (Table 5). The China-PAR and FRS performed modestly in the study cohort (C statistic for men: China-PAR 0.585 [95% CI: 0.555–0.615] FRS 0.577 [95% CI: 0.547–0.607]; the corresponding values for women were 0.620 [95% CI: 0.593–0.648] and 0.609 [95% CI: 0.582–0.637]). The results of the sensitivity analysis did not change the trend of the study conclusion.

Table 4
Comparison of discrimination and calibration of China-PAR and FRS.

Statistic	Total		Male		Female	
	China-PAR	FRS	China-PAR	FRS	China-PAR	FRS
C (95% CI)	0.613 (0.593, 0.633)	0.605 (0.584, 0.626)	0.584 (0.554, 0.614)	0.576 (0.546, 0.606)	0.619 (0.591, 0.647)	0.608 (0.580, 0.635)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Calibration x^2	33.723	37.781	15.959	11.221	24.190	33.681
P-value	< 0.001	< 0.001	0.043	0.189	0.002	< 0.001

C statistics, Harrell's C statistics; CI, confidence interval; FRS, Framingham risk score.

Table 5
Comparison of discrimination and calibration of China-PAR and FRS (sensitivity analysis).

Statistic	Total		Male		Female	
	China-PAR	FRS	China-PAR	FRS	China-PAR	FRS
C (95% CI)	0.615 (0.595, 0.635)	0.607 (0.586, 0.627)	0.585 (0.555, 0.615)	0.577 (0.547, 0.607)	0.620 (0.593, 0.648)	0.609 (0.582, 0.637)
P-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Calibration x^2	34.383	40.331	16.117	11.591	24.327	39.125
P-value	< 0.001	< 0.001	0.041	0.170	0.002	< 0.001

C statistics, Harrell's C statistics; CI, confidence interval; FRS, Framingham risk score.

Discussion

Calibration of risk prediction models and assessment of CVD risk directly impacts risk stratification and the subsequent implementation of interventions.[26] The use of CVD risk prediction models to assess future CVD risk has become an important approach to preventing CVD events. The sex-specific China-PAR equations provide a valuable tool for identifying high-risk individuals and matching the intensity of preventive interventions to an individual's absolute risk of CVD.[21] The FRS has had a profound impact on the prevention of CVD since its release;[8] however, with regional and ethnic differences, prediction tools developed by foreign cohorts are often not applicable to the Chinese population.[27,28]

Irrespective of the performance of various tools, studies have shown that physicians should consider multiple CVD risk factors rather than a single risk factor, as interventions on multiple influencing factors can reduce the risk of CVD by up to 55%.[29] In China, hypertension is an important risk factor for CVD, with high prevalence and incidence; however, there are low rates of awareness, control and treatment,[30] therefore, it is important to take measures to control multiple risk factors for hypertension. This study was conducted to compare China-PAR against FRS in predicting the 10-year CVD risk in hypertensive populations in Jiangsu Province to provide a reference for CVD prevention. The results show that in both models, the distribution of 10-year CVD risk varied by gender and risk level; more than 80% of men and about half of women were classified as high risk. These ratios were greater than those in the Yue et al.'s study (high risk 16.92% in China-PAR),[31] which may be because participants in the current FCSH study were hypertensive with higher blood pressure, WCs and BMI values.

The current results indicate that the China-PAR and FRS may not have ideal discriminatory ability (C statistics) to identify individuals who are at high risk of CVD. Several factors might explain this moderate discriminatory ability. First, although the China-PAR model was developed in 2016, data on the derivation cohort were collected in 1998; furthermore, the original Framingham cohort was established in 1948, whereas FCSH data started in 2010. In fact, the predictive models might be slightly outdated because the management of CVD risk factors has evolved considerably in the past 20 years. Second, FCSH participants were older than China-PAR participants (58.3 vs 48.6 years). In addition, FCSH participants had higher SBP, TC and WC, as well as a higher use of antihypertensive medication. Moreover, compared with the China-PAR and FRS models, the follow-up duration of the FCSH was relatively short.

The China-PAR and FRS performed better in males than in females in terms of calibration. The results from Tang et al.[5] also showed that using the China-PAR model resulted in good agreement between the predicted risk of CVD and the actual incidence, especially in the male population, which may be ascribed to biological and gender differences in CVD risk factors (e.g. the effect of female-specific risk factors, such as menopausal status on CVD was not considered in the model).[32] Further studies are required to add sex-specific risk factors to the risk assessment model, and this should be verified in a large population to provide more precise and targeted guidance for the prevention and control of CVD in the population.

The results showed that China-PAR and FRS models both overestimated CVD risk. This may be because study participants were hypertensive patients and the data included in the model were only baseline survey data, not dynamic changes (e.g. individuals may obtain early diagnosis and improve the control of CVD risk factors). In addition, the study cohort recruited for building the predicted model was young and did not reflect the current prevalence of CVD risk factors. Most results from external validation studies also indicated that the China-PAR tended to overestimate CVD risk.[5,21] A prospective cohort study in Beijing showed that China-PAR overestimated the atherosclerotic CVD (ASCVD) risk by 22.2% and 33.1% for men and women, respectively.[5] Similarly , the Chinese Study of the Community Intervention on Metabolic Syndrome cohort showed that China-PAR overestimated the risk of ASCVD by 12.0% in men and 27.5% in women.[21] However, a study conducted in a Mongolian population of 2589 participants demonstrated that the China-PAR underestimated the Mongolian CVD risk.[33] This discrepancy in performance of the China-PAR model between Chinese Mongolian and Han populations may be attributed to different genetic determinants and environmental exposures; for example, one study has found that the Mongolian population have more susceptibility to CVD than the Chinese Han population.[34] In addition, the proportion of current smokers in Mongolian participants and the prevalence of hypertension were higher than in the Chinese Han cohort.[27] Therefore, the applicability of the China-PAR model needs to be verified in more external populations and combined with characteristics of new risk factors to improve and perfect the model. The clustering of multiple risk factors has more detrimental cardiovascular effects than a single risk factor.[35,36]

Similarly, the results from the FRS model in the present study also showed an overestimation of CVD risk, and the effect was more pronounced than in the China-PAR model. These findings are similar to those of Sun et al.[37] who assessed the 10-year average risk of CVD among residents aged >40 years in Guiyang according to China-PAR and FRS; predicted risks were 1.83% and 4.93%, respectively, which showed the overestimation effect of both models. Moreover, a prospective national cohort study also showed an overestimation of the FRS model in 5453 adults aged 40–74 years in six Australian states and the Northern Territory.[38] Another study showed that the risk of CVD in Mongolia was as high as predicted in the FRS model; this may be because the Mongolian population maintain traditional dietary habits, including eating more saturated fats, and have other CVD risk factors compared with the Chinese Han population, which puts them at a higher risk of developing CVD.[33,39]

Strengths and limitations

The main strength of this study was the large-scale prospective cohort study design, with a representative population of 10,498 individuals, and consecutive 10-year follow-up. In addition, in the regression analysis, this study controlled for other possible influencing factors not included in the model and adjusted for

comprehensive confounding factors, as far as possible. In addition, participants recruited in the study cohort were hypertensive patients; these individuals are at high risk of CVD and have rarely been studied previously in this context. This is the first study to use representative models of China-PAR and FRS to predict CVD risk in the hypertensive population.

There were some limitations to the present study. First, the mean follow-up time of our study was 8.3 years, which less than the 10-year period predicted by the risk prediction models. This may be one of the reasons for overestimation of CVD risk in this study population. Second, some uncorrected confounding factors may not be taken into account, such as the types and numbers of antihypertensive drugs, which may lead to false estimates in the results. In addition, this study was in a hypertensive population in Jiangsu Province; thus, the results may not represent the status of hypertensive populations in other areas. Caution should be taken when extrapolating the results to other areas, and further independent verification is needed. Last, but not least, the included participants were those who signed the informed consent and volunteered to participate in the follow-up, which may lead to a selection bias; however, this study used survival analysis and sensitivity analysis to reduce any bias.

Conclusions

The China-PAR and FRS models overestimated the risk of CVD for participants in this study. In addition, the degree of discrimination was not ideal, and both models performed better in males than in females in terms of calibration. The results of this study suggest that a more suitable risk prediction model should be established according to the characteristics of the hypertensive population in Jiangsu Province.

Author statements

Acknowledgements

The authors thank Pin Lin, Lan Cui and Pengfei Luo (Department of Chronic Non-communicable Disease Control, Jiangsu Provincial Center for Disease Control and Prevention) for their constructive suggestions and the technical support. The authors thank all the colleagues involving in this survey from Peixian, Haian, Lianshui, Sihong County and Jianye District Center for Disease Control and Prevention.

Ethical approval

All participants signed the informed consent form, and the study protocol was approved by the ethical review committee of the Jiangsu Province Center for Disease Control and Prevention (SL2015-B004-01).

Funding

This study was supported by the Projects in the Chinese National Science and Technology Pillar Program during the 12th Five-year Plan Period, China (2011BAI11B01); and Chinese National Specific Fund for Health Research in Public Interest, China (200902001); and Jiangsu Province Health Research Project (H201224)

Competing interests

The authors declare that they have no conflicts of interest.

Data availability

The authors can provide the data request.

Author contributions

X.C. contributed to data curation and interpretation, formal analysis, visualisation, and writing the original draft. Q.T. contributed to data curation, investigation, formal analysis, and writing the original draft. D.W. contributed to conceptualisation, investigation, and reviewing and editing. J.L. contributed to conceptualisation, investigation, and reviewing and editing. Y.Q. and Y.Z. reviewing and editing. Q.X. reviewing and editing, funding acquisition, and supervision. All authors gave final approval of the version to be published and agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Public Health 220 (2023) 172–178

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Estimation of the size of the COVID-19 pandemic using the epidemiological wavelength model: results from OECD countries

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ARTICLE INFO

Article history:
Received 9 December 2022
Received in revised form
17 March 2023
Accepted 12 May 2023
Available online 16 May 2023

Keywords:
COVID-19
OECD
Extended wavelength
Epidemiological model
Pandemic
Epidemic

ABSTRACT

Objectives: This study aimed to simplify the previously developed epidemiological wavelength model and to expand the scope of the model with additional variables to estimate the magnitude of the COVID-19 pandemic. The applicability of the extended wavelength model was tested in Organisation for Economic Cooperation and Development (OECD) member countries.

Study design: The epidemiological wavelengths of OECD member countries for the years 2020, 2021 and 2022 were estimated comparatively, considering the cumulative number of COVID-19 cases.

Methods: The size of the COVID-19 pandemic was estimated using the wavelength model. The scope of the wavelength model was expanded to include additional variables. The extended estimation model was improved by adding population density and human development index variables, in addition to the number of COVID-19 cases and number of days since the first case reported from the previous estimation model.

Results: According to the findings obtained from the wavelength model, the country with the highest epidemiological wavelength for the years 2020, 2021 and 2022 was the United States ($W_e = 29.96$, $W_e = 28.63$ and $W_e = 28.86$, respectively), and the country with the lowest wavelength was Australia ($W_e = 10.50$, $W_e = 13.14$ and $W_e = 18.44$, respectively). The average wavelength score of OECD member countries was highest in 2022 ($W_e = 24.32$) and lowest in 2020 ($W_e = 22.84$). The differences in the periodic wavelengths of OECD countries were analysed with the dependent *t*-test for paired samples in two periods, 2020–2021 and 2021–2022. There was a statistically significant difference between wavelengths in the 2020–2021 and 2021–2022 groups ($t(36) = -3.670$; $P < 0.001$).

Conclusions: Decision-makers can use the extended wavelength model to easily follow the progress of the epidemic and to make quicker and more reliable decisions.

Introduction

COVID-19, which was first seen in Wuhan, China, in December 2019, spread throughout the world and was declared a pandemic by the World Health Organisation (WHO).[1–3] The COVID-19 pandemic, which can cause pneumonia in patients, damage organs, such as the liver, kidneys and heart, as well as organ systems, such as the immune system, has become a global public health crisis.[4–8]

Studies to determine the size and spread of the epidemic have increased significantly, especially during the pandemic period. By determining the spread and speed of the epidemic with epidemic models, the current situation and future trends of the epidemic can be revealed. The results from these studies help decision-makers, at macro and micro levels, to make decisions regarding public health strategies. Traditional epidemiological models used to understand the epidemiological features and transmission dynamics of the COVID-19 epidemic are the common mathematical models used to reveal the dynamics of infectious diseases. Of these, the SIR model consists of three components: S (susceptible), I (infected) and R (recovered) individuals.[9–12] The SEIR model, which is the expanded version of the SIR model, consists of four components: S (susceptible), E (exposed), I (infected) and R (recovered) individuals.[13,14] These compartment models were expanded by researchers and used to model the COVID-19 epidemic.[15–18,40,41] However, most of these models only use case numbers as the input variable, which does not provide a realistic representation of the general course of the epidemic. Therefore, to provide a more accurate estimate of the

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https://doi.org/10.1016/j.puhe.2023.05.013
0033-3506/

course of the epidemic, socio-economic and demographic conditions of the specific country or region should also be considered as inputs in the models.

This study aimed to simplify the previously developed epidemiological wavelength model[19] and to expand the scope of the model with additional variables to estimate the magnitude of the COVID-19 pandemic. The estimation model, which was expanded on the basis of cumulative COVID-19 cases since the emergence of the first case, was tested in Organisation for Economic Cooperation and Development (OECD) member countries.

This study aimed to go beyond traditional epidemiological rates, such as death rates and prevalence, and provide measurable results to decision-makers from a single source. This study determined the size of the COVID-19 pandemic using the estimation model in OECD member countries.

Methods

Data sets used for model development

Three different data sets were used to test the estimation model, as follows: (1) the first data set, obtained from the Human Data Exchange,[20] included confirmed COVID-19 cases in the world; (2) the second data set was the human development index (HDI) published by the United Nations (UN) Development Programme;[21] and (3) the last data set consisted of the population density per square kilometre, published by UN, Department of Economic and Social Affairs, Population Division.[22] The population density information consisted of the data set published as of 1 June each year by the Department of Economic and Social Affairs, Population Division. The data sets having 'csv' and 'xlsx' extensions were combined using data mining techniques. Microsoft Excel 2016[23] and mainly R programming language[24] were used in the data analysis and model development stages. Confirmed COVID-19 cases followed a cumulative course, and the data set included the number of cases of 37 OECD member countries, excluding Korea. Korea was excluded from the analysis because of the administrative division of the country of Korea in other data sets. Confirmed COVID-19 cases from the first COVID-19 case to 5 November 2022 (including this date) were evaluated in the expanded estimation model. The model was tested on the basis of cumulative case numbers. The reason for calculating the wavelengths of countries based on the cumulative number of COVID-19 cases was because of the fact that some countries had missing data on daily new case numbers.

The dependent *t*-test for paired samples, which is a parametric statistical test, was used to evaluate whether the periodic wavelengths of OECD countries, obtained from the wavelength model, were statistically different between 2020–2021 and 2021–2022. In addition, effect size was calculated using Cohen's d statistics[25] for the dependent *t*-test for paired samples, which demonstrates the practical importance of the quantitative study.[26] The *P*-value indicates whether there was an effect, in other words, statistical significance. However, statistical significance does not reveal the size of the effect. Therefore, both practical significance (effect size) and statistical significance should be evaluated and reported together.[27,28] Effect size is divided into three categories:[25] small effect ($d = 0.2$), medium effect ($d = 0.5$) and large effect ($d = 0.8$).

Theoretical framework of estimation model

Previous epidemiological wavelength models[19] that estimate the size of an epidemic have been simplified to a single model, and new variables were included. The wavelength model focused on the following four main input variables that are easy to obtain and understand: (1) the number of cases, (2) the time elapsed since the onset of the first case, (3) the HDI, and (4) the population density. The variables added to the extended model were the HDI and population density per kilometre, which include data from the periods 2019–2021. These two variables have been used in previous studies to analyse and evaluate epidemics, including one study using HDI[21] and a study conducted by the WHO in 2016 using population density per kilometre.[29] In the WHO study, epidemics in the African region were mapped, and variables that correlate with outbreaks were addressed.[29] Another study using the population density variable was the COVID-19 study conducted in 2021 by Pasha et al.[30] In addition, Md Iderus et al.[31] revealed that the risk of transmission of COVID-19 is higher in densely populated areas in Malaysia. In other words, there was a strong positive correlation between population density and risk of transmission. A similar study was conducted in Algeria by Kadi and Khelfaoui,[32] where a strong positive correlation was found between population density and the risk of the COVID-19 transmission.

The reason for including HDI and population density in the expanded model was that these are determinant variables in the spread of an epidemic, and there is a strong correlation between the spread of the epidemic and the population density, as reported in the literature. To determine the distance covered by the epidemic over time, the other two variables (i.e. the number of cases and the time elapsed since the beginning of the first case) were included in the model. The data sets of all these variables can be easily accessed; thus, the extended model aimed to present the current epidemic situation in a valid, reliable, inclusive and easily applicable way.

Parameters used in the wavelength model are presented in the supplementary material (Appendix 1). The parameters from the previous model and the parameters in the expanded model are as follows:[19] number of confirmed cumulative cases, number of days since the first case reported, the ratio of within the total day of the year of number of days since the first case reported and natural logarithm. As in the previous model, the reason for using the natural logarithm in the new model is the normalization of wavelength lengths.

With this new model, which was simplified and expanded with additional variables, a compact design that effectively and easily presents the current epidemic situation was created. The estimation equation used for the wavelength model is given in the supplementary material (Appendix 2). The size of the pandemic was estimated using W_e generated from the parameters in Appendix 1. The higher the positive value of W_e, the higher the wavelength and impact area of the pandemic.

Results

The epidemiological wavelength of the pandemic was estimated in the context of OECD countries based on cumulative confirmed cases of COVID-19. The findings from the extended wavelength estimation model are presented by wavelength in descending order. Note: since Turkey's name was changed to Türkiye, according to the decision taken by the UN, Türkiye was included in the figures as the country name.[33]

According to Fig. 1, the country with the highest wavelength in 2020 was the United States with 29.96 W_e, whereas the country with the lowest wavelength was Australia with 10.50 W_e. In the same period, the second and third countries with the highest wavelength were Italy and Germany, respectively. The scores of the three countries with the highest wavelength were much higher than the OECD average of 22.84 W_e. The number of countries below the OECD average in 2020 was 15.

In Fig. 2, the COVID-19 epidemiological wavelengths for 2021, based on the cumulative case numbers of OECD member countries, are given. In 2021, the three countries with the highest wavelengths

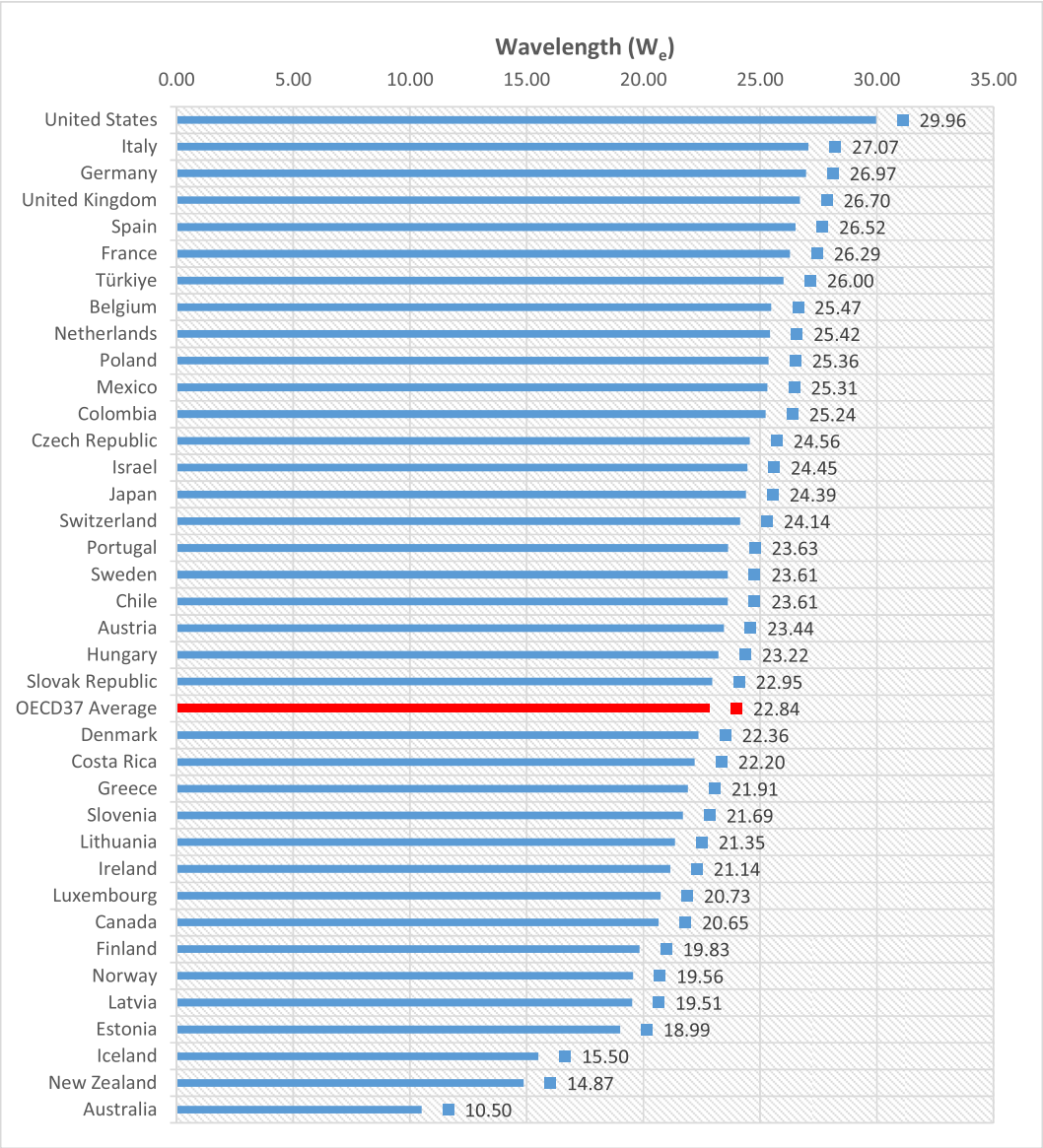

Fig. 1. COVID-19 epidemiological wavelengths in OECD countries, 2020.

in OECD member countries were the United States, the United Kingdom and France. The three countries with the lowest wavelengths were Australia, New Zealand and Iceland. The number of countries below the OECD average of 23.20 W_e was 15, and the number of countries above the average was 22.

Fig. 3 shows the COVID-19 epidemiological wavelengths in 2022 of OECD member countries. In 2022, the three countries with the highest wavelengths were the United States, Germany and France. The three countries with the lowest wavelengths were Australia, Iceland and Canada. The number of countries having a score below the OECD average of 24.32 W_e was 17, and the number of countries above the average was 20.

When OECD wavelength averages were compared by years, the year with the highest average wavelength was 2022. Thus, this indicates that the size of the epidemic increased over time.

To determine whether the differences in the wavelengths in the 2020, 2021 and 2022 periods obtained from the wavelength model were statistically different from each other, the dependent *t*-test for paired samples was performed. Differences in the periodic wavelengths of OECD member countries were examined in two groups, 2020–2021 and 2021–2022.

There was a statistically significant difference between the differences in wavelengths between 2020–2021 and 2021–2022 ($t(36) = -3.670$; $P < 0.001$; Table 1). At the same time, there was a positive correlation between the differences in wavelengths in the 2020–2021 and 2021–2022 periods, and this finding was statistically significant ($r = 0.416$; $P < 0.01$).

The effect size was calculated using the Cohen's *d* statistic and was found to have a medium effect ($d = -0.603$). The effect size shows that the difference between the two groups was large enough to be noticed.[25]

Discussion

This study aimed to estimate the size of the COVID-19 using the extended wavelength model. The scope of the extended wavelength model was expanded with additional variables, and the model was tested in the context of OECD member countries. The

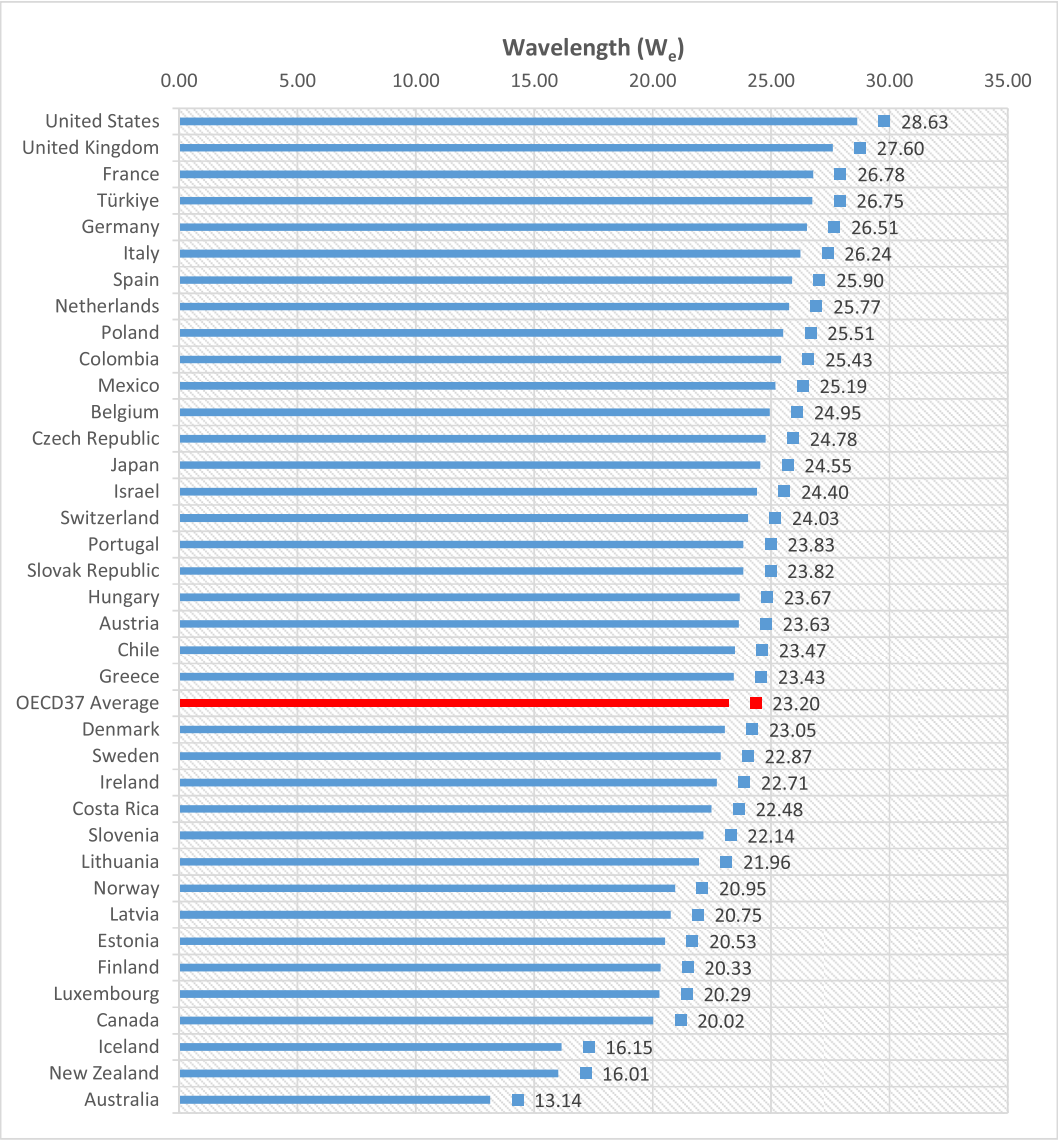

Fig. 2. COVID-19 epidemiological wavelengths in OECD countries, 2021.

results from the extended wavelength model provide information so that decision-makers can easily follow the progress of the epidemic and make instant, more reliable decisions.

The findings obtained from the extended wavelength model showed that the COVID-19 epidemiological wavelengths for the years 2020, 2021 and 2022 differed. One of the most important reasons for this may be that the reported cumulative number of COVID-19 cases varied by country. In addition, the HDI (h_i), time (t_r) and population density (p_d) parameters in the expanded model showed less variability than the number of cases (c_c) parameter. For these reasons, the case number parameter played a more decisive role in the differentiation of wavelengths produced from the model. The differences in the reported number of cases per country may be because of the following reasons: lack of capacity and infrastructure in health systems; lack of access to disease diagnosis and test kit; hesitancy and disinformation against vaccination; low vaccination rates; lack of access to vaccines; inadequate and inconsistent public health measures; and insufficient consideration of proven public health and social measures.[42]

When the results from the wavelength model were evaluated separately by year, there were several prominent findings. In 2020, the difference between the maximum wavelength and the minimum wavelength in OECD countries (i.e. the range was 19.47 W_e) and the population variance was 13.85. This value is higher than the interval values for 2021 (range = 15.49 W_e, variance = 10.39 W_e) and 2022 (range = 10.42 W_e, variance = 6.55 W_e). Therefore, the results show that the variability in wavelengths was at its highest level in 2020, whichbecause of the fact that OECD countries were not sufficiently prepared for the pandemic. The reasons for the variations in wavelengths between countries are as follows: an inadequate number of diagnostic tests at the beginning of the COVID-19 epidemic; delayed introduction of COVID-19 vaccines and hesitation about the effectiveness of vaccines; inadequacies in crisis management; delayed implementation of public health and social measures or failure to properly implement public health and social measures; and socio-economic differences between countries.[43–48,52]

In 2021, the wavelength variance of OECD countries decreased compared with 2020. This could be because of the fact that there

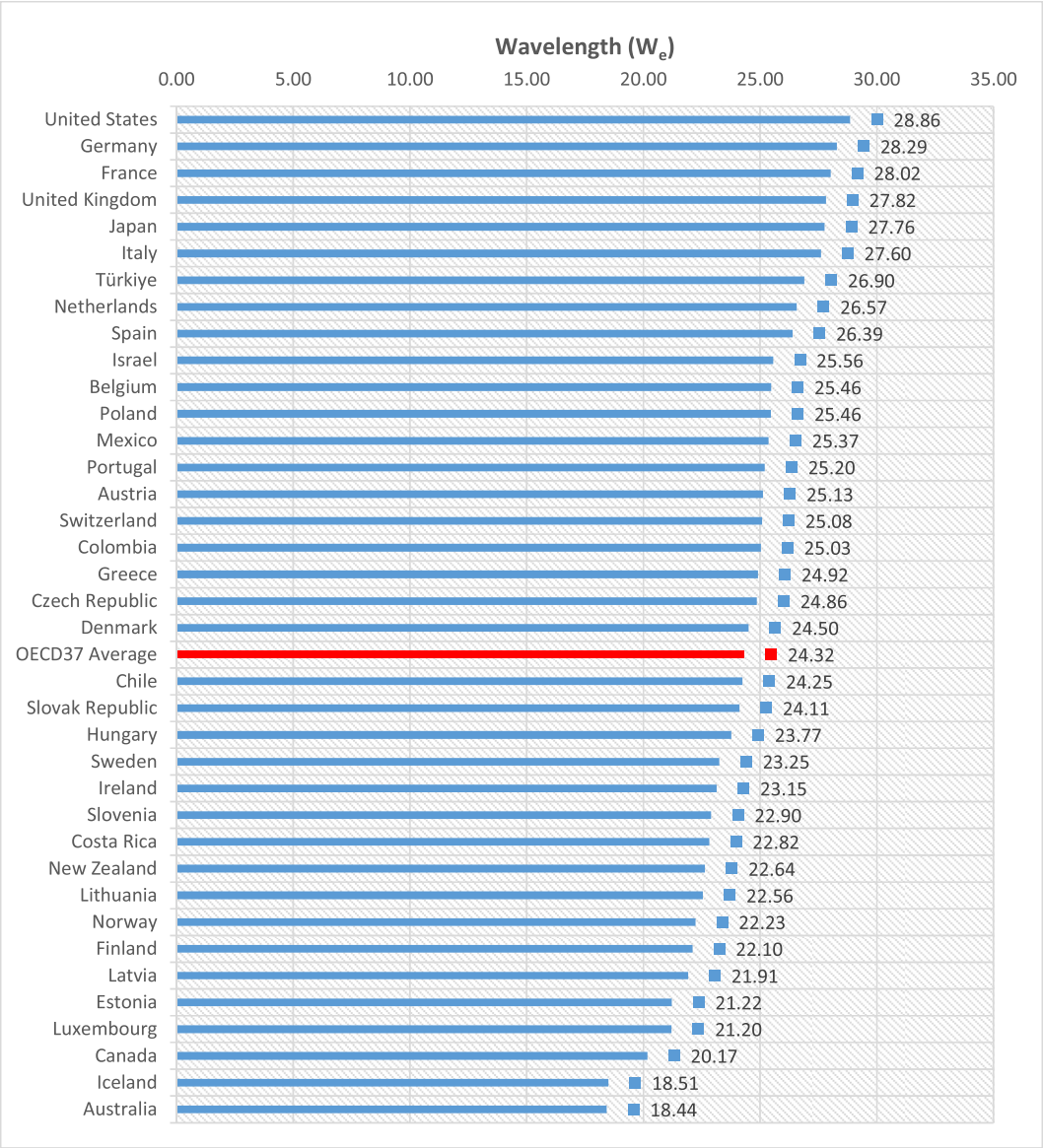

Fig. 3. COVID-19 epidemiological wavelengths in OECD countries, 2022.

was an increased awareness about COVID-19 in 2021, public health measures had reached a certain level and vaccination campaigns had started. However, it should be noted that the public health measures taken to mitigate the spread of COVID-19 differed between countries (and even within countries by region), and there were differences in implementation.[49]

In 2022, the population variance of wavelengths (variance = 6.55 W_e) was the lowest in OECD countries. The low variance in 2022 is thought to be because of the increase in vaccination within countries and the attainment and settlement of public health measures.[50,51] However, the epidemiological wavelength for the year 2022 was higher than in the other years. The main reasons for this were the increase in the cumulative number of COVID-19 cases and the cumulative increase in the number of days since the first reported case.

In terms of countries, the United States was the OECD member country with the highest COVID-19 epidemiological wavelength for all years. This may be because the United States, at the federal level, had an inadequate response to the COVID-19 pandemic. Chronic ongoing underinvestment in public health institutions for epidemic control was an important factor in the increase in the number of cases and deaths. The fragmented nature of the US healthcare system is not conducive to managing a pandemic in an effective and coordinated manner. In addition, hospitals did not have the

Table 1
Results from statistical analysis of the differences in wavelengths over two periods

Period	Mean	*n*	Standard deviation	Correlation coefficient (*r*)	*t*	df	*P*
2020–2021	0.354	37	0.808	0.416			0.010
2021–2022	1.127	37	1.386				
Pair 2020–2021 and 2021–2022	0.773		1.281		−3.670	36	0.001

capacity to meet the flow of COVID-19 patients.[34] Political authorities did not take a clear and consistent stance during the pandemic and did not encourage the necessary changes in the fight against the pandemic. Efforts to mobilise public health and health infrastructure were also hampered by political and economic conflicts of interest.[35] The unpreparedness for the pandemic in the United States and many other countries is a general reason for the failure to control COVID-19.[36]

In contrast, Australia was the OECD member country with the lowest COVID-19 epidemiological wavelength for all years. According to the estimation model, one of the main reasons for this result is that Australia has the lowest population density per ilometre among OECD member countries. As population density increases, the contagiousness of the epidemic also increases.[37,38] Population densities in Australia for 2019, 2020 and 2021 were 3.301, 3.341 and 3.374 people per square kilometre, respectively.[22] Other reasons for Australia having the lowest wavelengths could be as follows: public policy; and guidelines and practices of government at the national level were well coordinated during COVID-19, including the provision of comprehensive testing service, the successful establishment of a quarantine regime with patient isolation at the national level.[39]

Although indicators, such as fatality rate, prevalence and incidence, which are the main epidemiological indicators, give an idea about the spread of the epidemic, they do not provide information about the scale and size of the epidemic. For example, if the fatality rate of two countries is the same in different periods, it can be said that the fatality rate of the two countries is equal; however, this does not reveal the size of the epidemic because both countries could have different numbers of cases and deaths at different time intervals. The wavelength model is designed to overcome this problem. The number of cases and the time from the first case were therefore included in the extended model. Population density was also added to the model because the epidemic has the potential to spread more rapidly in densely populated areas. Thus, the epidemiological wavelength increases as population density increases. In addition, HDI was also included in the extended wavelength model to capture data on knowledge, having a long and healthy life and a good standard of living, which are the basic dimensions of human development.[21]

In this study, unlike the previous wavelength model, the current model was reduced to a single equation and expanded by adding additional variables. It was also tested in the context of OECD member countries to determine the applicability of the extended wavelength model. By using the epidemiological wavelength model, the progress of the epidemic can be followed more closely, in a practical way, by revealing both daily and cumulative wavelengths from the day of the first COVID-19 case in countries or regions. In this way, decision-makers can make faster and more reliable decisions because they have a better understanding of the progress of the epidemic. If the extended model is to be used to compare regions within a country, the HDI parameter in the denominator of the model can be removed as the HDI data are not available by region.

Limitations

This study aimed to determine the current size of the COVID-19 pandemic, but the wavelength findings do not forecast the future of the pandemic. However, the results can be used in future estimation studies using different methods. The evaluation of wavelengths specific to OECD countries is restricted because of limited data; therefore, the interpretation of the wavelength results could not be covered in depth in this study. Data on the extent of the measures taken by the countries against the epidemic would enable wavelength findings to be considered comprehensively in future research. In addition, because the number of new COVID-19 cases is underreported in most OECD member countries, wavelengths are estimated by cumulative cases.

Directions for future research

Similar epidemiological wavelength studies can be carried out in other regions, especially in the European region, and the wavelengths in these regions can be compared within and among themselves. Global and continental comparisons can also be made by conducting similar studies to the current research that include all countries in the world. The results from these extended studies would provide a global estimation of the size and progress of COVID-19 pandemic. Although this study is specific to COVID-19, it will also shed light on measuring the size of other outbreaks.

Author statements

Ethical approval

Ethical approval has not been obtained as the data are publicly available.

Funding

The authors declared that this study has received no financial support.

Competing interests

The authors declared no conflict of interest.

Author contributions

The authors have contributed equally.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.05.013.

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Public Health 220 (2023) 43–49

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Evaluating the effects of minimum unit pricing in Scotland on the prevalence of harmful drinking: a controlled interrupted time series analysis

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ARTICLE INFO

Article history:
Received 13 February 2023
Received in revised form
6 April 2023
Accepted 21 April 2023

Keywords:
Alcohol drinking
Alcohol dependence
Evaluation study
Policy analysis
Minimum unit pricing
Harmful drinking

ABSTRACT

Objectives: In May 2018, the Scottish Government introduced a minimum unit price (MUP) for alcohol of £0.50 (1 UK unit = 8 g ethanol) to reduce alcohol consumption, particularly among people drinking at harmful levels. This study aimed to evaluate MUP's impact on the prevalence of harmful drinking among adults in Scotland.

Study design: This was a controlled interrupted monthly time series analysis of repeat cross-sectional data collected via 1-week drinking diaries from adult drinkers in Scotland (N = 38,674) and Northern England (N = 71,687) between January 2009 and February 2020.

Methods: The primary outcome was the proportion of drinkers consuming at harmful levels (>50 [men] or >35 [women] units in diary week). The secondary outcomes included the proportion of drinkers consuming at hazardous (≥14–50 [men] or ≥14–35 [women] units) and moderate (<14 units) levels and measures of beverage preferences and drinking patterns. Analyses also examined the prevalence of harmful drinking in key subgroups.

Results: There was no significant change in the proportion of drinkers consuming at harmful levels (β = +0.6 percentage points; 95% confidence interval [CI] = −1.1, +2.3) or moderate levels (β = +1.4 percentage points; 95% confidence interval = −1.1, +3.8) after the introduction of MUP. The proportion consuming at hazardous levels fell significantly by 3.5 percentage points (95% CI = −5.4, −1.7). There were no significant changes in other secondary outcomes or in the subgroup analyses after correction for multiple testing.

Conclusions: Introducing MUP in Scotland was not associated with reductions in the proportion of drinkers consuming at harmful levels but did reduce the prevalence of hazardous drinking. This adds to previous evidence that MUP reduced overall alcohol consumption in Scotland and consumption among those drinking above moderate levels.

Introduction

The Scottish Government introduced a minimum unit price (MUP) for alcohol on 1 May 2018. This means retailers in Scotland cannot sell alcohol to consumers for less than £0.50 per unit (1 UK unit = 8 g/10 mL ethanol). In 2018, 44% of off-trade alcohol units were sold below £0.50 per unit in Scotland.[1,2] The associated legislation includes a 'sunset clause' that requires MUP to end after 6 years unless the Scottish Parliament votes for it to continue.[3] To inform this vote, the Scottish Government commissioned NHS Health Scotland (now part of Public Health Scotland [PHS]) to conduct a wide-ranging evaluation of MUP and report its findings in mid-2023.[3] PHS commissioned the present study as part of that evaluation to provide evidence of the impact of MUP on people drinking at harmful levels, typically defined in the United Kingdom

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https://doi.org/10.1016/j.puhe.2023.04.019

as women consuming more than 35 units of alcohol per week and men consuming more than 50 units per week.

The Scottish Government and public health advocates argue that MUP is a well-targeted policy that concentrates price increases on the cheapest alcohol that is disproportionately purchased by those drinking at hazardous levels (i.e. 14–35 units a week for women or 14–50 units a week for men; approximately 20% of the population) or harmful levels (approximately 5% of the population).[4,5] These arguments are informed by model-based appraisals that suggest MUP leads to larger reductions in alcohol consumption among those drinking at harmful levels than those drinking at moderate levels.[4,6,7] They are also informed by evaluations of similar policies in Canada, where increases in minimum prices led to reductions in deaths and hospitalisations for conditions closely associated with heavy drinking (e.g. alcoholic liver disease).[8,9] However, evidence in the wider literature on alcohol pricing is more equivocal, with some studies suggesting heavier drinkers make smaller reductions in their alcohol consumption than other drinkers when prices increase,[10,11] whereas others suggest the opposite.[12] Researchers usually attribute lower price responsiveness among heavier drinkers to them switching their purchasing to cheaper products instead of buying less when prices rises, a behaviour that MUP hinders by preventing the sale of products at a low cost per unit of alcohol.

Evidence is therefore required on whether MUP effectively reduces harmful alcohol consumption. Evaluation findings to date suggest the policy was implemented largely as intended and reduced off-trade alcohol sales in Scotland by 3.5%.[1,13] However, analyses of changes in alcohol consumption among heavier drinkers report mixed findings. Analyses of household panel data show that the fifth of households that purchased most alcohol pre-MUP reduced their purchasing by more than the remaining four-fifths after the policy was introduced.[14,15] In contrast, an analysis of market research drinking diary data suggests MUP led to reduced alcohol consumption for the lightest drinking 90% of women but no statistically significant change for the highest consuming 10%, whereas consumption among men did not change significantly except for an increase among the highest consuming 5%.[16] However, these previous studies were limited by short pre- and post-intervention time series (e.g. 2015–2018) and in some cases had full-year breaks in the series where data were not available.[14–17] They also focus only on levels of consumption in different groups rather than the overall prevalence of hazardous and harmful drinking across the population.[14–16]

This study aims to provide further evidence regarding the impact of MUP on people drinking at harmful levels by (1) evaluating the impact of the policy on the prevalence of harmful drinking among adult alcohol consumers in Scotland, (2) also evaluating the impact of MUP on the prevalence of moderate and hazardous drinking (see Methods for definitions), and (3) developing understanding of the mechanisms of any identified effects by evaluating the impact of MUP on the beverage preferences and drinking occasion dynamics (e.g. occasions per week) of people drinking at harmful levels and of how impacts differ across sociodemographic groups.

Methods

Research design

The study used a controlled interrupted time series design based on repeat cross-sectional survey data. Open Science Framework pre-registration: https://osf.io/xe89r.

Data

We used data from the market research company Kantar's Alcovision survey. Alcovision is a continuously collected online survey of adults (aged ≥18 years) who are residents in Great Britain. It draws weekly cross-sectional quota samples based on age, sex, social grade, and geographic region from Kantar's online managed-access panel. All participants gave informed consent.

Alcovision oversamples Scotland residents and 18- to 34-year-olds to allow detailed analyses of these smaller populations. We constructed weights using a raking technique to match social grade, geographic region, age, and sex to the UK Census.[18]

Alcovision includes a short behavioural survey and a detailed 7-day retrospective drinking diary where participants report the characteristics of their drinking occasions over the last week working back in time from the day before the survey is completed. The resulting data set also includes sociodemographic characteristics collected separately by the managed-access panel. Kantar defines an occasion as a significant time, such as lunchtime, and participants can report a maximum of two on-trade (e.g. pub) and two off-trade (e.g. home) occasions each day.

The analytical sample comprises respondents between January 2009 and February 2020 who report drinking at least once per year and who are residents in Scotland (total $N = 38{,}674$; average monthly $N = 267$) or the neighbouring control area, Northern England, defined as the North-East, North-West, and Yorkshire & Humberside regions (total $N = 71{,}687$; average monthly $N = 494$). We do not use data beyond February 2020 because of the substantial impact of the COVID-19 pandemic on alcohol consumption.[18]

Measures

Minimum unit pricing

We created a binary variable categorising drinking diary weeks starting before 1 May 2018 as preintervention and those starting on or after this date as post-intervention. This means we treat any diary weeks containing dates both before and after 1 May as pre-MUP data, reflecting the potential for alcohol purchased before the introduction of the policy to be consumed afterwards.

Outcome measures

The primary outcome was the proportion of adult drinkers who drink at harmful levels. To align with previous MUP analyses,[6] we defined drinking at harmful levels as consuming more than 35 units of alcohol for women or more than 50 units for men across the diary week.

We calculated consumption in the diary week by summing the units consumed in each drinking occasion. Participants report the amount consumed in 'serves', which we converted to units by combining information on the packaging size (e.g. 440 mL can) of each serving with additional information we collected online on products' alcoholic content (alcohol by volume [ABV]). Where product-level ABV information was unavailable, particularly for wines, we used standard beverage-specific assumptions (approximately 10% of products; Supplementary Table 1). As a small number of respondents report unrealistically high levels of alcohol consumption within some occasions, we applied a capping process following consultation with clinicians.[18] We sequentially capped the maximum units reported for each single drink type on an occasion, each occasion, and each day to 40 (equivalent to a litre bottle of whisky). This process constrains weekly consumption to a maximum of 280 units.

There were 10 planned secondary outcomes split across three groups: other consumption levels, beverage types associated with harmful drinking in Scotland and occasion dynamics. For other consumption levels, we examined change in the proportion of adult drinkers who are (1) drinking moderately and (2) drinking hazardously. For beverage type, we examined change in the mean

proportion of alcohol consumption in the diary week among those drinking at harmful levels that is accounted for by (3) strong beer (≥6% ABV), (4) strong cider (≥6% ABV), (5) vodka and (6) alcohol consumed in the off-trade, as MUP particularly affects the price of these beverage types. For occasion dynamics, we examined change in the mean for people drinking at harmful levels of (7) number of drinking days per week, (8) number of units per drinking occasion, (9) maximum number of units in a single drinking occasion during the week and (10) the number of drinking occasions involving drinking alone. In addition to these measures of occasion dynamics, we conducted an unplanned secondary analysis of change in mean number of units per week for people drinking at harmful levels.

Subgroup analyses

We also examined change in the proportion of adult drinkers who are consuming at harmful levels within the following subgroups: married or living with a partner, living with one or more children aged <16 years, and social grade DE (semiskilled and unskilled manual workers, state pensioners, casual and lowest grade workers, and unemployed with state benefits only). Social grade is an occupation-based measure of socio-economic status based on the National Readership Survey. We selected these groups because of interest from policy-makers (e.g. living with children) or because prior evidence suggests MUP should particularly impact them (e.g. social grade DE).[6]

Statistical analysis

We used SARIMA models to evaluate the immediate effect of implementing MUP in Scotland on our primary outcome (the proportion of adult drinkers consuming at harmful levels), secondary outcomes, and the proportion within three sociodemographic subgroups drinking at harmful levels.[17]

We analysed monthly time series where possible, considering bi-monthly or quarterly series where the monthly series had zero observations in some periods. This was the case for two secondary outcomes: (1) the mean proportion of harmful drinkers' consumption that was strong beer (bi-monthly) and (2) strong cider (quarterly). Models were adjusted using data from the same period in Northern England and terms for autocorrelation, seasonality and the trend over time. To identify autocorrelation in the model residuals, we used autocorrelation and partial autocorrelation plots, which informed the selection of autoregressive (AR), moving average (MA), and seasonal terms. We then used Akaike information criterion (AIC) and Bayesian information criteria (BIC) statistics to select the most parsimonious model and performed portmanteau (or Q) tests to confirm that model residuals resembled a white noise process. When model residuals did not resemble white noise, we used the Kwiatkowski–Phillips–Schmidt–Shin (KPSS) unit root test and considered integration. To identify potential outliers or breakpoints, we used visual inspection of the outcome data series and included terms to adjust for these where model parsimony was improved.

Following model specification, we calculated sharpened q-values as described by Anderson et al. to adjust for multiple testing.[19] This was an unplanned additional robustness check. We used $\alpha = 0.05$ to determine statistical significance.

Sensitivity analyses

We conducted three planned sensitivity analyses for the primary outcome as follows. First, we moved the intervention point from May 2018 to June 2018 to allow for those drinking at harmful levels to deplete any alcohol stockpiled pre-MUP. Second, the gradual introduction of Universal Credit across the intervention period substantially affected the value and timing of social security payments in the United Kingdom and may have affected the financial position of adults consuming at harmful levels, with subsequent effects on their alcohol purchasing. We controlled for this in a sensitivity analysis by including a covariate in the model that measured the monthly number of households registered for Universal Credit in Scotland.[20] Third, we included an additional term in the SARIMA model to test for a change in the time trend after the implementation of MUP. Our primary analyses assume a step change, in line with modelling undertaken before the introduction of MUP,[4] but it is possible that those drinking at harmful levels changed their behaviour more gradually.

We also carried out further planned and unplanned sensitivity analyses using uncapped estimates of alcohol consumption. These analyses focused on only secondary outcomes affected by the capping process. Specifically, the mean proportion of alcohol consumption in the diary week among those drinking harmfully that is accounted for by strong beer (≥6% ABV), strong cider (≥6% ABV), vodka, and drinking in the off-trade, as well as the average number of units consumed per occasion, maximum number of units consumed during a single occasion in the diary week (all planned) and average number of units consumed per week among those drinking harmfully (unplanned).

All analyses were of weighted data using Stata version 16.

Results

Table 1 presents descriptive statistics for the yearly sample size and trends in outcome measures.

Primary outcome

There was no significant change in the proportion of drinkers consuming at harmful levels in Scotland ($\beta = 0.006$; 95% confidence interval [CI] = −0.011 to +0.023; Table 2, Fig. 1). This finding was consistent across the sensitivity analyses that used the subsequent data point in the series as the intervention point (June 2018), controlled for the rollout of Universal Credit in Scotland and included a term to capture a change in the postintervention trend (Supplementary Table 2).

Secondary outcomes

Immediately after the introduction of MUP, there was a significant reduction in the proportion of drinkers consuming at hazardous levels in Scotland (−3.5 percentage points; 95% CI = −0.054 to −0.017; Table 2, Fig. 1). However, there was no significant change in the proportion of drinkers consuming at moderate levels ($\beta = 0.014$; 95%CI = −0.011 to 0.038). This model controls for a breakpoint in the data series at the beginning of 2017.

There were no significant changes in the mean proportion of alcohol consumption in the diary week that is accounted for by strong beer ($\beta = 0.000$; 95% CI = −0.010 to +0.010), strong cider ($\beta = -0.003$; 95%CI = −0.009 to 0.003), vodka ($\beta = 0.017$; 95% CI = −0.011 to +0.045) or drinking in the off-trade ($\beta = 0.026$; 95% CI = −0.012 to +0.063). These findings were consistent in sensitivity analyses using an uncapped measure of alcohol consumption (Supplementary Table 2).

There were also no significant changes in the patterns of consumption during the diary week for most outcome measures, specifically, the number of drinking days per week, maximum number of units consumed in a single occasion during the week and the number of occasions involving drinking alone, including in sensitivity analyses using uncapped alcohol consumption. The direction of effect indicated a reduction in the mean number of drinking days per week, the mean number of units per occasion and the mean number of units per week for drinkers consuming at

Table 1
Sample size and weighted mean values of outcome measures (2009–2020).

Measure	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020[a]
Sample size												
Total	9989	10,094	10,287	10,484	10,385	10,338	10,162	10,067	8711	9290	9051	1503
Northern England	6489	6508	6604	6879	6781	6724	6615	6565	5687	6023	5860	952
Scotland	3500	3586	3683	3605	3604	3614	3547	3502	3024	3267	3191	551
Proportion of adult drinkers who are consuming at:												
Harmful levels												
Scotland	11.9%	12.1%	13.1%	13.5%	10.8%	9.7%	11.2%	11.9%	9.1%	8.8%	10.1%	9.0%
Northern England	13.5%	11.7%	13.3%	13.2%	11.8%	11.6%	11.6%	11.2%	10.6%	10.0%	9.7%	9.7%
Hazardous levels												
Scotland	29.9%	28.2%	27.7%	29.0%	28.6%	29.3%	26.7%	29.1%	26.7%	23.8%	23.5%	25.9%
Northern England	31.7%	30.2%	30.8%	31.1%	29.9%	29.8%	28.2%	28.3%	28.4%	25.2%	26.5%	25.9%
Moderate levels												
Scotland	58.1%	59.7%	59.2%	57.4%	60.6%	61.0%	62.1%	59.0%	64.2%	67.4%	66.4%	65.1%
Northern England	54.8%	58.1%	55.9%	55.7%	58.3%	58.7%	60.2%	60.5%	61.0%	64.8%	63.8%	64.4%
Mean proportion of harmful drinkers' consumption that is:												
Strong beer (≥6% ABV)												
Scotland	0.9%	0.9%	1.2%	0.5%	2.3%	0.4%	0.3%	0.8%	0.9%	0.6%	1.1%	0.1%
Northern England	1.3%	1.4%	1.5%	0.7%	0.9%	1.1%	0.5%	1.0%	0.8%	0.8%	1.0%	0.3%
Strong cider (≥6% ABV)												
Scotland	0.5%	0.4%	0.8%	0.5%	0.9%	0.8%	0.9%	1.2%	0.5%	0.8%	0.6%	0.2%
Northern England	0.8%	0.7%	0.6%	1.0%	1.1%	1.0%	1.9%	1.1%	0.8%	0.8%	1.1%	1.0%
Vodka												
Scotland	14.9%	16.3%	14.5%	16.3%	15.4%	11.7%	11.9%	12.3%	14.8%	15.3%	14.1%	20.2%
Northern England	6.5%	6.9%	8.8%	8.1%	6.9%	7.9%	7.1%	7.2%	9.8%	9.5%	7.8%	10.4%
Consumed in the off-trade												
Scotland	67.4%	72.9%	72.8%	67.0%	66.8%	69.3%	67.1%	66.4%	69.3%	71.0%	72.4%	69.0%
Northern England	68.5%	67.6%	65.4%	67.3%	66.8%	69.0%	69.6%	67.2%	68.8%	69.9%	71.5%	70.5%
Patterns of harmful drinkers' consumption												
Mean number of drinking days per week												
Scotland	4.2	4.5	4.2	4.0	4.0	4.0	4.1	3.8	3.6	3.4	3.6	3.2
Northern England	4.8	4.9	4.5	4.6	4.5	4.6	4.5	4.5	4.1	4.0	4.0	4.0
Mean number of units per occasion												
Scotland	12.9	12.4	12.5	12.8	13.2	12.6	12.5	13.0	15.0	17.0	14.4	16.5
Northern England	10.9	10.9	11.7	11.3	11.4	11.2	11.5	11.7	13.0	14.0	14.2	13.8
Mean units consumed on the heaviest occasion of the week												
Scotland	23.3	22.6	22.9	23.6	23.9	22.5	22.8	23.8	25.2	26.9	24.2	26.6
Northern England	20.2	20.0	21.6	21.0	20.9	20.7	20.5	21.4	22.7	23.7	23.9	23.8
Mean number of occasions involving drinking alone												
Scotland	1.0	1.2	1.1	1.2	1.2	1.4	1.6	1.1	1.1	1.0	1.2	1.1
Northern England	1.3	1.3	1.2	1.4	1.5	1.5	1.4	1.5	1.4	1.5	1.4	1.5
Mean number of units per week												
Scotland	69.0	68.3	68.6	71.2	69.4	67.0	68.1	69.2	64.5	68.9	63.0	61.2
Northern England	66.0	66.8	67.8	69.1	66.8	68.3	67.1	70.0	68.7	68.4	68.2	70.5
Proportion of adult drinkers who are harmful drinkers in the following population subgroups:												
Married or living with a partner												
Scotland	11.4%	11.7%	12.8%	12.7%	10.5%	8.5%	10.4%	11.4%	9.9%	8.5%	9.6%	8.4%
Northern England	12.8%	12.1%	13.1%	12.7%	11.6%	10.8%	11.0%	10.8%	9.5%	8.7%	9.1%	9.3%
Living with one or more children in the household												
Scotland	12.2%	12.5%	14.6%	16.9%	12.0%	8.6%	11.1%	12.4%	9.8%	9.1%	10.4%	9.3%
Northern England	13.3%	13.2%	13.8%	14.8%	12.6%	12.1%	11.4%	10.1%	10.6%	9.9%	11.9%	9.7%
Lower socio-economic group (DE)												
Scotland	11.4%	12.9%	13.4%	13.2%	12.1%	10.2%	10.9%	9.6%	7.7%	7.7%	8.4%	11.8%
Northern England	12.6%	11.2%	14.1%	13.4%	12.9%	9.7%	11.6%	10.7%	9.9%	11.7%	10.9%	9.9%

[a] January and February only in 2020. All outcome measures are time series of weighted measures constructed using data from self-reported drinking occasions in a 1-week retrospective drinking diary. Consumption levels are based on total units reported. Harmful = 35+/50+ units for women/men. Hazardous = 14–35/14–50 units for women/men. Moderate = 0–14 units. Those in social grade DE are defined as National Readership Survey social grade D or E (semiskilled and unskilled manual workers, state pensioners, casual and lowest grade workers, unemployed with state benefits only).

harmful levels. The magnitude of these reductions was similar to the 3.0–3.5% fall in alcohol sales by volume found in analyses of population-level sales data,[21] although the uncertainty around the effect estimates was high and the direct of effect reversed in sensitivity analyses.

For people drinking at harmful levels, there was a statistically significant drop in the mean number of units consumed per occasion ($\beta = -0.9$ units; 95% CI = −1.651 to −0.091) and mean number of units consumed per week ($\beta = -3.2$ units; 95% CI = −6.076 to −0.283). However, these results were not robust based on the sharpened q-values, which adjust for multiple testing ($q = 0.172$) or the sensitivity analysis using uncapped alcohol consumption, which found no significant change.

Subgroup analyses

There were no significant changes in the proportion of drinkers consuming at harmful levels among those who report being married or living with a partner, living with one or more children in the household or who are in a lower socio-economic group (DE) (Table 2). All model specification details are provided in Supplementary Table 3.

Discussion

The results above suggest the introduction of MUP in Scotland did not lead to a decline in the proportion of adult drinkers consuming alcohol at harmful levels. It also did not lead to any

Table 2
Estimated immediate effects of implementing minimum unit pricing among adult drinkers in Scotland.

Outcome measure	B	95% Confidence interval	*P*-value	*q*-value	*R*-sqr
Proportion of adult drinkers who are consuming at:					
Harmful levels	0.006	−0.011, 0.023	0.500	N/A	33.5%
Hazardous levels	−0.035	−0.054, −0.017	0.000	0.003	30.0%
Moderate levels	0.014	−0.011, 0.038	0.269	N/A	47.0%
Mean proportion of consumption for drinkers consuming at harmful levels:					
Strong beer (6%+ ABV)	0.000	−0.010, 0.010	0.988	N/A	8.5%
Strong cider (6%+ ABV)	−0.003	−0.009, 0.003	0.333	N/A	24.5%
Vodka	0.017	−0.011, 0.045	0.238	N/A	8.8%
Consumed in the off-trade	0.026	−0.012, 0.063	0.177	N/A	7.9%
Patterns of consumption for drinkers consuming at harmful levels:					
Mean number of drinking days per week	−0.023	−0.247, 0.201	0.839	N/A	48.1%
Mean number of units per occasion	−0.871	−1.651, −0.091	0.029	0.172	42.3%
Mean units consumed on the heaviest occasion of the week	0.565	−0.608, 1.737	0.345	N/A	29.2%
Mean number of occasions involving drinking alone	0.058	−0.251, 0.367	0.714	N/A	9.7%
Mean number of units per week	−3.180	−6.076, −0.283	0.031	0.172	18.5%
Proportion of adult drinkers who are consuming at harmful levels in population subgroups:					
Married or living with a partner	0.004	−0.014, 0.023	0.644	N/A	23.7%
Living with one or more children in the household	0.021	−0.006, 0.047	0.133	N/A	31.8%
Lower socio-economic group (DE)	0.000	−0.021, 0.020	0.982	N/A	25.7%

B = regression coefficient; *R*-sqr = *R*-squared; *q*-value = sharpened two-stage q-values. All outcome measures are time series of weighted measures constructed using data from self-reported drinking occasions in a 1-week retrospective drinking diary. Consumption levels are based on total units reported. Harmful = 35+/50+ units for women/men. Hazardous = 14–35/14–50 units for women/men. Moderate = 0–14 units. Those in social grade DE are defined as National Readership Survey social grade D or E (semiskilled and unskilled manual workers, state pensioners, casual and lowest grade workers, unemployed with state benefits only).
ABV, alcohol by volume; N/A, not available.

change in the types of alcoholic beverage consumed by this group, their drinking patterns, the extent to which they consumed alcohol while on their own or the prevalence of harmful drinking in key subgroups. However, the secondary analyses suggest the proportion of drinkers consuming at hazardous levels did decline.

The key strengths of this study are the large sample size and long time series provided by Alcovision, the controlled interrupted time series design and the testing of a wide range of secondary outcomes. There are three main limitations. First, the non-random sampling strategy used by Alcovision means our sample may not be wholly representative. This is a common problem across alcohol consumption surveys;[22] although we attempt to correct for it by weighting to census data some biases may remain. Second, although Alcovision uses largely consistent methods over time, we did identify and control for an unexplained breakpoint in 2017. Incomplete information on problems of this kind is commonplace when using commercial market research data but is often an acceptable limitation to gain the benefits of data sources that now play an increasingly large role in evaluating public health interventions. Third, self-reported alcohol consumption typically underestimates true consumption, although Alcovision combined methods, including recent recall and detailed occasion-focused reporting, that typically deliver more accurate estimates than the standard beverage-specific quantity frequency method.[23,24]

The decline in the prevalence of hazardous drinking in our findings is consistent with the decline in alcohol consumption found in previous evaluations of MUP in Scotland.[14,25] However, the lack of evidence for a decline in the prevalence of harmful drinking arising from MUP is contrary to model-based evidence that informed the introduction of the policy.[6] It also adds to previous inconsistent evidence on the impact of MUP in Scotland on those consuming at harmful levels.[14,16,26] One important caveat is the

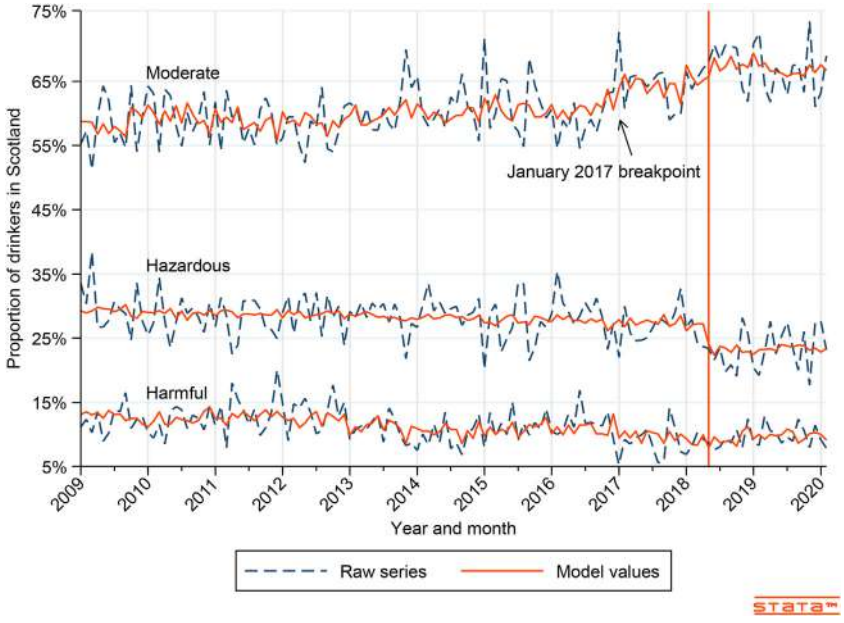

Fig. 1. Monthly proportion of drinkers consuming at harmful, hazardous and moderate levels in Scotland. Vertical line = implementation of minimum unit pricing, 1 May 2018.

measures used here and in previous studies do not map directly onto the standard measures of hazardous and harmful drinking used in key studies that informed the policy decisions on MUP.[6] Although those standard measures relate to individuals' typical weekly drinking, the evaluation studies use measures of household purchasing or individuals' alcohol consumption in the previous week. Moreover, the standard measures typically find approximately 5% of Scottish adults consume alcohol at harmful levels, but the studies of household purchasing only disaggregate the population into quintiles, while Table 1 suggests approximately 10% of adults drink at harmful levels. This implies caution is needed when comparing findings and translating categories of drinkers between evidence sources. Nonetheless, our findings add to consistent evidence that MUP led to reductions in alcohol consumption among those drinking above moderate levels but offers less certainty regarding the impact on those drinking at harmful levels.

The lack of change in the prevalence of harmful drinking may arise for several reasons. First, people drinking at harmful levels may be less responsive to price changes than lighter drinkers. Previous qualitative research and studies of purchasing behaviour among people with alcohol dependence (i.e. a group that comprises approximately 20% of those drinking harmfully in the United Kingdom and thus 1% of the overall population[27]) supports this view.[28,29] However, the very large price increases imposed by MUP on people drinking harmfully, their inability to switch to cheaper products and clear evidence of successful policy implementation and compliance,[1,30] mean their price responsiveness would need to be extremely low to negate any impact on consumption. Second, the changes in harmful drinking may have primarily affected those consuming at the highest levels and thus not affected the prevalence of harmful drinking. However, a recent study of the impact of MUP on people with alcohol dependence found no clear evidence of reduced alcohol consumption.[26] We have not presented any analyses examining this hypothesis because of small sample sizes and unreliable measurement of very high alcohol consumption levels. Third, people drinking at harmful levels may have adopted unsustainable strategies to temporarily manage the price rises caused by MUP. For example, there is evidence a minority of people with alcohol dependence responded to MUP by reducing spending on essentials, borrowing money and using their savings.[26] Longer term evaluation may therefore be required to fully understand the policy's impact on consumption. Finally, the current MUP may be set too low to generate detectable impacts. The £0.50 was initially proposed circa 2011 and would have affected approximately 70% of off-trade alcohol units sold at that time compared with 44% in 2018 when the policy was introduced.[1,2] The real-term value of the MUP has also fallen over time due to inflation. A review of the current £0.50 level is currently underway, with public health organisations calling for MUP to be uprated in 2024.[31] Although this weakens the effectiveness of the policy, it is not sufficient to explain the null results identified here because those drinking harmfully still faced significant price increases.

Further research that would strengthen understanding of the impact of MUP on people drinking at harmful levels include studies of alcohol-related harm. Such analyses have recently been published, showing a 13.4% reduction in alcohol-attributable deaths and a 4.1% reduction in alcohol-attributable hospitalisations in Scotland.[32] This provides the most direct evidence on the public health impact of MUP to date. Evidence from other jurisdictions that have introduced MUP, including Wales, Ireland and Australia's Northern Territory, would ideally strengthen conclusions, but a combination of the confounding from the COVID-19 pandemic and lower availability of high-frequency time series data for evaluation research in other jurisdictions means the Scottish evaluation offers the most robust evidence.[33] Finally, further understanding of how those drinking harmfully managed the price rises caused by MUP, if they did not reduce their consumption, would strengthen the understanding of the impact of pricing policies on those at greatest risk from their drinking.

Conclusions

MUP in Scotland was not associated with reductions in the prevalence of harmful drinking but was associated with reductions in the prevalence of hazardous drinking. This adds to a wider evidence base that MUP led to a reduction in overall alcohol consumption and consumption among those drinking above moderate levels.

Author statements

Acknowledgements

This article presents independent research commissioned by Public Health Scotland, with funding from The Scottish Government.

Data preparation underpinning this report was partially supported by a grant from the Economic and Social Research Council (grant number ES/R005257/1). For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission.

Ethical approval

This study was approved by the University of Sheffield's ethics committee and conforms to the principles embodied in the Declaration of Helsinki. Use of these data is allowed under the terms of the contract and non-disclosure agreement between Kantar Worldpanel and the University of Sheffield, which requires research outputs to be submitted to the data provider ahead of publication. The data provider played no role in the conception, design, analysis, interpretation or write-up of the research and their right to request changes to written material is limited to matters of accuracy regarding the description of the Alcovision survey data, as this is a commercial product.

Funding

The funders of the study (Scottish Government) provided feedback on study design as part of the wider MUP Evaluation Advisory Group. Public Health Scotland commissioned the research and provided feedback on some aspects of the design, analysis plan, interpretation and write-up in line with the research governance procedures of the wider MUP evaluation programme. The authors retained the right to make final decisions. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Competing interests

No conflicts to declare.

Data sharing statement

The Alcovision survey is a commercial product and therefore cannot be made publicly accessible.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.019.

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Public Health 220 (2023) 179–186

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Exploring the link between adverse childhood experiences and mental and physical health conditions in pregnant Palestine refugee women in Jordan

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ARTICLE INFO

Article history:
Received 25 November 2022
Received in revised form
14 March 2023
Accepted 6 May 2023

Keywords:
Adverse childhood experiences
Refugees
Pregnancy
Chronic disease
Mental health

ABSTRACT

Objectives: Adverse childhood experiences (ACEs) are linked to negative pregnancy outcomes. However, little is known about the prevalence of ACEs and their relationship to mental and health outcomes among pregnant Palestine refugee women.
Study design: This was a cross-sectional study.
Methods: Data were collected from 772 pregnant Palestine refugee women with a median (interquartile range) age of 27 (23, 32) years, attending five antenatal clinics in Jordan between February and June 2021. The modified 33-item ACE International Questionnaire was used to assess eight domains of ACEs: (1) marriage and family, (2) relationship with parents, (3) neglect, (4) household dysfunction/domestic violence, (5) abuse, (6) peer violence, (7) community violence, and (8) collective violence. Multivariate logistic regression was used to examine the association between ACEs and mental and health outcomes. The ethical approval was obtained from United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA) Research Review Board in May 2020.
Results: Eighty-eight percent of women experienced at least one type of ACE, and 26% of women experienced ≥4 types of ACEs. Compared with women with 0–3 types of ACE exposure, those with ≥4 types of ACEs had 1.58 (95% confidence interval [CI] 1.10–2.28) times higher prevalence of obesity before pregnancy, 3.28 (95% CI 1.79–6.03) times higher prevalence of depression during pregnancy, and 2.01 (95% CI 1.39–2.91) times higher prevalence of ever been smoking cigarettes or hookah.
Conclusions: Exposure to ACEs is prevalent among pregnant Palestine refugee women. Exposure to multiple types of ACEs was associated with obesity, mental health conditions, and smoking.

Introduction

Adverse childhood experiences (ACEs) refer to traumatic events that occur before the age of 18 years, such as abuse, neglect, witnessing household violence, and peer, community, and collective violence.[1] ACEs are a public health concern because it negatively affects physical, mental, and health outcomes throughout life.[2,3] Previous research on childhood adversity and pregnancy found associations with gestational diabetes, gestational hypertension,[4] obesity, depression and anxiety,[5–8] and substance use.[9,10] Traumatic childhood experiences lead to chronic stress affecting the development of nervous, endocrine, and immune systems, which may then result in impaired cognitive, social, and emotional functioning.[11,12] Women with ACEs might find difficulty in coping with substantial physiological and emotional changes during pregnancy, which may in turn have long-lasting health impact on themselves and their children.[13–16]

Globally, ACEs are common[17] and are disproportionately prevalent among those facing social and economic adversities, including refugees and displaced populations.[18–20] Due to conflicts,

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https://doi.org/10.1016/j.puhe.2023.05.005
0033-3506/

war, and violence, the number of refugees has increased over the last decade worldwide.[21] However, ACE studies are concentrated in high-income counties,[20] and many developing countries continue to lack extensive research on ACEs and comprehensive data on exposure to childhood adversity. This is especially true among vulnerable refugee population, who may experience structural racism and poverty within the host communities.[22]

Palestine refugees represent the world's largest refugee population.[23] Across the Middle Eastern Region, Jordan hosts the largest number of Palestine refugees, with more than 2 million currently residing in the country. Approximately 18% of these refugees live in 10 officially recognized refugee camps.[24] United Nations Relief and Works Agency for Palestine Refugees in the Near East (UNRWA) operates 25 primary care health clinics across four areas, Irbid, South Amman, North Amman, and Zarqa, providing antenatal care services to ~22,000 pregnant women annually.[23] It is estimated that UNRWA services reach 41% of pregnant Palestinian refugee women in Jordan, of whom 76% complete their first antenatal care visit during the first trimester. In 2021, Palestinian gravida living in Jordan visited UNWRA antenatal care clinics an average of five times before childbirth, with 78% having visited at least four times.[23] During antenatal visits, pregnant women receive a comprehensive physical examination and regular follow-up care, including screening for gestational hypertension, diabetes, anemia, oral health, and other health risks.[25] Informed by the World Health Organization (WHO) model of antenatal care, UNRWA assesses and classifies pregnant women into “low,” “alert,” and “high-risk” groups. In 2021, 27% of registered pregnant women were categorized as a “high-risk group” because of life-threatening conditions, such as cancer, renal failure, uncontrolled severe hypertension, advanced cardiovascular disease, and hepatic conditions.[23,25] In addition, 30% of the pregnant women were categorized as an “alert group,” characterized by having at least one or more risk factors, such as diabetes, hypertension, obesity, sexually transmitted diseases, thyroid disease, medications, immunization needs, drug, alcohol and/or tobacco use, micronutrient deficiencies, poor dietary habits, and other psychosocial risks.[23,25] Over the last few decades, coupled with ongoing political conflicts, violence, lack of security, joblessness, and encampment, the burden of non-communicable disease has been exacerbated among Palestine refugees, representing the highest financial burden to UNRWA health system.[23,26] Pregnancy offers a critical window of opportunity for prevention of chronic conditions and for improving the health of women and children.[3,27] Interventions during the optimistic and malleable period of pregnancy have the potential to disrupt the mechanisms by which ACE exposure can deteriorate the health of both women and children. This transformation offers an opportunity for promoting healing and well-being, which is greatly needed by Palestine refugees who have endured decades of hardships. For this reason, it is extremely important to study ACEs among pregnant Palestine refugee women, to assess the prevalence of exposure, and to understand the relationships between ACEs and the leading cause of morbidity among pregnant Palestine refugee women.

The study aims to assess the prevalence of ACEs among pregnant Palestine refugee women seeking antenatal care in five UNRWA clinics located inside officially recognized camps and to examine the relationship between ACE exposure and various mental health, physical health, and behavior outcomes.

Methods

The cross-sectional study was conducted in five mid-to-large-sized UNRWA antenatal care clinics in Jordan from February to June 2021. Due to the COVID-19 pandemic, the clinics that met certain criteria were purposefully selected. Criteria included agreements from the heads of clinics, an adequate number of monthly antenatal visits to finish data collection timely, and appropriate clinic infrastructure with enough space and a room for data collection. After receiving an approval from the UNRWA Jordan Field Office, five clinics located within the official camps in urban settings were selected across four geographic areas of Jordan: Marka clinic in Zarqa area, Baqaa clinic in North Amman area, Amman New Camp clinic in South Amman area, and Irbid New and Jerash clinics in Irbid area. Jerash camp, also known as Gaza camp, was added to allow data collection in the most vulnerable camp in Jordan.[24] Ethical approval was obtained from UNRWA Research Review Board in May 2020.

Two sets of data collection tools were used: (1) demographic and health questionnaire and (2) ACE International Questionnaire (ACE-IQ) questionnaire. Both questionnaires were translated to Arabic and then back-translated to English by professional interpreters to assure accuracy. Data collection was conducted in a private room on recipient of verbal informed consent. Following face-to-face interviews conducted by a trained data collector to gather demographic and health questionnaires, women were given the ACE questionnaire to complete independently. To ensure confidentiality, a woman was asked to not write her name or any personal identifiers and to close the questionnaire with a cover page before leaving a room. If the women were illiterate or needed help answering the questions, the data collectors provided assistance. If a woman asked for further psychosocial support dealing with the traumatic experiences, a referral was made to psychosocial support services at each clinic for further assessment and care.

Adverse Childhood Experience International Questionnaire

The WHO's ACE-IQ[1] was modified to enhance its cultural acceptability and language appropriateness in the context of Palestine refugee communities in Jordan through an iterative process of interviews and focus group discussions with key informants, such as chiefs of Maternal Health programs, head of protection services from UNRWA headquarters, and health officers, physicians, and nurses from the Jordan Field Office. In the original ACE-IQ, there were a total of 36 questions across seven domains: (1) marriage (five questions), (2) relationship with parents/guardians (five questions), (3) family environment (eight questions), (4) abuse (eight questions), (5) peer violence (three questions), (6) witnessing community violence (three questions), and (7) exposure to war/collective violence (four questions). During the iterative modification process, two questions related to witnessing physical abuse/violence in a household were merged into one question, and four questions related to sexual abuse were merged into two questions to improve linguistic and cultural acceptability in the context of Palestine refugee communities. The final version of modified ACE-IQ (Supplemental Fig. 1) included 33 questions across eight domains of adverse experiences during the participant's first 18 years of life: (1) marriage (five questions), (2) relationship with parents (two questions), (3) neglect (three questions), (4) household dysfunction/domestic violence (seven questions), (5) emotional, physical, and sexual abuse (six questions), (6) peer violence (three questions), (7) community violence (three questions), and (8) collective violence (four questions). The modified ACE-IQ had the answer choices of “yes” or “no” to some questions and “never,” “rarely,” “a few times,” and “many times” to other questions. Respondents were defined as exposed to a domain of ACEs if they responded “yes,” “rarely,” “a few times,” or “many times” to any questions within the category. Before the initiation of data collection, the modified ACE-IQ was piloted with pregnant Palestine refugee women at UNRWA clinics. To create ACE scores, we

summed seven domains of childhood adversity, excluding marriage domain, to calculate ACE scores, ranging from 0 (unexposed) to 7 (exposed to all domains).

Demographic and health questionnaire

Demographic information included age, education level (no schooling, elementary [grade 1–6], basic [grade 7–10], high school [grade 11–12], post-high school), employment status (unemployed or employed), and residence (inside or outside the camp).

Based on a review of reports and literature,[2,28,29] we chose a range of mental and physical health outcomes that may contribute to the burden of non-communicable diseases among Palestine refugees.[30–32] Self-reported health conditions before pregnancy were assessed by "yes" or "no" to the question, "Before you were pregnant, did your doctor or health worker tell you that you had any of the following health conditions: (a) type 1 diabetes, (b) type 2 diabetes, (c) hypertension, (d) depression, or (e) anemia?" Health conditions during pregnancy were assessed by "yes" or "no" to the question, "During your pregnancy, did your doctor or health worker tell you that you have any of the following health conditions: (a) gestational diabetes, (b) gestational hypertension, (c) depression, (d) anemia?" Self-reported mental health conditions, were assessed by "yes" or "no" to the question, "Have you ever been told by a health care provider that you have: (a) anxiety, (b) eating disorder, or (c) suicidal thoughts?" Smoking status before pregnancy was assessed by "yes" or "no" to the question, "Have you ever been smoking before?" Current smoking status was assessed by "yes" or "no" to the statement, "I currently smoke cigarettes or hookah."

Preconception weights, height, and the last date of the menstrual period were obtained from the maternal and child health (MCH) handbook,[33] which is provided to all the pregnant women seeking care at UNRWA. Height and preconception weights were measured and recorded by a midwife during the clinical visits. If a woman did not attend the preconception care at UNRWA clinics nor her weight before pregnancy was unrecorded in the MCH handbook, then a woman was asked by data collectors, "Just before you got pregnant, how much did you weigh?" and women provided their weight in kilograms to one decimal point. Preconception body mass index (BMI) was calculated by dividing the preconception weight in kilograms by squared height in meters (kg/m^2), which was categorized into underweight (<18.5), normal (18.5–24.9), overweight (25–29.9) and obese (>30) according to the WHO criteria.[34]

Sampling method

Within each antenatal clinic, pregnant women were recruited for a study using simple random sampling. Women aged <18 years were excluded. The sampling interval was decided based on the average number of antenatal visits per month in each clinic divided by the total sample size per clinic (Supplemental Table 1). For example, the sampling interval was calculated to be 4 for Marka clinic. Therefore, midwives in Marka clinic were instructed to ask every fourth woman attending the antenatal services to go to a trained data collector in the clinic. If a woman agreed to participate, informed consent was obtained verbally by a trained data collector.

The sample size was calculated to ensure the 95% confidence interval (CI) estimate of the proportion of pregnant women with hypertension within 2% of the true proportion. The prevalence of hypertension among pregnant women seeking antenatal care at UNRWA clinics in Jordan was estimated to be 7.4% in 2019.[28] Using the sample size formula for estimating a proportion, the sample size was calculated to be 659 women. With an attrition rate of 10%, the final sample size was calculated to be 725 women.

Statistical analysis

Descriptive analysis was performed to present the numbers and proportion of binary and categorical variables, as well as means with standard deviations and medians with interquartile range (IQR) for continuous variables. ACE scores were dichotomized into four or more types of ACEs (≥4 ACEs) and three or less types of ACEs (0–3 ACEs). We performed logistic regression to assess the unadjusted and adjusted associations between ACE scores and outcomes. After performing simple logistic regression, multiple logistic regression was performed, adjusting for the following covariates: age, education level, and locations of health clinics. The selection of covariates was informed by the previous literature.[2,29] As our study only included women and ~96% of women were unemployed, we adjusted for age and education of women. We also adjusted for the location of clinics to control for any unobservable heterogeneity across geographic area. Several meetings with data collectors, clinic staff, health officers, and chiefs at UNRWA headquarters were held to interpret the results in the context of Palestine refugees. All analyses were conducted using Stata version 16 (College Station, TX).

Results

A total of 781 pregnant women were asked to participate in the study. Of these, only nine women declined to participate; thus, the participation rate was 99%, including 772 women included in the analysis. Table 1 summarizes the characteristics of pregnant women who participated in the study. The median (IQR) age of women was 27 (23, 32) years, and 67% of women were aged <30 years. Eighty-one percent of women had high school education or less, 96% were unemployed, and 56% lived inside the camp. The median (IQR) gestational age among women at the time of the

Table 1
Characteristics of pregnant women, who consented to participate in the study at five UNRWA antenatal clinic, Jordan, February to June 2021 ($n = 772$).

	Total, *n* (%)
Total	772 (100)
Age in years	
Mean (SD)	27.5 (6.2)
Median (IQR)	27 (23, 32)
Age stratum in years, *n* (%)	
<20	71 (9.2)
20–24.9	206 (26.8)
25–29.9	221 (28.8)
30–34.9	152 (19.8)
35–39.9	84 (10.9)
≥40	34 (4.4)
Education	
No schooling	5 (0.7)
Elementary (Grade 1–6)	63 (8.2)
Basic (Grade 7–10)	270 (35.1)
High school (Grade 11–12)	287 (37.3)
Post-high school	145 (18.8)
Employment status	
Unemployed	738 (95.8)
Employed	32 (4.2)
Clinic location	
Amman New Camp	157 (20.3)
Baqaa	155 (20.1)
Irbid	149 (19.3)
Jerash	159 (20.6)
Marka	152 (19.7)
Residence	
Inside the camp	339 (44.1)
Outside the camp	430 (55.9)

IQR, interquartile range; SD, standard deviation.

interview was 24 (15, 32) weeks, and 82% were in the second-to-third trimesters. Twenty-three percent and 52% of women were overweight and obese before pregnancy, respectively (Table 2). The prevalence of physical conditions before and during pregnancy was 2% and 5% for diabetes, 5% and 7% for hypertension, 4% and 7% for depression, and 14% and 16% for anemia, respectively. The most common self-reported mental health condition was anxiety (11%), followed by eating disorder (9%) and suicidal thoughts (4%). Twenty-eight percent of women reported ever smoking (cigarettes or hookah), and 13% of them reported currently smoking during their pregnancy.

The median (IQR) age of first marriage was 20 (18, 22) years. Twenty-three percent of women reported that she did not choose a husband themselves. The median (IQR) age of the first pregnancy was 21 (3, 9) years. Among the seven ACE domains used to compute ACE scores, excluding the marriage domain, household dysfunction/domestic violence was most prevalent (69%), whereas collective violence was the least prevalent (11%; Table 3). Eighty-eight percent of pregnant women experienced at least one domain of ACEs, and 26% reported exposure to more than four domains of ACEs (Fig. 1).

Table 4 presents the crude and adjusted prevalence odds ratios assessing the association between dichotomized ACE scores and selected outcomes. Women who were exposed four or more types of ACEs were 1.58 (95% CI, 1.10–2.28) times more likely to be obese (BMI $\geq$30 kg/m^2), 2.83 (95% CI, 1.37–5.83) times more likely to be depressed, and 1.96 (95% CI, 1.27–3.02) times more likely to be anemic before pregnancy than those with 0–3 types of ACEs while adjusting for age, education, and locations of clinics. The prevalence odds ratios for depression and smoking cigarettes or hookah during pregnancy were 3.28 (95% CI, 1.79–6.03) and 2.04 (95% CI, 1.30–3.21), respectively, for women with four or more types of ACEs compared with those with three or less types. Women with four or more types of ACEs had significantly higher prevalence odds ratios for depression (2.76; 95% CI, 1.61–4.73), anxiety (2.05; 95% CI, 1.26–3.32), eating disorders (1.95; 95% CI, 1.15–3.30), suicidal thoughts (4.20; 95% CI, 1.83–9.66), and smoking (2.01; 95% CI, 1.39–2.91) compared with those with fewer types of ACEs.

Table 2
Gestational age and anthropometric measures of pregnant women, UNRWA antenatal clinic, Jordan, February to June 2021 (n = 772).

	Total, n (%)
Gestational age (weeks)	
Mean (SD)	23.2 (9.9)
Median (IQR)	24 (15, 32)
Gestational trimesters at the time of interview	
First trimester (0–12 weeks)	130 (17.7)
Second trimester (13–26 weeks)	313 (42.6)
Third trimester (27–40+ weeks)	292 (39.7)
BMI before pregnancy (kg/m^2)	
Underweight (BMI <18.5)	35 (4.5)
Normal weight (BMI 18.5–<25)	275 (35.2)
Overweight (BMI 25–<30)	176 (22.5)
Obese (BMI $\geq$ 30)	286 (51.6)
Physical health conditions, before pregnancy	
Type 1 or 2 diabetes	14 (1.9)
Hypertension	35 (5.0)
Depression	33 (4.3)
Anemia	109 (14.2)
Physical health conditions, during pregnancy	
Gestational diabetes	34 (4.5)
Gestational hypertension	50 (6.5)
Depression	50 (6.5)
Anemia	121 (15.7)
Mental health conditions	
Anxiety	85 (11.2)
Eating disorder	70 (9.2)
Suicidal thoughts	27 (3.6)
Smoking status	
Ever smoker	215 (27.9)
Current cigarettes/hookah smoker	102 (13.3)

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Discussion

To our knowledge, this is the first study that has examined the prevalence of ACEs and its association with mental and physical health outcomes among pregnant Palestine refugee women. Our results indicated that ACEs are extremely prevalent among the women, as approximately 90% and 30% experienced at least one type of ACEs and four or more types of ACEs, respectively. The estimated prevalence of ACEs among women in our study was much higher than the previously reported estimates for ACEs elsewhere. For example, a systematic review of 37 articles estimated that 57% experienced at least one ACE and 13% experienced at least four ACEs globally.[17] In 2010 World Mental Health Survey, the exposure to at least one type and four or more ACEs were estimated to be 59.6% and 6.8% among high-to-middle-income countries and 66.2% and 4.5% among low- to lower-middle-income countries, respectively.[35] Another systematic review of 14 ACE studies conducted in low- and middle-income countries reported exposure to at least one type of ACE ranged from 1.9% in Lebanon[36] to 80% in Saudi Arabia.[20,29] Palestine refugee women may have an increased risk for being exposed to ACEs due to ongoing political instabilities, violence, lack of security, poverty, food insecurity, joblessness, and encampment, coupled with the recent COVID-19 pandemic.[23,26] Compared with the women in Jordan, where the host country is politically stable, it is plausible that Palestine refugee women living in Lebanon, Syria, the West Bank and Gaza Strip may experience higher exposure to ACEs due to repeated conflicts, and financial crises, legal and movement restrictions, poor camp infrastructure, family disruption, and poverty that continue to affect women's lives.[32] Furthermore, the participants of the study were the descendants of those who were directly affected by the wars of 1948 or 1968. Yet, the prevalence of ACEs among our participants appears to be common. These findings suggest that the life stressors experienced by refugees, such as a residency instability, poverty, family loss, and disruption, may have intergenerational effects and contribute to ACEs among their descendants, including their children and grandchildren.[22,37] Furthermore, subsequent generations of Palestine refugees may be exposed to an additional source of stress by keeping their identities as Palestinians and holding cultural norms and traditions within a host country.

In our study, the prevalence of gestational diabetes, gestational hypertension, and anemia were estimated to be 4.5%, 6.5%, and 15.7%, respectively, which may present conservative estimates for pregnant Palestine refugee women in Jordan. For instance, the clinic-based estimates of gestational diabetes, gestational hypertension, and anemia in the first trimester and second-to-third trimesters were reported to be 8.5%, 8.1%, 18%, and 25%, respectively, among pregnant women attending 25 antenatal clinics operated by UNRWA in Jordan in 2021.[23] The differences in estimates may be explained by the differences in the study population, data collection methodology, such as self-report versus clinic-based data, and sample size. On the other hand, our estimates are generally higher than the prevalence reported among Jordanian women. For example, the recent study conducted among Jordanian women attending the birthing hospitals reported the prevalence of gestational diabetes and hypertension to be 1.8% and 5.8%.[38] In our study, 23% and 52% of women were overweight and obese before pregnancy, which is much higher than the prevalence among Jordanian women of reproductive age based on the Jordan demographic

Table 3
Characteristics and prevalence of adverse childhood experiences by ACE-IQ domain among pregnant women at UNRWA antenatal clinics, Jordan, February to June 2021 ($n = 772$).

	Total	
	n	%
Domain 1: Marriage		
Age in years of first marriage		
Mean (SD)	20.1	(3.6)
Median (IQR)	20	(18, 22)
Did not choose a husband herself	174	23.1
Age in years of first pregnancy		
Mean (SD)	21.0	(3.9)
Median (IQR)	20	(18, 23)
Domain 2: Relationship with parents	160	25.0
Parents never understood your problems and worries	97	14.7
Parents never really knew what you were doing in your free time	108	16.4
Domain 3: Neglect	169	23.4
Not given enough food	100	13.9
Household member was intoxicated	15	2.0
Not sent to school	84	11.3
Domain 4: Household dysfunction/ domestic violence	511	69.1
Household member was an alcoholic/ drug abuser	37	4.9
Household member had depression	36	4.7
Household member was jailed	103	13,6
Parents were separated/divorced	57	7.5
Parent/guardian died	171	22.4
Saw/heard a parent or household member verbally insult	359	49.3
Saw/heard a parent or household member physically hurt	153	20.5
Domain 5: Abuse	419	56.6
Emotional abuse	388	52.1
Family member verbally insult you	379	50.7
Family member threatened to abandon you	39	5.1
Physical abuse	64	8.5
Household member spank, slap, kick, punch or beat you	30	4.0
Household member cut or burned you	48	6.3
Sexual abuse	88	11.8
Ever been verbally harassed	80	10.7
Ever been physically harassed	18	2.4
Domain 6: Peer violence	325	44.8
Often bullied	213	28.8
Physical fight with peers	189	25.6
Domain 7: Community violence	211	29.9
Saw someone beaten up	295	63.7
Saw someone stabbed or shot	318	51.5
Saw someone threatened with a knife or gun	184	27.4
Domain 8: Collective violence	81	10.7
Forced to leave home	33	4.3
Home destroyed	32	4.2
Beaten up by military, police, militia group etc.	2	0.3
Family members killed by military, police, militia group etc.	41	5.4
ACE score, ordinal		
0	91	11.8
1	146	18.9
2	174	22.5
3	160	20.7
4	126	16.3
5	55	7.1
6	17	2.2
7	3	0.4
ACE score, dichotomous		
0–3	571	74.0
≥4	201	26.0

ACE-IQ, Adverse Childhood Experience International Questionnaire; IQR, interquartile range; SD, standard deviation.

health survey 2017–2018, which were 32% and 22% for overweight and obese, respectively.[39] For smoking, our study estimated 28% of women were ever smokers, compared with 12% in Jordanian women.[39] Comparisons in these estimates suggest that maternal health conditions and smoking are more prevalent among pregnant Palestine refugee women than the general population of Jordanian women who tends to be the "better offs."

Our results were consistent with existing international literature that childhood trauma and adverse experiences are associated with negative health outcomes, including antenatal depression and anxiety,[5–7,40] substance use such as smoking,[10] and obesity.[41] Some studies suggest that women are prone to developing depressive and anxiety disorders following childhood adversity more than men.[5–8,32,42,43] Women may be more inclined to blame themselves or be blamed after victimization and are more likely to manifest internalizing behaviors compared with men after exposure to childhood adversity.[44] Furthermore, female victims of childhood adversity in Palestine refugee communities may suffer in silence, especially when victimized by a family member or neighbor, so as not to tarnish their honor or family reputation or break family unity.[42] Previous studies also report a correlation between child abuse and obesity among women.[41] One study found a 46% increase in the odds of adult obesity after exposure to multiple ACEs.[45] A meta-analysis found a positive dose–response association between child abuse and adult obesity, suggesting that an elevated inflammatory response to stress increases craving for palatable foods.[46] Our study also found that exposure to many types of ACEs is associated with anemia diagnosed before pregnancy. Women with histories of childhood adversity may be prone to consuming comfort foods that are high in saturated fat and sugar, energy dense, but poor in micronutrients, such as iron, as a coping mechanism for traumatic childhood experiences. In nutrition, transition countries, such as Jordan, experience a double burden of malnutrition, where an increase in non-communicable diseases and overweight, obesity, and chronic micronutrient deficiencies coexist.[47] Particularly, refugees that live in urban, crowded camps, are increasingly exposed to foods that are highly processed, energy-dense foods but are poor in micronutrients.

This study has some important implications for policy and practice. Non-communicable diseases represent the leading cause of morbidity among Palestine refugees.[23] These conditions result from compensatory lifestyle habits such as smoking and unhealthy eating habits, which provide immediate partial relief from chronic stress caused by traumatic childhood experiences, coupled with socioeconomical and political hardships faced by Palestine refugees. However, the efforts to prevent ACEs and provide support for those affected by ACEs have been slow to move up the political agendas. First, it is critical to expand the knowledge of ACEs among public health practitioners and policymakers working on the health of Palestine refugees. Second, potential strategies to prevent and address childhood adversity that are culturally appropriate to the Palestinian communities should be identified. For example, routine screening for ACEs in clinical settings may need to move beyond professionals responding ad hoc to spontaneous disclosure of childhood adversity. Equipping primary healthcare providers with additional training on ACEs may empower them to sensitively and proactively inquire about a patient's childhood experiences and refer them to appropriate support services.[48] However, the pros and cons of such screening should be carefully weighed, especially in the health systems in low- and middle-income countries such as UNRWA, which has often been challenged by the financial crisis, shortage in clinical staff, and many competing health, social, and political issues of Palestine refugees across the Middle Eastern countries. In addition, ACE inquires require sensitivity to cultural norms in the context of the Palestinian community. Thus, routine

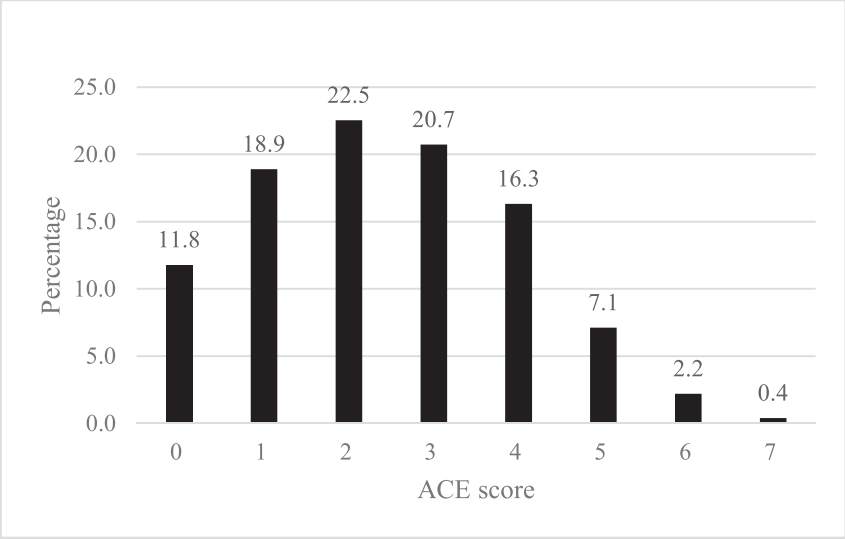

Fig. 1. ACE score among Palestine refugee pregnant women ($n = 772$). ACE, adverse childhood experience.

Table 4
Crude and adjusted prevalence odds ratios (PrORs)[a] for selected maternal outcomes, ACE sore of four or more compared with 0–3 ACEs, among pregnant women at UNRWA clinics, Jordan, 2021 ($n = 772$).

	Crude PrOR	95% CI	Adjusted PrOR[a]	95% CI
Preconceptional BMI[b]				
Underweight (BMI <18.5)	1.54	0.75, 3.15	1.72	0.82, 3.58
Overweight (BMI 25 to <30)	1.07	0.73, 1.56	1.06	0.72, 1.56
Obese (BMI ≥30)	1.42*	1.01, 2.00	1.58*	1.10, 2.28
Physical health conditions, before pregnancy[c]				
Type 1 or 2 diabetes	0.77	0.21, 2.78	1.54	0.42, 5.71
Hypertension	1.26	0.61, 2.61	1.13	0.53, 2.38
Depression	2.81*	1.39, 5.68	2.83*	1.37, 5.83
Anemia	2.09*	1.37, 3.20	1.96*	1.27, 3.02
Physical health conditions, during pregnancy[d]				
Gestational diabetes	1.39	0.67, 2.91	0.78	0.37, 1.66
Gestational hypertension	1.31	0.69, 2.46	1.39	0.73, 2.65
Depression	3.38*	1.89, 6.04	3.28*	1.79, 6.03
Anemia	1.37	0.90, 2.10	1.30	0.84, 1.99
Mental health conditions[e]				
Anxiety	2.17*	1.36, 3.46	2.05*	1.26, 3.32
Eating disorder	2.15*	1.29, 3.56	1.95*	1.15, 3.30
Suicidal thoughts ever	4.49*	2.04, 9.84	4.20*	1.83, 9.66
Smoking status				
Ever smoker[f]	2.08*	1.45, 2.98	2.01*	1.39, 2.91
Current cigarettes/hookah smoker[g]	2.03*	1.31, 3.14	2.04*	1.30, 3.21

*Prevalence odd ratios significant at $P < 0.05$.
[a] aPrOR was controlled for women's age, education level, and clinic location.
[b] Body mass index (BMI) was calculated by using a formula, kg/m^2, and height and preconceptional weights obtained from MCH booklet.
[c] Self-reported health conditions before pregnancy include affirmative responses to questions asking if a woman had ever been told by a doctor or health worker she had type 1 diabetes, type 2 diabetes, hypertension, depression, or anemia before pregnancy.
[d] Self-reported health conditions during pregnancy include affirmative responses to questions asking if a woman had ever been told by a doctor or health worker she had gestational diabetes, gestational hypertension, perinatal depression, or anemia during pregnancy.
[e] Self-reported mental health conditions include affirmative responses to questions asking if a woman had ever been told by a doctor or health worker that she had anxiety, eating disorder, or suicidal thoughts ever.
[f] Ever smoker include affirmative responses to a question, “have you ever been smoking before?”
[g] Current smoker include affirmative responses to a statement, “I currently smoke cigarettes or hookah.”

ACE screening practices should be carefully discussed among clinicians and policymakers and supported by community leaders.

Several potential limitations need to be considered when interpreting the results of this study. The ACEs are obtained by retrospectively self-reported data and are subject to recall bias. Although the data collection procedure was carefully planned to protect the privacy and confidentiality of participants, some women may have underreported exposure to ACEs. In addition, follow-up studies of adults with childhood abuse have documented that their retrospective reports of childhood abuse provide underestimates of actual occurrence.[49,50] Therefore, our estimates of the relationship between ACEs and selected outcomes are likely to be conservative. Second, our study used self-report measures in data collection, except for women's heights and weights obtained from the MCH handbook. As such, measures of mental and health status, ACEs, and smoking status may have been over- or under-

reported when women completed the survey. Third, because of the impact of the COVID-19 pandemic, we purposefully chose five clinics that were willing to participate in the study and had the necessary staff capacity and infrastructure to collect data. This may have limited the generalizability of the study findings to broader contexts. Fourth, modification of ACE-IQ may have reduced the comparability of our findings to other studies. Finally, data cannot definitively establish the temporal relationship between ACEs and selected outcomes; however, it is conceivable that the onset of smoking and mental and health conditions may have preceded exposure to ACEs.

Our study revealed that pregnant Palestinian refugee women with exposure to multiple types of ACEs had increased odds of having obesity and anemia before pregnancy, being diagnosed with depression, anxiety, eating disorder, and experienced suicidal thoughts, and being an ever smoker and smoking during pregnancy. Moreover, ACEs are extremely common among pregnant women in the Palestinian communities in Jordan. The multifaceted effects on mental and health status should be recognized among policymakers, public health practitioners, and clinicians. To alleviate the effects of ACEs among Palestinian communities, further efforts may be considered to increase awareness, provide clinical tools to identify ACEs, establish a referral system to psychosocial services, implement public health programming to support vulnerable families, and develop ACE surveillance.

Author statements

Acknowledgments

The authors would like to thank Drs Majed Hababeh and Rami Habash for sharing their experience and knowledge on maternal health services at UNRWA. The authors acknowledge the contribution and support of staff from the Jordan Field Office and UNRWA clinics. The first author greatly acknowledges support from the Ministry of Foreign Affairs of Japan, and from the Sight and Life Global Nutrition Research Institute, Baltimore, MD.

Ethical approval

Research Review Board at United Nations Relief and Works Agency for Palestine Refugees in the Near East, Headquarters.

Funding

This research was supported by a grant from the World Health Organization, Eastern Mediterranean Regional Office Special Grant for Research in Priority Areas of Public Health 2020–2021 (Grant number: 2020/1063371, Proposal number: RPPH 20-169).

Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.05.005.

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Public Health 220 (2023) 99–107

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/puhe

Original Research

Facilitators and barriers to attending postpartum screening in women with a recent pregnancy complicated by gestational diabetes mellitus: a qualitative study

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ARTICLE INFO

Article history:
Received 5 October 2022
Received in revised form
6 April 2023
Accepted 25 April 2023

Keywords:
Gestational diabetes
Type 2 diabetes
Postpartum screening
Barriers
Facilitators

ABSTRACT

Objective: Pregnant women with gestational diabetes mellitus (GDM) are 50% more likely to develop type II diabetes (T2D) within 6 months to 2 years after giving birth. Therefore, international guidelines recommend it is best practice for women diagnosed with GDM to attend screening for T2D 6–12 weeks postpartum and every 1–3 years thereafter for life. However, uptake of postpartum screening is sub-optimal. This study will explore the facilitators of and barriers to attending postpartum screening for T2D that women experience.

Study design: This was a prospective qualitative cohort study using thematic analysis.

Methods: A total of 27 in-depth, semistructured interviews were conducted over the telephone with women who had recent GDM. Interviews were recorded and transcribed, and data were analysed using thematic analysis.

Results: Facilitators of and barriers to attending postpartum screening were identified at three different levels: personal, intervention, and healthcare systems level. The most common facilitators identified were concern for their own health and having the importance of screening explained to them by a health professional. The most common barriers identified were confusion over the test and COVID-19.

Conclusion: This study identified several facilitators of and barriers to attending postpartum screening. These findings will help to inform research and interventions for improving rates of attendance at postpartum screening to reduce the subsequent risk of developing T2D.

Introduction

Gestational diabetes mellitus (GDM) refers to any level of high blood sugar intolerance that presents itself during pregnancy.[1] Affecting up to 25% of all pregnancies globally,[2] it is known as the most common medical presentation and metabolic issue associated with pregnancy.[3] Prevalence of GDM varies across the globe because of the ethnic and racial makeup of a population.[4] However, it is expected to increase significantly in coming years due to factors, such as increasing maternal age, increasing rates of obesity, and the adoption of modern lifestyles in developing countries.[5,6] In 2011, it was found that GDM affected 12.4% of all pregnant women in Ireland using the International Association of Diabetes and Pregnancy Study Group (IADPSG) diagnostic thresholds.[7] Annually, it is estimated to affect approximately 7440 women in Ireland.[8]

GDM is known to cause adverse outcomes for both the mother and the fetus.[3,9] It can cause maternal complications, such as pre-eclampsia, hypertension and premature labour, and foetal complications, such as hypoglycaemia, congenital anomalies and potential future childhood and adolescent obesity.[10] Management of GDM during pregnancy includes monitoring, lifestyle modifications, pharmacological therapy (insulin) and obstetric management.[11]

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https://doi.org/10.1016/j.puhe.2023.04.022

Although GDM normally resolves postpartum, women with prior GDM have a 10-fold higher risk of developing type II diabetes (T2D) later in life.[12] The rate of recurrent GDM in subsequent pregnancies is also high, with 50% of women receiving the same diagnosis.[13] In Ireland, it is recommended a 75 g oral glucose tolerance test (OGTT) is carried out on all women who had GDM between 6 and 12 weeks after delivery. It is also recommended that the test is repeated every 1–3 years after the initial postpartum test.[14] While the American Diabetes Association also recommends an OGTT 6–12 weeks postpartum,[15] the British National Institute for Clinical Excellence guidelines suggest a fasting plasma glucose test 6–13 weeks postpartum, as they do not routinely offer OGTTs.[16]

Attendance rates for postpartum screening vary from country to country; however, it is generally thought to be poor, with studies reporting between 18% and 60% compliance.[17–20] Non-adherence to screening can lead to undiagnosed diabetes, which can cause serious lifelong complications.[21] Early detection and treatment of diabetes is key to prevent complications such as neuropathy, retinopathy, cardiovascular disease, and stroke.[22–24] Undiagnosed T2D can also cause complications for any future pregnancies. Women with T2D, when compared with healthy women without diabetes, have a 2.1-fold higher risk of congenital abnormalities and a 2.3-fold higher risk of perinatal death.[25] Women with pre-existing diabetes in pregnancy are over threefold higher risk of pre-eclampsia and needing caesarean sections, whereas the unborn child is a 3.5-fold higher risk of stillbirth and 3.4-fold higher risk of perinatal mortality.[26] Attendance to postpartum screening is important to avoid undiagnosed T2D and these accompanying complications. Therefore, postpartum maternal screening is considered best practice.[27]

Despite its importance, there is a paucity of literature exploring the reasons why women choose to either attend or not attend postpartum screening, particularly for women in Ireland. While studies have recently been conducted in places such as Scotland, London, Norway, Singapore, and America,[28–32] there is a need to explore this area relevant to an Irish context. When we understand the facilitators of and barriers to attending postpartum screening, there is an opportunity to address them and improve the suboptimal levels of attendance. Therefore, this article will investigate the lived experiences and perspectives of women to identify the facilitators of and barriers to attending postpartum screening that they experienced following a pregnancy complicated with GDM.

Methods

Study design and recruitment

A qualitative, phenomenological study was undertaken at the University of Limerick, Ireland. Ethical approval was granted by the HSE Mid-Western Area Research Ethics Committee (REC ref. 052/2021). Women who gave birth at University Maternity Hospital Limerick (UMHL) between April 2020 and April 2022, with a diagnosis of GDM confirmed by an OGTT in accordance with the IADPSG diagnostic criteria, were eligible to participate in the study. A list of eligible participants was generated, and women were contacted directly and consecutively until the desired number of participants were recruited or data saturation was achieved. In-depth, semistructured interviews were conducted and recorded over the phone after informed consent. The recruitment process is shown in Fig. 2 in the Results section.

Data collection and analysis

An in-depth, semistructured interview guide using open-ended questions was developed by three investigators (A. Cronin, E.B., and A. Cremona). This can be found in Supplementary file S1. This was reviewed by a team member who has extensive experience in qualitative research (D.O.D.). The interview guide was intended to get insight into the women's experiences with GDM during and after their pregnancy. The interviewers also used reflective probes and intuition to encourage participants to elaborate further on their responses. Interviews were conducted by two investigators (A.C. and E.B.) over the telephone over the course of a week.

Interviews were recorded and transcribed digitally using the transcription software Otter.ai. After the transcripts were reviewed for completeness, they were then uploaded to NVivo (V.12) where they were subsequently analysed using thematic analysis as outlined by Braun and Clarke.[33] This process involves the progressive phases of "familiarizing yourself with the data, generating initial codes, searching for themes, defining and naming themes, and producing the report." Initial codes were developed using an inductive and iterative process. Once all interviews were reviewed, the codes were further analysed and grouped by similarities into themes. These themes were further reviewed and evolved into subthemes, with overarching themes developed for each category. Three investigators (A. Cronin, A. Cremona, and D.O.D.) came together to finalise the themes and subthemes, their names, and definitions. Throughout this process, there was a constant, iterative process of defining and refining codes and themes as outlined in a study by Braun and Clarke.[33] Fig. 1 outlines the coding process used in this study. Pearson Chi-squared test was used to establish whether there was an association between the characteristics of the study participants ($P < 0.05$ was considered statistically significant).

Results

Participant recruitment

Thirty-two women consented to participate in the study; 28 interviews were conducted, whereas four participants could not be contacted. The recruitment process of participants is shown in Fig. 2.

Participant demographics

The average age was 34 ± 4 years (mean ± standard deviation). Sixty-nine percent ($n = 22$) of respondents were reported to have attended postpartum screening for T2D, whereas 31% ($n = 10$) of respondents were reported to have not attended screening. Thirty-seven percent ($n = 10$) of participants were primigravid. Of the 63% of participants ($n = 17$) who had previous pregnancies, 47% ($n = 8$) had prior GDM, whereas 53% ($n = 9$) did not. Forty-four percent ($n = 12$) of participants required insulin to manage their GDM. Demographic characteristics of the participants in the study are shown in Table 1.

There was no significant difference in age ($P = 0.125$), insulin use during pregnancy ($P = 0.282$), prior history of GDM ($P = 0.393$), and previous pregnancies ($P = 0.237$) between the participants who did and did not attend postpartum screening (Table 2).

Facilitators to and barriers of postpartum screening

Perceived facilitators and barriers are generally multifaceted; therefore, they were organised into three categories: personal, intervention and health system levels, which are presented in Table 3. A table containing all quotes can be found in Supplementary files S2 and S3.

Facilitators of postpartum screening

Of the 27 participants, 20 (74%) were able to identify facilitators of postpartum screening.

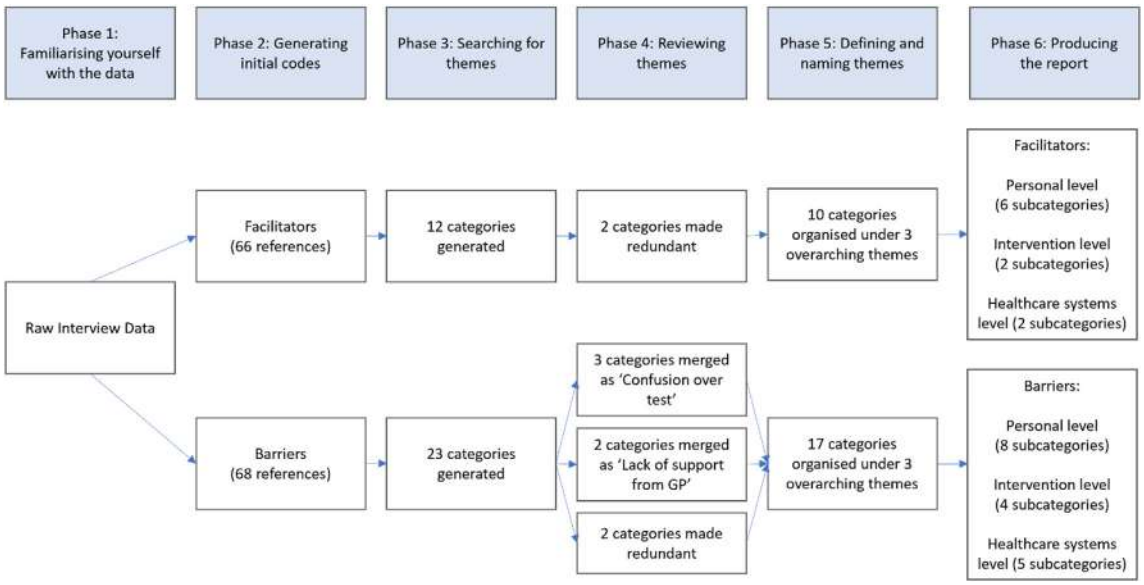

Fig. 1. Coding tree for thematic analysis.

Personal level

Seventy percent ($n = 19$) of participants identified facilitators of postpartum screening at the personal level. Fifty-nine percent ($n = 16$) of participants claimed that it was concern for their own health that encouraged them to go for the screening. They wanted to make sure that the GDM was resolved and that it had not developed into T2D without their knowledge.

> "*I wanted to know myself whether or not it was gone… I didn't want to be in a situation where I had major health issues because I hadn't dealt with it or buried my head in the sand" (P18).*

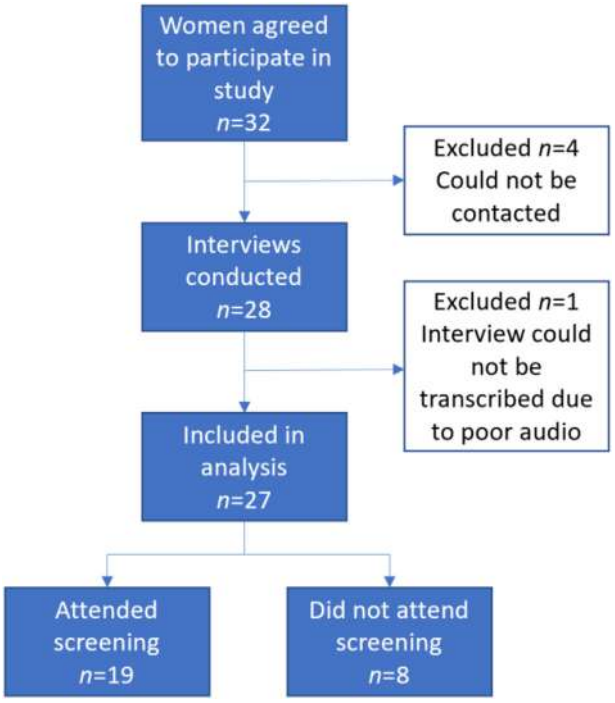

Fig. 2. Recruitment process of participants.

Perceived severity of T2D was identified as a facilitator by 22% of participants ($n = 6$). They expressed knowledge about T2D and considered it to be a serious disease.

> "*People don't realise… the ramifications of it. That, like, you could lose a limb, you know… if you don't look after it. […] It's an awful disease. People don't know. They really think it's not as serious as it is" (P25).*

In addition to this, 19% of participants (n = 5) claimed that they would be concerned about developing T2D because of the higher propensity of diabetes in their family. *"I suppose with the family history I was afraid maybe the type two diabetes might occur … I would be a little bit concerned about diabetes with the family history" (P13). Consequently, 11% of participants (n = 3) expressed concern for the effect on their family if they were to develop T2D. The main concern was in relation to the possibility of relying on their children for care in the future. "Because like, if I have it [type II diabetes] … it's then the two kids who'd be effected … It effects everyone else, I suppose, in the house really, it's not just about me, you know" (P22).*

Seven percent of participants (n = 2) claimed that they attended postpartum screening due to family planning. They intend to have more children in the future and want to be prepared for when they conceive. *"I suppose the main thing would be family planning for us … we'd be hoping to look forward and to plan, and I'd like to know that*

Table 1
Demographic characteristics of study participants.

Demographic characteristic ($n = 27$)		
Age (years), mean (±SD)		33.8 (4.2)
No. of children	1	10 (37%)
	2	15 (55%)
	3	2 (8%)
Women with previous pregnancies		17 (63%)
History of GDM in previous pregnancies	Yes	8 (47%)
	No	9 (53%)
Management of GDM	Diet	15 (56%)
	Insulin	12 (44%)
Postpartum screening	Attended	22 (69%)
	Did not attend	10 (31%)

GDM, gestational diabetes mellitus; SD, standard deviation.

Table 2
Comparison of demographic characteristics of women who attended or did not attend screening.

Demographic characteristic	Attended ($n = 19$)	Did not attend ($n = 8$)	*P*-value
Age (years) at time of delivery (mean ± SD)	34.5 ± 4.6	32.4 ± 2.7	0.125
Insulin used during pregnancy (%)	40.9	30.0	0.282
Prior history of GDM (%)	22.7	30.0	0.393
Previous pregnancy (%)	50.0	60.0	0.237

GDM, gestational diabetes mellitus; SD, standard deviation.

I'm in full health and [there is] nothing underlying going into the pregnancy" (P27). Seven percent of participants (n = 2) stated that they were able to attend postpartum screening as they had family living nearby; therefore, childcare was available to them. *"Like, I had my mom and I had [husband] to mind [the baby]. It was grand" (P10).*

Intervention level

Nineteen percent of participants ($n = 5$) identified facilitators of postpartum screening at the intervention level. Eleven percent of participants ($n = 3$) expressed that the process was easy as the appointment was made for them. One woman stated that her consultant organised the appointment for postpartum screening, whereas the other two claimed their general practitioner (GP) organised it. *"My consultant organized it [the appointment] … they organized it for me I'm pretty sure" (P16).* Another two participants (7%) explained that their appointment was doubled with one of their baby's check-ups to make the whole process quicker and easier. *"The GP actually rang me. So when I brought my new-born for the check-up, he gave me an appointment for myself as well. It was easy."* (P24).

Healthcare systems level

Thirty-seven percent of participants ($n = 10$) identified facilitators of postpartum screening at the healthcare systems level. Thirty-seven percent of participants ($n = 10$) stated that the importance of screening was explained to them throughout the process. Obstetricians, GPs, diabetes nurses, and midwives were all mentioned as clinicians who stressed this.

> *My GP, my consultant, and the diabetic nurses in the hospital [explained the importance of getting tested]. And it was very, very clear… it was very much promoted" (P19).*

Nineteen percent of participants ($n = 5$) explained that their medical team was very supportive during and after their pregnancy. GPs and consultants were mentioned as very good at keeping track of everything and reminding the women about screening and general check-ups.

> "*I was lucky now, my own GP was so you know, insightful into it… the obstetrician as well… There was just plenty of help and guidance. Maybe that led to it [attending screening] and if people weren't as supportive, I may not have bothered with it" (P13).*

Barriers to postpartum screening

Of the 27 participants, 19 (70%) were able to identify barriers to postpartum screening.

Personal level

Forty-eight percent ($n = 13$) of participants identified barriers to postpartum screening at the personal level. Fifteen percent ($n = 4$) of participants explained that they continued to self-monitor and check blood sugar levels themselves after they gave birth. As their levels returned to normal, they did not feel the need to return for formal screening.

> "*I still have my little monitoring machine and I often just give it a check here and there. My sugars are fine. […] So I didn't, I was never retested for it. I just kept an eye on my sugars myself" (P3).*

Eleven percent of participants ($n = 3$) stated that returning for screening was not a priority for them, as they were focusing on caring for their newborn.

> "*It was busyness, really… It was all about the baby, really… I kind of just never even thought about it… it was about three or four months before I even thought about myself really. So that's why I didn't go back. It wasn't really a priority, being honest" (P4).*

Eleven percent of participants ($n = 3$) claimed that they would attend postpartum screening, but they had not been made aware that it was necessary. *"I hadn't planned to go annually; I wasn't actually told that it was a recommendation. But if it was, I would have, you know, but like, look it again, that wasn't communicated to me" (P18).* Another 11% of participants ($n = 3$) said that they were aware

Table 3
Perceived facilitators (F) of and barriers (B) to postpartum screening at the personal, intervention and healthcare systems level.

	Facilitators $n = 20$ (74%)	Barriers $n = 19$ (70%)
Personal level F = 70% ($n = 19$) B = 48% ($n = 13$)	• Own health concerns ($n = 16$) 59% • Perceived severity of type II diabetes ($n = 6$) 22% • Family history of type II diabetes ($n = 5$) 19% • Concern for effect on family ($n = 3$) 11% • Family planning ($n = 2$) 7% • Childcare available ($n = 2$) 7%	• Self-monitoring ($n = 4$) 15% • Not perceived as a priority ($n = 3$) 11% • Not aware testing was necessary ($n = 3$) 11% • Not concerned about type II diabetes ($n = 3$) 11% • Fear of needles ($n = 2$) 7% • Childcare not available ($n = 2$) 7% • Stigma/shame ($n = 2$) 7% • Work ($n = 1$) 4%
Intervention level F = 19% ($n = 5$) B = 44% ($n = 12$)	• Appointment made for them ($n = 3$) 11% • Doubling up the appointment with the baby ($n = 2$) 7%	• Confusion over test ($n = 9$) 33% • Having to organise the appointment ($n = 3$) 11% • Access to glucose drink ($n = 2$) 7% • Cost ($n = 1$) 4%
Healthcare systems level F = 37% ($n = 10$) B = 37% ($n = 10$)	• Importance of screening explained ($n = 10$) 37% • Supportive medical team ($n = 5$) 19%	• COVID ($n = 7$) 26% • Lack of care after birth ($n = 5$) 19% • Lack of support from GP ($n = 3$) 11% • Access to GP ($n = 1$) 4% • HSE hack ($n = 1$) 4%

GP, general practitioner; HSE, Health Service Executive.

that postpartum screening was necessary but are not concerned about T2D, so it does not worry them. *"No, I'm not concerned about type two diabetes. I don't believe I should be at the minute. Like, I don't have any symptomatic problems with my health at the minute. So it's not a concern at the minute"* (P9).

Seven percent of participants ($n = 2$) explained that they did not return for screening as they have a fear of needles and find the screening too stressful. *"You probably think I'm a drama queen … [screening would be] traumatic because I hate needles. I hate them"* (P2). Seven percent of participants ($n = 2$) said that they could not attend as they did not have childcare available to them at the time. *"It's a three-hour test … I didn't have childcare in place at the time … my husband works nights, so it wouldn't be practicable to do it in the afternoon, obviously, it's morning test. […] if I had childcare I would have attended. That was my only stumbling block"* (P6).

Another 7% of participants ($n = 2$) explained that they felt there was shame or stigma attached to attending the screening. They said they felt judgement from both the GPs office and people in their personal lives, as they were unaware of GDM.

> "*For me, it 'would just mostly be… I don't know if it's a bit of stigma or something around it […] going into a totally new setting [after giving birth]… they weren't sure or familiar with my history in relation to the gestational diabetes. That kind of made it a bit awkward for me" (P17).*

One participant (4%) said that she was unable to go to the screening due to work commitments. *"I had blood tests booked in yesterday, but I'm just so busy with work that I had to cancel. When I get some free time maybe, I want to go back"* (P28).

Intervention level

Forty-four percent ($n = 12$) of participants identified barriers to postpartum screening at the intervention level. Thirty-three percent of participants expressed confusion over the screening. Some participants said they were unsure whether they were supposed to go to their GP or UMHL for the test, whereas others said they were unsure what test to ask for.

> "*I don't know whether I should still go back to my GP and have them screen it, or do I need to go back to [the maternity], like I'm not exactly sure of where to go to have the screening done. So I kind of just left it" (P17).*

Eleven percent of participants ($n = 3$) claimed they did not attend, as they had to organise the appointment themselves and subsequently forgot to book it.

> "*I think if I had like, got an appointment from someone, and it was arranged for me, I think I would have went, yeah. When it was on me I didn't*" *(P4).*

Seven percent of participants ($n = 2$) explained that they had attempted to do the screening, but their GP did not have the glucose drink for the test, and they could not source it themselves.

> "*But they didn't have the mixture, the glucose, they didn't have it at the GPs, I… went in and then they told me I was supposed to bring it, which I wasn't aware of… I ran around the whole day to all the pharmacists, and nobody had it because they said there was a shortage" (P14).*

One participant (4%) said that the cost of the screening, after the expense of having GDM during their pregnancy, initially discouraged them from attending. *"I suppose, if we didn't have to pay 60 euros to get it done it might have been a little bit more pleasant. […] Like it's not covered by any medical card scheme or whatever. Which is mental"* (P13).

Healthcare systems level

Thirty-seven percent ($n = 10$) of participants identified barriers to postpartum screening at the healthcare systems level. Twenty-six percent ($n = 7$) of participants identified the COVID-19 pandemic as a significant barrier. Many participants experienced delays and cancellations due to lockdowns and vaccination clinics. While two of these women attended at a later stage, five (71%) did not reschedule their appointment and never attended.

> *We were in the height of COVID at the time, so just a lot of things were like delayed… a lot of the appointments were cancelled and whatnot. That was no one's fault at the time, it was just COVID unfortunately" (P13).*

Nineteen percent of participants ($n = 5$) felt that there was a lack of care after giving birth, which discouraged them from attending the screening. They felt they were left to navigate everything by themselves, which led to them feeling isolated.

> "*It was like, you know, you were kind of dropped off the system once you give birth. […] Like, it seems just you're expected to know what to do after the fact that you've given birth, but like nobody does. […] I feel it should have been more supportive. Not just dropped off the system after you deliver… the aftercare was zero" (P9).*

Eleven percent of participants ($n = 3$) also felt like they did not get sufficient support from their GP. Two women said that their GP was very unsure about the testing process and did not know what to do, whereas the other woman felt that the GP should follow up with her when screening is necessary. *"[The GP] make you feel like you're causing drama for asking for a test … they kind of made me feel like a crazy person. […] You do feel like it's a big deal asking for it. […] I feel like I just being a drama queen"* (P20). One participant (4%) reported problems with accessing her GP. Due to lengthy waiting times, she did not attend postpartum screening. *"There was a four-week waiting list for the bloods and I'm just like, no forget about it … I'm not even getting it done"* (P2).

One participant (4%) explained that her appointment was cancelled due to the HSE hack and did not reschedule it afterwards. The HSE was subject to a cyberattack in May 2021, which resulted in loss of access to all information systems, including patient information. This caused disruption to all healthcare services across the country, as many appointments had to be cancelled and rescheduled. *"I tried [to do the screening], but it was the week of the hack, the HSE hack … I didn't get to do it that week … and I haven't rebooked"* (P8).

Discussion

This study explored the facilitators of and barriers to attending postpartum diabetes screening experienced by Irish women. Although a lot of the findings were congruent with those identified in systematic reviews,[20,34,35] new themes also emerged. These findings give important insight into the postpartum lives of women with GDM and allow for better understanding of their experiences to understand the reasons for compliance or non-compliance with recommendations for postpartum follow-up care in this vulnerable cohort.

Facilitators of postpartum screening

In this study, concern for their own health was the biggest facilitator of attending postpartum screening. Similarly, Dennison

et al.[20] reported that health consequences coupled with understanding of the severity of T2D were significant motivators that encouraged attendance at screening. Women also claimed that important facilitators to attending screening were having the importance of the screening explained to them by healthcare professionals, having a supportive medical team, and having the appointment made for them. Similar to this, an Australian study found that when clinicians properly explained the importance of testing, women put a higher priority on postpartum screening and were more likely to attend.[36] Kilgour et al.[36] also found that when good relationships were built between the women and healthcare professionals, they were more likely to complete the advised postpartum care. This finding was reflected in a study conducted in London, where women who had a good relationship with clinicians were more likely to attend postpartum screening.[28] A good relationship can be fostered by reminding the mothers about screening, giving appropriate time and attention to discuss any concerns they were having, and accommodating the mother's appointment at the same time as the baby's.[36] Sunny et al.[30] reported that mothers in Singapore expressed the desire to double up the screening with their baby's appointments, along with their own other postpartum check-ups, such as pap smears, for convenience. Similar to the present study, Tang et al.[37] found that when women had a family history of T2D, coupled with not wanting to be a burden on their family if they end up getting sick, they acted as motivators to attending postpartum screening. Women also claimed that family planning and having childcare available were reasons that they attended postpartum screening. Both these findings were echoed by Bennett et al.[38] who reported that women were more likely to return for screening if they intended to continue growing their family in the future and wanted to be healthy for that.

Barriers to postpartum screening

Confusion over the test was reported as the major barrier to attending postpartum screening. Women expressed confusion over both where they had to go for the test and what test they had to get. Many participants claimed they could have been told after giving birth in UMHL, but because of tiredness, they could not remember the information they were given. Similarly, Nielsen et al.[39] found that insufficient information about follow-up care and treatment resulted in patients not attending for postpartum screening. COVID-19 was identified as the second biggest barrier to postpartum screening by women in this study. As all participants had given birth between April 2020 and April 2022, they were all attempting to access services during the pandemic. Many healthcare services were suspended to restrict contact with highly infectious environments such as GP offices and hospitals to reduce the risk of infection. Therefore, the pandemic delayed postpartum screening for T2D across the globe, with some national guidelines recommending delaying screening by 6–12 months.[40]

Further barriers to attending postpartum screening that was expressed were the lack of care after birth, lack of support from their GP, and having to organise the appointment themselves. In Scotland, it was found that poor aftercare and having to organise follow-up care themselves led to women believing they were not at high risk of developing T2D and not continuing postpartum follow-up care.[32] Furthermore, in London, women echoed the sense of abandonment they felt after giving birth after the close monitoring they experienced during pregnancy, making it harder to manage their own health demands.[28] Dennison et al.[20] found that patients' interactions with healthcare professionals influenced their decision to attend postpartum screening. The behaviour of the clinician can either encourage or discourage patients to attend screening.[20] In Missouri, a study found that negative interactions and experiences with healthcare professionals created societal mistrust in the medical system, creating a significant barrier for women attending postpartum diabetes screening.[29] Therefore, a feeling of isolation or lack of care after giving birth could further discourage women from seeking postpartum follow-up care. Some women were not aware that postpartum testing was necessary. Sterne et al.[18] also found that inadequate knowledge of the importance of postpartum screening was a significant barrier in women with GDM in Australia. Again, this can be linked to ineffective communication or lack of education from healthcare professionals. Although self-monitoring was identified as a barrier to attending postpartum screening, a study conducted in America found no significant association between self-monitoring and postpartum screening.[41] Dennison et al.[20] also reported patients not seeing screening as a priority because of demands of the new baby, not being concerned about T2D, and not having childcare available as significant barriers to attending postpartum screening. Similarly, Sinha et al.[29] and Parsons et al.[28] found that when pregnant, patients place a high priority on their own health, whereas after delivery, their focus shifts to the health of the newborn, and their own health is no longer a priority. Shame and stigma were reported by some participants as a barrier. This finding is reflected by women in Norway, where some patients claimed that they did not continue follow-up care due to embarrassment and judgement from others.[31]

Implications for practice

This study uncovered different avenues that can be explored to improve uptake of postpartum screening, most notably (1) improved education about postpartum care, (2) reminder system for appointments, (3) improved continuity of care, and (4) more convenient testing.

Women described postpartum education and information about screening to be insufficient. This is reflected in the number of women who were confused about postpartum screening and those that did not realise its necessity. Sterne et al.[18] also found this to be a significant barrier and reported that it was because of unsatisfactory clinician communication. The fertility rate in Ireland amounted to 1.82 children per woman in 2016.[42] The increased risk of recurrent GDM in subsequent pregnancies,[13] coupled with an increasing maternal age,[5] poses a risk for increased prevalence of GDM. Therefore, there is a need for improved education amongst clinicians about gestational diabetes and the risks postpartum so it can be communicated effectively to women. There is also opportunity to establish a perinatal education programme about postpartum care, as most women claimed they were told in hospital after giving birth but could not recall the information afterwards. The National Diabetes Prevention Programme in America has demonstrated the effectiveness of educational interventions in preventing the development of GDM to T2D.[43] Educational classes could be held during pregnancy to stress the importance of postpartum follow-up care and explain the complications that can arise with non-compliance. Postpartum lifestyle modifications to reduce the risk of progression from GDM to T2D should also be discussed at these educational classes, for example, dietary and exercise recommendations.

Throughout the course of the interviews, four women mentioned that they wanted a reminder system for the screening appointments. There are many studies that have reported improved attendance at postpartum diabetes screening once a reminder system was put in place.[44–46] One study found that postal reminders sent directly to the patient increased attendance from 14.3% to 55.3%.[47] Reminder systems are not a new intervention but can be relatively easy and beneficial to put in place. Another study found that SMS reminders, when compared with no reminders, increased the rate of attendance at healthcare appointments (risk ratio 1.14 [95% confidence interval 1.03 to 1.26]).[48] Jeppesen et al.[46] found that adding personal touches

to the reminders appears to influence the women's reaction to them in a positive manner. The format of the reminder system can vary depending on patient needs and available resources, for example, SMS, email, postal, and phone call. Women in this study mentioned text messages and letters as their preferred method of communication for such a system.

There is a need for an improved transition of care from secondary to primary care. Fragmented care has been previously highlighted and discussed as significant barrier to attending postpartum screening.[29,30] Lithgow et al.[49] reported that clinicians faced difficulty during the handover between primary and secondary care for postpartum GDM follow-up. As there was no clear system as to who should be conducting the postpartum screening, patients end up falling through the gaps and never receiving proper care.[49] These feelings were echoed by the women in this study. There seems to be no national systematic approach to continuity of care in Ireland. Therefore, there is a need for defined national guidelines as to who will carry out the postpartum screening, how they will do it and where it will be done. Van Ryswyk et al.[50] also reported that clinicians identified this as a need, along with improved education and training for clinicians regarding postpartum GDM care.

There is also opportunity to research into more convenient testing approaches for women. One woman in this study suggested an at-home testing kit. Dennison et al.[20] suggest a movement towards the HbA_{1c} test as the standard test, as it requires just one non-fasting blood sample. They also suggest further consideration into innovative approaches such as very early postpartum testing before the mother leaves the hospital.[20] Although it is not as accurate as screening conducted at 6–12 weeks, it has the potential to achieve 100% uptake.[51]

Strengths & limitations

This qualitative study has several limitations that should be considered. It is possible that this study may have been influenced by recruitment bias. It has been proven that certain personality traits determine whether they volunteer.[52] Therefore, women who agreed to participate in the study in comparison to those who refused may be more knowledgeable about GDM and T2D and more determined to impact greater change. Furthermore, screening for GDM during pregnancy is not conducted universally in Ireland. It is only carried out on patients who are at a high risk of developing GDM due to older maternal age, high body mass index, pre-existing medical conditions, or a family history of GDM or other diabetes conditions. Consequently, this can be seen as a limitation to this study. Most participants in this study were Irish Caucasian. This can be seen as both a strength and a limitation, as findings can inform practice here, but they cannot be extrapolated to other ethnicities. Although 82% of the population in Ireland are Caucasian, there is an increasingly diverse ethnic population.[53] There was some representation of other ethnicities in this study; however, they made up a small proportion. Some of this research team have previously conducted a retrospective analysis on the same cohort in Limerick.[54] They used ethnic details for the cohort as outlined by Unterscheider et al.[55] who found that 90% of the cohort is Irish/European. Therefore, with this information, coupled with the absence of universal screening, it can be assumed that the barriers and facilitators experienced by women in Ireland are relevant to the country and its medical system, not to ethnicity. Despite this, the viewpoints of women of different ethnic backgrounds would require further research. The interview guide and methodology were conceptualised by two Public Health master's students. They had not previously worked in the service; therefore, they did not have any unconscious bias towards the women they were interviewing. In reflection of this and the high quality of data retrieved during the interviews, we believe that the participants felt more comfortable discussing the details of their experiences with the interviewers, as they were not involved in the women's routine clinical care. The main investigator was a female, whereas a portion of the interviews were conducted by a male. If this study were to be conducted again, ideally both investigators would be present for all interviews to ensure consistency of questions being asked and prompts being offered to the participants during the interviews. There is also danger of recall bias because of the length of time between the interviews and when the women gave birth. If this study was to be conducted again, ideally all women would have given birth in the past year to reduce this risk. These findings might not necessarily apply to other settings, as these perspectives represent the women within one health service in a high-income country.

Conclusion

This study has shown that women experience a variety of different factors that affect their intention to attend postpartum screening for T2D. Non-attendance in follow-up screening can be impacted by factors such as confusion over the test, feeling isolated after giving birth, having to organise the appointment themselves, and not perceiving T2D as a serious disease. Attendance at follow-up screening can be influenced by women's own health concerns, having the importance of screening explained to them by healthcare professionals, having the appointment made for them and perceiving T2D as a serious disease. This study has highlighted that there is opportunity to increase participation in postpartum screening. This can be done through improved education about postpartum care, implementation of a reminder system for appointments, improved continuity of care and more convenient testing.

Author statements

Acknowledgements

We would like to thank the women who participated in this study for their time and openness.

Ethical approval

Ethical approval was granted by the HSE Mid-Western Area Research Ethics Committee (REC ref. 052/2021).

Funding

Open access funding is supported by the Health Research Institute, University of Limerick, Ireland.

Competing interests

All authors declare no conflicts of interest.

Author contributions

A.C. contributed to conceptualisation, methodology, resources, data curation, supervision, funding acquisition and writing the original article. Á.C. contributed to writing the original article, investigation, visualisation, project administration and formal analysis. E.N. contributed to review and editing the article. D.O'.D. contributed to visualisation and formal analysis. S.B. contributed to reviewing and editing the article. E.B. contributed to validation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.022.

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Public Health 220 (2023) 33–34

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Short Communication

Factors influencing herpes zoster vaccination among older people in China: results from a discrete choice experiment

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ARTICLE INFO

Article history:
Received 5 March 2023
Received in revised form
12 March 2023
Accepted 28 April 2023

Keywords:
Herpes zoster vaccine
Discrete choice experiment
Preference
Older people

ABSTRACT

Objectives: Vaccination is the most effective way to prevent herpes zoster (HZ) and related complications. This study aimed to investigate the preference of HZ vaccine among older people.
Study design: A discrete choice experiment was performed.
Methods: In total, 178 adults aged ≥50 years were invited to choose between HZ vaccination scenarios using six vaccine attributes. Two equations were used to calculate participants' willingness to pay for the vaccine and their predicted choice probability.
Results: The attributes that significantly influenced participants' vaccine choices were lower cost, higher effectiveness, reduced side-effects and vaccination of others in their surroundings.
Conclusions: Improving medical insurance coverage or reducing the cost of the HZ vaccine will encourage more people to be vaccinated, resulting in reduced burden of disease among older people.

Introduction

Herpes zoster (HZ) and related complications lead to an economic burden to individuals as well as to society.[1] With limited therapies available, vaccination is the most effective way to control HZ and related complications.[2,3] In May 2019, a new HZ vaccine received fast-track approval by China's National Medical Products Administration and has been available for individuals aged ≥50 years since June 2020. This discrete choice experiment (DCE) recruited adults aged ≥50 years to explore their preference for this novel vaccine. The data presented here could help improve policymaking for the HZ vaccine in China.

Methods

The DCE survey was conducted between November 2021 and February 2022. After literature searches, consultation with experts and pretest interviews and six vaccination attributes, with their corresponding response categories, were determined as follows: (1) vaccine cost (2500 Chinese Yuan (CNY) [US$362], 3500 CNY [US$507] or 4500 CNY [US$652]); (2) vaccine effectiveness (87%, 90% or 93% reduction of HZ cases); (3) risk of mild-to-moderated side-effects (20%, 50% or 80%); (4) vaccination of people in their surroundings (yes or no); (5) vaccination hour (8 AM–11 AM Monday to Friday, 8 AM–11 AM Monday to Saturday, or 8 AM–11 AM and 1:30 PM–3 PM Monday to Saturday); and (6) number of doses (single dose or double dose at least 2 months apart).

To reduce the burden of completing the survey, 16 hypothetical choices, paired with eight choice sets, were generated by a fractional factorial design based on orthogonal arrays.

All participants provided written consent to take part in the study before commencing the survey. Personal information, such as names and contact details, were not collected, and data were thus fully anonymised.

Participants' willingness to pay (WTP) for a certain attribute was assessed using the equation WTP (x) $= \frac{\beta(x)}{\beta(cost)}$, where β (x) and β (cost) are the coefficients of attribute x and cost, respectively.

An HZ vaccination choice with a cost of 2500 CNY (US$362), 87% effectiveness, 20% risk of mild-to-moderate side-effects and vaccination of people in their surrounding was set as the baseline; the predicted choice probability (likelihood of choosing a vaccine) was predicted using the equation $P_i = \frac{e^{\beta' v_i}}{\sum e^{\beta' v_j}}$, where i and j represent two different HZ choices, P is the choice probability and v is the utility score.

All data were entered into Epidata 3.1, with double entries from two investigators. The vaccine-choice data generated from the DCE

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https://doi.org/10.1016/j.puhe.2023.04.025
0033-3506/

Table 1
Preferences and willingness to pay (WTP).

Attribute	Coefficient (standard error)	WTP (CNY)
Vaccine cost (for every 100 CNY [US $14] increase)	−0.04*** (0.01)	–
Vaccine effectiveness (for every 1% increase)	0.05* (0.02)	119.37 (US $17.28)
Risk of mild-to-moderate side-effects (for every 10% increase)	−0.23*** (0.02)	−607.11 (−US $87.91)
Vaccination hour		
8 AM–11 AM, Monday to Friday	1.00	–
8 AM–11 AM, Monday to Saturday	0.35 (0.23)	–
8 AM–11 AM and 1:30 PM–3 PM, Monday to Saturday	−0.02 (0.12)	–
Vaccination of people in their surroundings		
Yes	1.00	–
No	−0.41*** (0.09)	−1079.01 (−US $156.24)
Number of doses		
Single dose	1.00	–
Double dose at least 2 months apart	−0.12 (0.09)	–

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
CNY, Chinese Yuan.

survey were analysed using a random parameter logit model with Stata 16.0. All analyses were performed using IBM SPSS 25.0.

Results

In total, 170 of 178 (95.5%) participants completed the survey (eight participants were excluded as a result of incomplete questionnaires). Four vaccination attributes had significant influences on participants' choices; the coefficients of each attribute indicated that older people preferred the HZ vaccine with lower cost, higher effectiveness, lower risk of mild-to-moderate side-effects and vaccination of people in their surroundings (Table 1).

Investigation of WTP showed that participants chose to pay another 119.37 CNY (US $17.28) for every 1% increase in vaccine effectiveness. However, a decrease in WTP of 607.11 CNY (US $87.91) was seen for every 10% increase in mild-to-moderate side-effects. Interestingly, participants' WTP dropped another 1079.01 CNY (US $156.24) when no one in their surroundings had been vaccinated.

In terms of the probability of choice, when the occurrence of mild-to-moderate side-effects increased from 20% to 80%, there was a resulting 21% decrease in participants' choice of the HZ vaccine. The choice probability dropped by 13% when the cost increased from 2500 CNY (US $362) to 4500 CNY (US $652). When no one in their surroundings had been vaccinated, the choice probability dropped by 6%, and when the effectiveness increased from 87% to 93%, the choice probability increased by 2%.

Discussion

HZ occurs most frequently in older people, and China has one of the fastest-growing ageing populations in the world. Improving vaccination coverage for vaccine-preventable diseases among older people would ease the increasing disease burden. Currently, the HZ vaccine is the most expensive vaccine per dose in China. Consistent with results from a DCE study in the United States,[4] the present study showed that older people in China prefer vaccines at a lower cost. However, the current results also show that participants would pay more if people in their surroundings were vaccinated. This imitation behaviour should be considered when designing strategies to promote HZ vaccination in China. It can be assumed that if the government adjusts policies such as expanding medical insurance coverage or centralising procurement to reduce out-of-pocket costs, more people will be vaccinated. Thus, individuals may imitate the vaccination behaviour of others and would be willing to pay more for this vaccine.

Author statements

Acknowledgements

The authors wish to thank the study participants for their contribution to the research.

Ethical approval

The study was approved by the Ethics Committee of Zhejiang Chinese Medical University. All the participants provided consent before the study.

Funding

This research was supported by the National Social Science Fund of China (No. 22BGL316).

Competing interests

None declared.

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Public Health 220 (2023) 65–71

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/puhe

Original Research

Incidence and characteristics of aspiration pneumonia in adults in Beijing, China, 2011–2017

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ARTICLE INFO

Article history:
Received 16 December 2022
Received in revised form
21 April 2023
Accepted 26 April 2023

Keywords:
Aspiration pneumonia
Incidence
Silent aspiration
Community-acquired pneumonia

ABSTRACT

Objectives: This study aimed to estimate aspiration pneumonia (AP) incidence and describe comorbid characteristics and mortality in Beijing, China.
Study design: A historical cohort study was conducted based on medical claim records.
Methods: Patients admitted with a primary diagnosis of AP were identified from approximately 12 million adults who enrolled in the Urban Employee Basic Medical Insurance program in Beijing, China, from January 2011 to December 2017. The incidences of AP and pneumonia with risk factors for aspiration (PRFA) were estimated by a Poisson distribution. The estimated annual percentage change was reported to represent the average percentage change in incidence per year. Characteristics and 6-month and 1-year all-cause mortality rates for AP and suspected AP patients were described and compared with community-acquired pneumonia (CAP).
Results: The incidence rates of hospitalized AP and PRFA were 9.4 (95% confidence interval [CI]: 7.6, 11.3) and 102.9 (95% CI: 95.8, 110.3) per 100,000 person-years, respectively. The incidences increased rapidly with age and were stable across the observed years. Patients with AP and PRFA possessed a greater burden of comorbidities than CAP (mean age-adjusted Charlson comorbidity indices for AP: 7.72, PRFA: 7.83, and CAP: 2.84). The 6-month and 1-year all-cause mortality rates for those with AP and PRFA were higher than those for patients with CAP (6-month mortality, AP: 35.2%, PRFA: 21.8%, CAP: 11.1%; 1-year mortality, AP: 42.7%, PRFA: 26.6%, CAP: 13.2%).
Conclusions: The incidence of AP and PRFA in Beijing was reported, presenting a full picture of the disease burden. The results provide baseline information for AP prevention.

Introduction

Lower respiratory tract infection is the fourth leading cause of death worldwide, accounting for 3.8% of disability-adjusted life-years in the world.[1] Aspiration pneumonia (AP) is a special category of lower respiratory tract infection, which is defined as pneumonia caused by inhalation of oral or gastric contents into the lower respiratory tract.[2] Compared with patients with non-AP, patients with AP are more likely to be older, have a higher comorbidity burden, and have longer hospital stays.[3–5] Lanspa et al. reported that the inpatient mortality of AP was twice as high as that of non-AP (23% vs 9%),[6] whereas Hsu et al. reported that the 1-year mortality of AP was almost twice that of non-aspiration community-acquired pneumonia (CAP; 40.4% vs 22.1%).[7] Hayashi et al. reported that the proportion of recurrent pneumonia in AP was 54.0%, much higher than the 15.8% in non-AP. Teramoto et al. reported that three-quarters of hospitalized patients with pneumonia were aged ≥70 years, and 80% of pneumonia patients aged ≥70 years were diagnosed with AP.[8] Estimating the incidence of AP in an aging region is helpful in directing prevention activities, planning health services, and setting public health goals.

Efforts have been made to describe the epidemiology of AP by reporting its proportion in total CAP, although the proportions vary widely across regions and populations (5%–60%).[2–4,6,8–11] Several

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https://doi.org/10.1016/j.puhe.2023.04.021
0033-3506/

studies have reported the incidence of AP in patients with stroke,[12,13] head and neck cancer,[14,15] or Parkinson's disease.[16] However, only two studies have reported the incidence of AP in the general population.[17,18] The incidences of AP admission were 309/100,000 in Americans aged >65 years[17] and 347/100,000 in Spanish individuals aged >75 years.[18] There has been a concern about the potential underestimation of the incidence.[17,19] The diagnosis of AP depends on a characteristic clinical history (witnessed macroaspiration), risk factors, and compatible findings on chest radiography.[2] However, given the rare opportunity to witness, a significant amount of silent aspiration may be neglected,[20–22] which poses difficulty in assessing the actual incidence of AP in a region.[2,17,23]

Dysphagia and impaired consciousness are important causes of aspiration. People with stroke or dementia and those using sedation medication have a higher risk of aspiration.[2,3,24,25] As aspiration is difficult to observe directly, a list of risk factors has been used as the proxy for aspiration, such as dysphagia, gastroesophageal reflux, and sedative drug abuse, for the diagnosis of AP.[2,3,8,9,24–27] It has been suggested that pneumonia with risk factors for aspiration (PRFA) should be considered a subphenotype of pneumonia.[3] Therefore, combining clinically diagnosed AP and PRFA would be a practical way to obtain a full picture of the AP burden in a region.

China has a fast pace of population aging. There are high disease burdens of neurologic disorders,[28–30] which are associated with dysphagia and put the Chinese population at a high risk of AP. However, little is known about the incidence of AP in China. In this study, we aimed to estimate the incidence of AP in Beijing, China, including PRFA in addition to clinically diagnosed AP, and further describe the comorbid characteristics and mortality in the patients.

Methods

Study design and data source

A historical cohort study was conducted based on the Beijing Medical Claim Data for Employees (BMCDE). The BMCDE keeps track of all the medical claim records for adults who enrolled in the Urban Employee Basic Medical Insurance (UEBMI) program in Beijing, China. According to statistics, the UEBMI program covered more than 80% of adult residents in Beijing in 2017.[31] The details of this database have been described previously.[32] It has been validated to be useful for epidemiological studies.[33–35] Briefly, the database contains every billable medical record from all types of healthcare facilities, including hospitals, outpatient clinics, community health service centers, and pharmacies. Anonymized data for UEBMI beneficiaries who enrolled in the program over 1 year from January 2011 to December 2017 were extracted to estimate the incidence.

Identification of AP episodes

After quality control and data standardization, diagnostic codes of the *International Classification of Diseases, Tenth Revision* (ICD-10), are recorded in the database by physicians on the basis of the hospital's real diagnostic process. AP was diagnosed by qualified physicians in each hospital. The diagnostic criteria for AP were a combination of pneumonia and aspiration. The patients presented with symptoms of pneumonia, including increased inflammatory markers and chest imaging findings, and had a typical clinical history, such as witnessed macroaspiration or choking on food or liquids. Episodes of AP were identified according to the following criteria: (1) hospital admissions from January 2011 to December 2017; (2) a primary diagnosis of AP according to the ICD-10 code J69.0 or diagnosed with medical terms of “aspiration pneumonia”;[4] and (3) complete information on birth date and sex. In this study, 13 records were deleted because of incomplete information.

Many missed diagnoses caused by silent aspiration are an objective problem in the current diagnostic process of AP.[17,23] Previous researchers have recommended a careful review of medical history to discover risk factors for aspiration in patients.[23] To understand the maximum possible range of disease burden attributable to AP in Beijing, PRFA episodes were identified as hospital admissions with a primary diagnosis of pneumonia in patients who had at least one risk factor for aspiration in reference to the study by Taylor et al.[3] The pneumonia episodes were identified by similar criteria to AP, using the ICD-10 code J10-J18 and the medical term “pneumonia.”[5,36] Both primary and secondary diagnoses were recorded in the database. As the pneumonia was identified only by the primary diagnosis, it can be assumed that identified pneumonia cases developed in the community (i.e. CAP).[17] Patients with a primary diagnosis of other diseases and secondary pneumonia during hospitalization were not included. The risk factors for aspiration include dysphagia, cerebrovascular disease, head and neck cancer, gastroesophageal reflux, dementia, Parkinson's disease, hemiplegia, epilepsy, multiple sclerosis, lateral sclerosis, cardiac arrest, alcohol dependence, and sedative drug abuse[2,3,24,25] (Supplementary material). For differentiation, AP episodes were not included in the PRFA episodes.

Repeat episodes within 30 days for the same person were excluded. Both outpatient and inpatient episodes were identified in our study. Patients hospitalized with AP were excluded from outpatients with AP in the same year to distinguish outpatients from admitted patients.

Estimation of incidence

Beneficiaries who withdrew from UEBMI due to death, job transfer, or other reasons were excluded each year. The population at risk was determined by the number of UEBMI beneficiaries from 2011 to 2017 (approximately 12.3 million adults). The denominator was the total person-years that the population at risk accrued during the observational period. Because patients in the current admissions could not contribute to another episode in the following 30 days, person-time was accordingly excluded from the denominator. The numerator was the number of episodes identified according to the criteria mentioned previously. The annual incidence rate was expressed as the age- and sex-standardized incidence rate in person-years, using the 2010 Beijing population as the standard population. Age-specific and sex-specific incidence rates were also calculated.

Statistical analysis

The incidence and the 95% confidence intervals (CIs) were estimated using a Poisson distribution. The trend of annual incidence from 2011 to 2017 was further evaluated by the indicator estimated annual percentage change (EAPC).[37] The EAPC was calculated from a regression line fitted by

$$ln(annual\ incidence) = \alpha + \beta \times (calendar\ year) + \varepsilon,$$

where EAPC equals $100 \times (e^{\beta} - 1)$, representing the average percentage change per year. An increasing trend was indicated when both the EAPC point estimate and the lower limit of its 95% CI were larger than zero. Conversely, a decreasing trend was indicated when both the EAPC point estimate and the upper limit of its 95% CI were less than zero. Otherwise, the annual incidences were stable across the years.

The comorbid characteristics and mortality of AP and PRFA were described and compared with CAP (without risk factors for aspiration). The age-adjusted Charlson comorbidity index (ACCI) was used to describe the comorbid characteristics of patients[38] (Supplementary material). The 6-month (1-year) all-cause mortality rates were calculated as the ratio of the number of cases who died within 6 months (1 year) after onset to the total number of cases. The mean (and standard deviation) was reported for continuous variables, and the number (and percentage) was reported for categorical variables. Continuous variables were subjected to an analysis of variance, and categorical variables were subjected to the Chi-squared test. A two-tailed P value <0.05 was considered statistically significant.

Results

Incidence of hospitalized AP

After observation of 47,182,987 person-years for approximately 12.3 million adults, a total of 2562 hospitalized AP episodes (for 1875 patients) and 28,293 hospitalized PRFA episodes (for 24,302 patients) were identified. The incidence rates of hospitalized AP and PRFA were 9.4 (95% CI: 7.6, 11.3) and 102.9 (95% CI: 95.8, 110.3) per 100,000 person-years, respectively (Table 1). The incidences in males were significantly higher than those in females for both AP and PRFA (Table 1, Fig. 1). The incidences of AP and PRFA increased rapidly with age (Table 1, Fig. 1). From 2011 to 2017, the incidences of hospitalized AP were stable across the years (EAPC: −4.3%, 95% CI: −10.2%, 2.0%). Similarly, the incidences of PRFA were also stable across the years (EAPC: 2.8%, 95% CI: −0.9%, 6.6%; Fig. 2).

Comorbid characteristics of hospitalized patients with AP

Patients with AP and PRFA possessed a greater burden of comorbidities than patients with CAP, with mean ACCIs of 7.72 and 7.83, respectively (Table 2). The proportions of AP and PRFA patients comorbid with cerebrovascular diseases (87.1%, 94.2%), dementia (19.4%, 8.6%), and hemiplegia (6.3%, 2.9%) were much higher than those of patients with CAP (cerebrovascular diseases 0.0%, dementia 0.1%, and hemiplegia 0.2%, respectively; Supplementary Table 1).

Mortality of hospitalized AP

For hospitalized patients, the 6-month all-cause mortality rates for those with AP and PRFA were 35.2% and 21.8%, respectively, whereas the 1-year all-cause mortality rates were 42.7% and 26.6%, respectively (Table 3). The mortality rates were significantly higher than those of CAP. Older patients and patients with a higher burden of comorbidities had higher mortality rates (Fig. 3).

Table 1
Incidence (1/100,000 person-years) of hospitalized AP and PRFA in Beijing, 2011–2017.

Group	AP (95% CI)	PRFA (95% CI)
All	9.4 (7.6, 11.3)	102.9 (95.8, 110.3)
Sex		
Male	11.7 (9.7, 13.8)	106.3 (99.7, 113.2)
Female	7.0 (5.4, 8.8)	99.2 (91.6, 107.1)
Age group in years		
18-44	0.07 (0.01, 0.14)	3.03 (2.00, 4.17)
45-54	0.73 (0.22, 1.36)	29.49 (24.97, 34.20)
55-64	6.73 (4.63, 9.04)	119.44 (109.66, 129.47)
65-74	26.16 (20.03, 32.69)	373.24 (349.03, 397.95)
75-84	131.63 (114.44, 149.45)	1221.77 (1167.98, 12,76.28)
≥85	379.23 (303.52, 459.30)	2781.22 (2574.84, 2992.45)

AP, aspiration pneumonia; 95% CI, 95% confidence interval; PRFA, pneumonia with risk factors for aspiration.

Incidence, comorbidity, and mortality of outpatient AP

For outpatient episodes, a total of 599 AP and 87,123 PRFA were observed. The incidence rates of outpatient AP and PRFA were 5.6 (95% CI: 4.1, 7.4) and 701.9 (95% CI: 681.4, 722.7) per 100,000 person-years, respectively (Supplementary Table 2). The incidences increased rapidly with age (Supplementary Fig. 1). From 2011 to 2017, the trends of the incidences of outpatient AP and PRFA were stable across the years (Supplementary Fig. 2). Similar to inpatients, outpatients with AP and PRFA had higher mean ACCI scores and higher mortality rates than those with CAP (Supplementary Tables 3 and 4).

Discussion

To our knowledge, this is the first report estimating the incidence of AP in the Chinese population. We used different criteria to identify AP episodes to obtain a full picture of the AP burden. According to the results, the incidences of hospitalized AP and PRFA were 9.4 and 102.9 per 100,000 person-years, respectively, among adults in Beijing. Compared with patients with CAP, patients with AP and PRFA have a greater comorbidity burden and much higher mortality rates at 6 months and 1 year.

According to the results, hospitalized AP cases accounted for 5.6% of hospitalized CAP cases in the study population, which is similar to the reports from Shariatzadeh, Lanspa, and Lindenauer (8.7%–13.6%).[4,6,10] Two large studies investigated the incidence of hospitalized AP in the general population.[17,18] The incidence of hospitalized AP in Americans older than 65 years was 309/100,000, which is slightly higher than the rate in our results (83.5/100,000),[17] whereas the incidence in Spain populations aged 75–84 years was 159.7/100,000, which is comparable with the rate estimated in our study (131.6/100,000).[18]

According to the results, the incidence of hospitalized PRFA (102.9/100,000) was much higher than that of AP, posing a potential underestimation in the AP incidence. As Wu and Sanivarapu commented in previous studies, potential underestimation of AP exists.[17,19] Evidence of pneumonia and aspiration are both required for the diagnosis of AP. However, the determination of aspiration is difficult. In addition to overt aspiration and witnessed aspiration, there is a significant amount of silent aspiration.[20–22] To solve the potential underestimation problem, we used PRFA to identify the potential AP burden among adults in Beijing. The risk factors for aspiration are important causes of pneumonia. Previous studies suggested that the possibility of aspiration and dysphagia should be considered in older patients with pneumonia.[23] Taylor et al. suggested that PRFA should be considered an independent phenotype of pneumonia.[3] In addition, they found that patients with pneumonia at risk for aspiration were older than those with ordinary pneumonia and had a higher risk of short-term and long-term mortality. As patients have more risk factors for aspiration, the risk of aspiration may increase. A study showed that the more risk factors for aspiration, the higher the α-amylase level in bronchoalveolar lavage specimens, which should only exist in the mouth or digestive tract.[39] The study by Kawai et al. showed that the more risk factors for aspiration, the higher the risk of developing AP.[40] Combining estimation of the incidences of AP and PRFA would reflect the whole burden in a regional population, which provides a basis for the local management of AP.

The incidence rate of AP in males was higher than that in females, which was consistent with previous studies.[17,18] In the

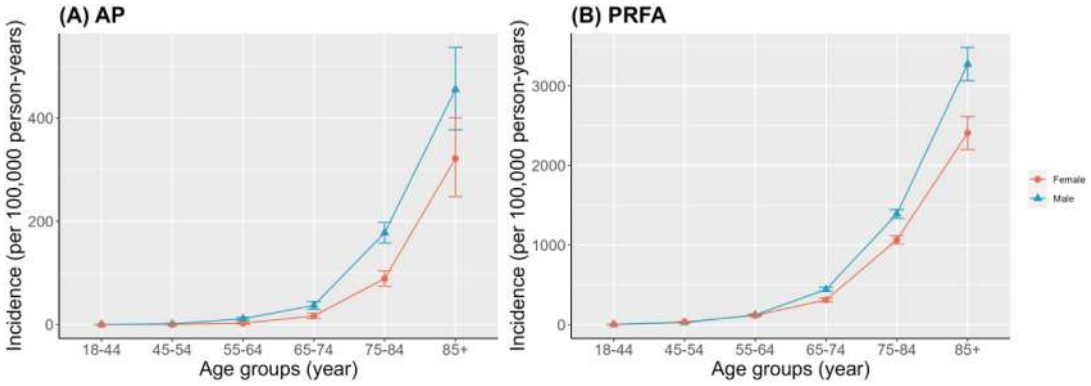

Fig. 1. Incidence of hospitalized AP and PRFA in different age groups, Beijing, 2011–2017. AP, aspiration pneumonia; PRFA, pneumonia with risk factors for aspiration.

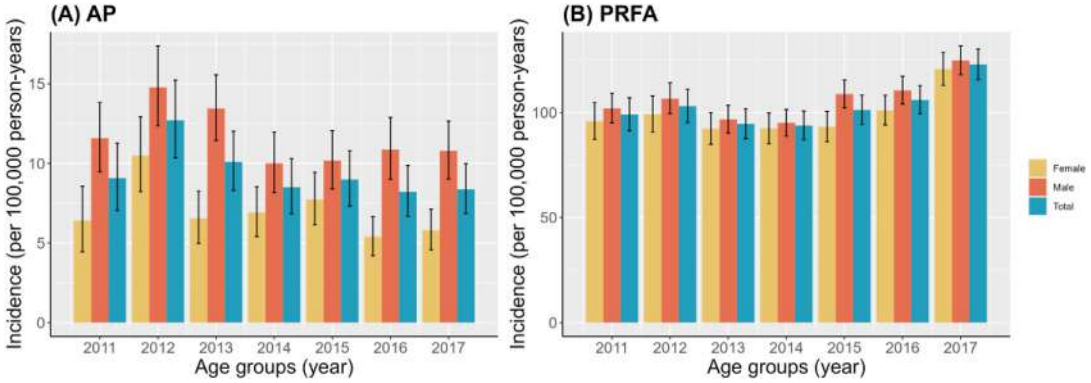

Fig. 2. Incidence of hospitalized AP and PRFA in each year, Beijing, 2011–2017. AP, aspiration pneumonia; PRFA, pneumonia with risk factors for aspiration.

Table 2
Age-adjusted Charlson comorbidity index (ACCI) among patients with AP, PRFA, and CAP (unit, score).

Group	AP	PRFA	CAP
Overall	7.72 (2.86)	7.83 (2.94)	2.84 (2.69)
Sex subgroups			
Male	7.75 (2.88)	7.89 (2.93)	2.87 (2.64)
Female	7.68 (2.84)	7.75 (2.94)	2.79 (2.76)
Age subgroups in years			
18–44	2.00 (2.61)	2.24 (1.91)	0.31 (0.85)
45–64	4.84 (2.34)	5.76 (2.74)	2.22 (2.03)
65–74	7.26 (3.16)	7.39 (2.74)	4.26 (2.29)
75–84	8.04 (2.67)	8.46 (2.68)	5.22 (2.10)
≥85	8.40 (2.52)	8.98 (2.52)	5.75 (1.82)

ACCI, age-adjusted Charlson comorbidity index; AP, aspiration pneumonia; CAP, community-acquired pneumonia (without risk factors for aspiration); PRFA, pneumonia with risk factors for aspiration.
Among patients with AP, PRFA, and CAP, the differences were all significant ($P < 0.001$).

Table 3
Mortality rate comparison among patients with AP, PRFA, and CAP.

Category	Overall	Male	Female
6-month all-cause mortality, *n*[a] (%)			
AP	902 (35.2)	649 (37.6)	253 (30.3)
PRFA	6169 (21.8)	3994 (25.1)	2175 (17.6)
CAP	1625 (11.1)	1061 (12.5)	564 (9.2)
1-year all-cause mortality, *n* (%)			
AP	1093 (42.7)	781 (45.2)	312 (37.4)
PRF	7532 (26.6)	4897 (30.8)	2635 (21.3)
CAP	1930 (13.2)	1264 (14.9)	666 (10.9)

ACCI, age-adjusted Charlson comorbidity index; AP, aspiration pneumonia; CAP, community-acquired pneumonia (without risk factors for aspiration); PRFA, pneumonia with risk factors for aspiration.
[a] *n*: number of deaths. The differences between males and females were all significant ($P < 0.001$).

Spanish population aged >75 years, the incidence of AP is 330.2/100,000 in males and 235.5/100,000 in females.[18] In the United States, 62.6% of patients aged 18–65 years and 52.9% of patients aged >65 years were males.[17] The higher incidences in males may be explained by higher incidences of stroke, parkinsonism, dysphagia, or other risk factors for aspiration in males.[28,29,41] In addition, men are more likely to have poor life habits, such as smoking and drinking,[28] which are associated with pulmonary and neurological adverse effects. The incidence of AP increased with increasing age, consistent with previous studies.[6,17,18] With increasing age, people experience a decline in swallowing function and an elevated risk of neurologic disorders, such as stroke and dementia.[24,28,30,42] These factors put older adults at higher risk of aspiration.

In our study, the 1-year mortality rates were 42.7% and 26.6% for AP and PRFA, respectively, which were significantly higher than the rate of CAP. The results were consistent with those of previous studies. Yoon et al. reported that the 1-year mortality rate of AP was 49.0%.[43] Hsu et al. reported that the 1-year mortality of AP was almost twice that of CAP patients (40.4% vs 22.1%).[7] The difference in mortality between AP and PRFA may be explained by the fact that the mortality from AP is largely dependent on the volume and content of aspiration.[19] Most AP patients have overt aspiration, with larger aspiration volumes than patients with PRFA. In-hospital mortality may be more relevant to the volume of aspiration than the 1-year mortality. However, in-hospital mortality was not analyzed because of the data availability.

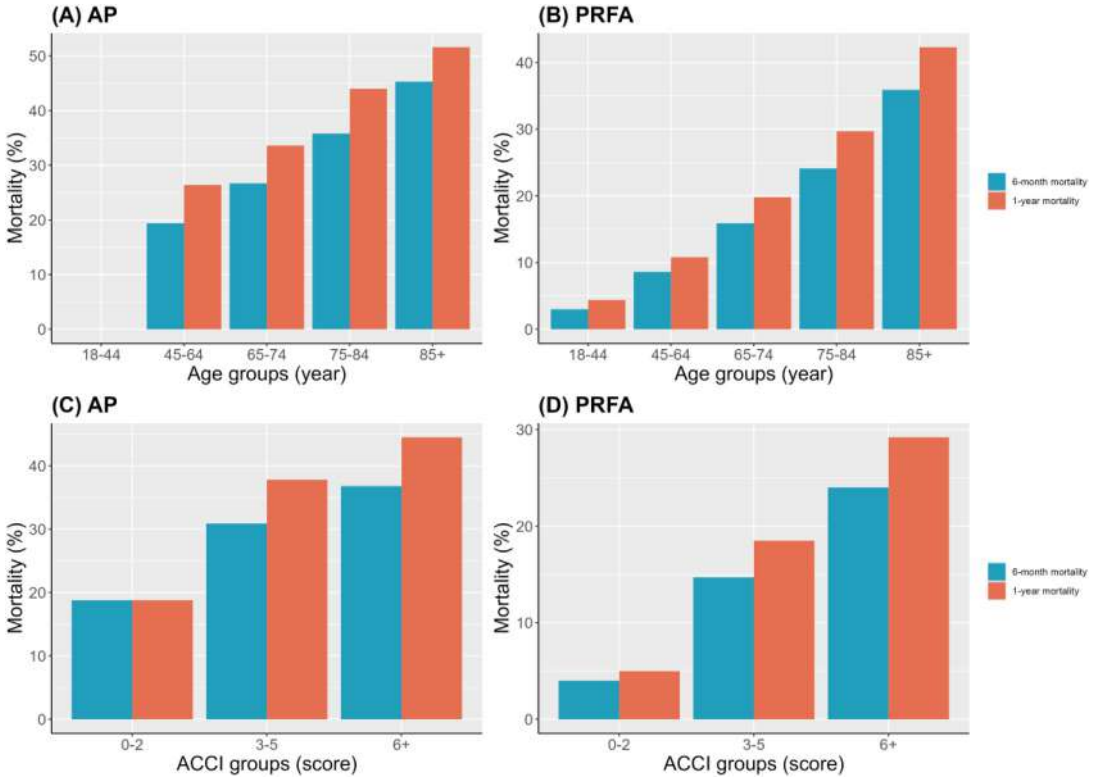

Fig. 3. Mortality rate of hospitalized AP and PRFA patients in different age groups and ACCI groups. (A) and (B): Mortality rate of hospitalized AP and PRFA in different age groups; (C) and (D): Mortality rate of hospitalized AP and PRFA in different ACCI groups. ACCI, age-adjusted Charlson comorbidity index; AP, aspiration pneumonia; PRFA, pneumonia with risk factors for aspiration.

The incidence of outpatient AP was 5.6 (95% CI: 4.1, 7.4) per 100,000 person-years in our study, accounting for approximately one-third of the overall AP incidence. In China, CURB-65 is used to judge the hospital admission needs of patients with pneumonia,[44] and patients with scores of 0–1 should be treated as outpatients in principle. It is noteworthy that among outpatients with pneumonia, outpatients with AP (1-year all-cause mortality: 22.4%) had a much higher mortality rate than those with CAP (2.1%). Care for AP outpatients should be emphasized, such as taking thick food and oral hygiene care.[45,46]

The high incidence of AP in older patients is an important feature of AP. In our results, the AP incidences were stable from 2011 to 2017. However, due to the rapid aging process in China,[47] there would be a year-on-year increase in the absolute number of AP episodes without effective measures. A downward trend in AP incidence has been reported in the United States, which was attributed to community and outpatient health care, the use of oral care, and rehabilitation for dysphagia.[17] Similar and other effective preventive measures should be implemented to combat the disease burden in regions with a high incidence of AP.[45,48–51]

Considering PRFA episodes, we estimated the whole burden of AP in a large Chinese city. Based on a comprehensive database, the study had a large sample size. To our knowledge, this is the first report on AP incidence in the Chinese population. Nevertheless, several limitations exist in this study. First, there is a potential misclassification in AP episodes. The incidence of confirmed AP may be underestimated because of the neglected patients with silent aspiration, whereas the PRFA incidence may be overestimated by including patients without actual aspiration. The aim of reporting PRFA was to represent patients with silent aspiration, describing the maximum possible range of disease burden attributable to AP based in Beijing. Indeed, this method may not be sufficiently specific. We suspect that a proportion of these patients who have PRFA might actually have had AP, but we do not know how many. Nevertheless, combining results with different criteria is currently the best way to estimate the whole burden of AP in a region. Second, different characteristics may exist between the study population and those not included. China has a vast territory. Medical resources, climate conditions, and economic conditions vary greatly among different cities. Beijing is representative of a large city in China. The extrapolation of the results should be done with caution. Third, because of data availability, more detailed characteristics, such as relevant information on in-hospital deaths, smoking status, microbiological diagnostic tests, laboratory test data, and imaging data, could not be described in the study.

Conclusion

In this study, we reported the incidence of AP in adults in Beijing using different criteria to obtain a full picture of the disease burden. The results provide baseline data for AP prevention.

Author statements

Ethical approval

Not needed.

Funding

This work was supported by the National Key R&D Program of China grant: 2020YFC2005401) and the Xicheng financial, scientific, and technological project grant: XCSTS-SD2021-02).

Competing interests

The authors have no conflicts of interest to declare.

Author contributions

Y.W. and L.L. contributed to the study concept. Y.H. had full access to all the data in the study. K.W. and H.Y. take responsibility for the integrity of the data. Y.Z. and Y.W. analyzed the data, interpreted the findings, and drafted the article. L.L., X.Q., D.C., and T.W. interpreted the data. K.W. and H.Y. contributed to illustrating the results. All the authors contributed to the critical revision of the article for important intellectual content. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

Summarized health data can be accessed by contacting the National Insurance Claims for Epidemiological Research Group, School of Public Health, Peking University (0016156078@bjmu.edu.cn).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.021.

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Public Health 220 (2023) 57–64

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Independent and combined associations of upper and lower limb strength with all-cause mortality in community-based older adults: findings from the Chinese Longitudinal Healthy Longevity Survey

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ARTICLE INFO

Article history:
Received 3 December 2022
Received in revised form
27 March 2023
Accepted 25 April 2023

Keywords:
Upper limb strength
Lower limb strength
Older adult
Mortality

ABSTRACT

Objective: With the acceleration of aging progress, China is projected to have the largest older population globally. This study aimed to examine the association of upper limb strength (ULS) and lower limb strength (LLS) with all-cause mortality based on the Chinese Longitudinal Healthy Longevity Survey (2012–2018).

Study design: This is a prospective cohort study.

Methods: Participants were 2442 older adults (aged 84.98 ± 11.94 years) recruited from eight longevity areas in China. Limb muscle strength was evaluated using handgrip strength and objective physical examinations. Cox proportional hazards regression was used to analyze the association of limb muscle strength with all-cause mortality. Demographic characteristics, health status, and biological markers were included as confounders.

Results: Over a median follow-up period of 42.2 months, 993 older people died. After adjusting for all covariates, low ULS was associated with higher mortality risk (hazard ratio [HR] = 1.51, 95% confidence interval [CI] = 1.25–1.84), and the association of low LLS with all-cause mortality was only significant in women (HR = 1.36, 95% CI = 1.04–1.79). Participants with combined low ULS and low LLS had the highest risk of mortality than those with normal limb muscle strength (hazard ratio = 2.06, 95% confidence interval = 1.61–2.63). The combined association of ULS and LLS with mortality was robust in subgroup and sensitivity analyses.

Conclusion: Low ULS and low LLS were independently and synergistically associated with higher all-cause mortality risk. Considering the high prevalence of limb muscle weakness among Chinese older adults, especially the oldest-old, limb strength could be considered as a potential doable mortality predictor for community health care.

Introduction

Decreased limb muscle strength is a typical symptom of malnutrition, frailty, and sarcopenia in older adults with the aging process.[1,2] A number of observational studies reported that low limb muscle strength was associated with early death and poor health outcomes.[3,4] Furthermore, there is growing evidence that low upper limb strength (ULS) and low lower limb strength (LLS) are independently associated with mortality in older adults, yet previous studies have failed to confirm a joint effect. With aging and comorbidity progression, older people often experience combined muscle strength declines of different areas of the body. Considering that leading causes of death in older persons, such as sarcopenia and falls, are simultaneously associated with upper and

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https://doi.org/10.1016/j.puhe.2023.04.023
0033-3506/

lower limb muscle strength, it is necessary to investigate their independent and combined associations with the risk of mortality.

In a systematic review including 38 studies, high handgrip strength was associated with lower risk of death.[5] Another meta-analysis including 44,636 participants revealed that grip strength, walking speed, and chair rises ability were associated with subsequent mortality.[6] However, older people from China, especially those aged >80 years, were rarely included in published reviews. Several prospective studies, including the UK Biobank study, found a positive association between low ULS and increased risk of all-cause and cardiovascular mortality.[7,8] Comparatively, low LLS has received less attention, although it is considered to be of great importance in daily activities and falls prevention.[9,10] Gao et al. conducted a nationwide study and found that decreased upper and lower limb muscle strength were associated with a 13% and 9% increased risk of mortality in Chinese older people, respectively.[11] However, only the independent effect of limb muscle strength was explored in Gao's study.

The study populations of previous studies have been mainly from Western countries or middle-aged groups; thus, knowledge of the association between limb muscle strength and mortality among Chinese older adults, especially the oldest-old, is limited. With the acceleration of aging progress globally, China was predicted to become a super-aged society and have the largest older population by 2033.[12] To address these knowledge gaps, we used the physical examinations and biomarker data from three waves (2012, 2014, and 2018) in the Chinese Longitudinal Healthy Longevity Survey (CLHLS) to investigate the independent and combined association of limb muscle strength with all-cause mortality in community-based older people.

Method

Study population

Baseline data were collected from the 2012 and 2014 waves of CLHLS, an ongoing longitudinal study involving Chinese older adults since 1998. The details of the cohort design and its sampling method were described previously.[13] Participants were recruited from eight longevity areas (Henan, Jiangsu, Guangxi, Hubei, Hunan, Hainan, Shandong, and Guangdong), which accounted for one-third of the longevity areas selected by the Chinese Society of Gerontology in 2011.[14] A total of 3022 participants aged ≥60 years with complete demographic characteristics, lifestyle, physical examination, and serum biomarker data were recruited in the baseline survey and were followed up until 2018. A total of 336 subjects who were lost to follow-up for the first interview were excluded due to inconclusive survival time. Twenty-one subjects with invalid death data were also excluded. Finally, 2442 participants (84.98 ± 11.94 years, 52.83% female), including 1618 oldest-old adults (aged ≥80 years), were included in the present study. The flowchart of participant recruitment is shown in Fig. 1. Participants who were lost to follow-up were more likely to be older, were female, have low education level, and have poor cognitive function. The CLHLS was approved by the Ethics Committee of Peking University (No. IRB00001052-13074). All participants or their guardians provided signed written informed consent before the survey.

Survival data

The survival data were collected from officially issued death certificates or participants' next-of-kin. Survival time (in months) was calculated based on the duration between the first interview date and death. For subjects who were lost to follow-up, censored time was calculated from the interview date at baseline to the last valid follow-up interview date.

Limb muscle strength

Upper limb strength

Trained investigators measured participants' handgrip strength (HS) using a hand dynamometer (WL-1000, Nan Tong). Participants should stand and keep their upper body upright and then press the hand dynamometer with maximum force for 2 s. HS was measured twice with each hand, and the maximal hand strength was recorded. Low HS was defined according to the Asian Consensus on Sarcopenia Diagnosis (2019), with a cutoff of HS <28 kg for men and <18 kg for women.[15] In addition, participants were asked to lift a bucket containing 5 kg of water from the ground with their dominant hand. The investigators recorded whether they could complete this lifting test independently. Participants were classified as having low ULS if they had low grip strength or failed to lift the bucket.

Lower limb strength

LLS was assessed using the sitting-up and squat tests. First, participants sat in a 45-cm chair, with arms crossed over their chest and their back against the backrest of the chair. When ordered, they stood up completely and then returned to the sitting position. To perform the squat test, participants were asked to stand on a flat surface, squat three times without external assistance, and hold the standing position for 3 s after the test. Trained investigators recorded the completion of each physical examination. Participants were defined as having low LLS if they were unable to complete either the sitting-up or squat test independently.

Blood samples

Fasting venous blood samples (5 mL) from all individuals who fasted overnight were collected by trained nurses, and the blood sample was centrifuged at 2500 RPM and 20°C for 10 min. The plasma was transported by −20°C cold chain and stored at −80°C for analysis. Levels of albumin, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TGs), fasting blood glucose, hemoglobin (HB), creatinine, and high sensitivity C-reactive protein (hs-CRP) were measured using a sequential automatic analyzer (Hitachi 7108, Tokyo, Japan) with a commercial diagnostic kit (Roche Diagnostic). Serum 25-hydroxyvitamin D [25(OH)D] levels were measured using an enzyme-linked immunosorbent assay (Bolton, UK). All laboratory tests were performed at Capital Medical University in Beijing, and the details of examinations have been published elsewhere.[16]

Covariates

The following covariates were included in this study.

Sociodemographic characteristics: age (as a continuous variable), sex (female vs male), ethnicity (Han vs others), education (≥1 vs <1 year of schooling), marital status (have no spouse vs other), living status (live alone vs others), and residence (urban vs rural)

Health behaviors and status: Current smoking (yes vs no) and current drinking (yes vs no). Height, weight, waist circumference (WC), and calf circumference (CC) were measured using a standard scale when participants were barefoot and wearing light clothing.

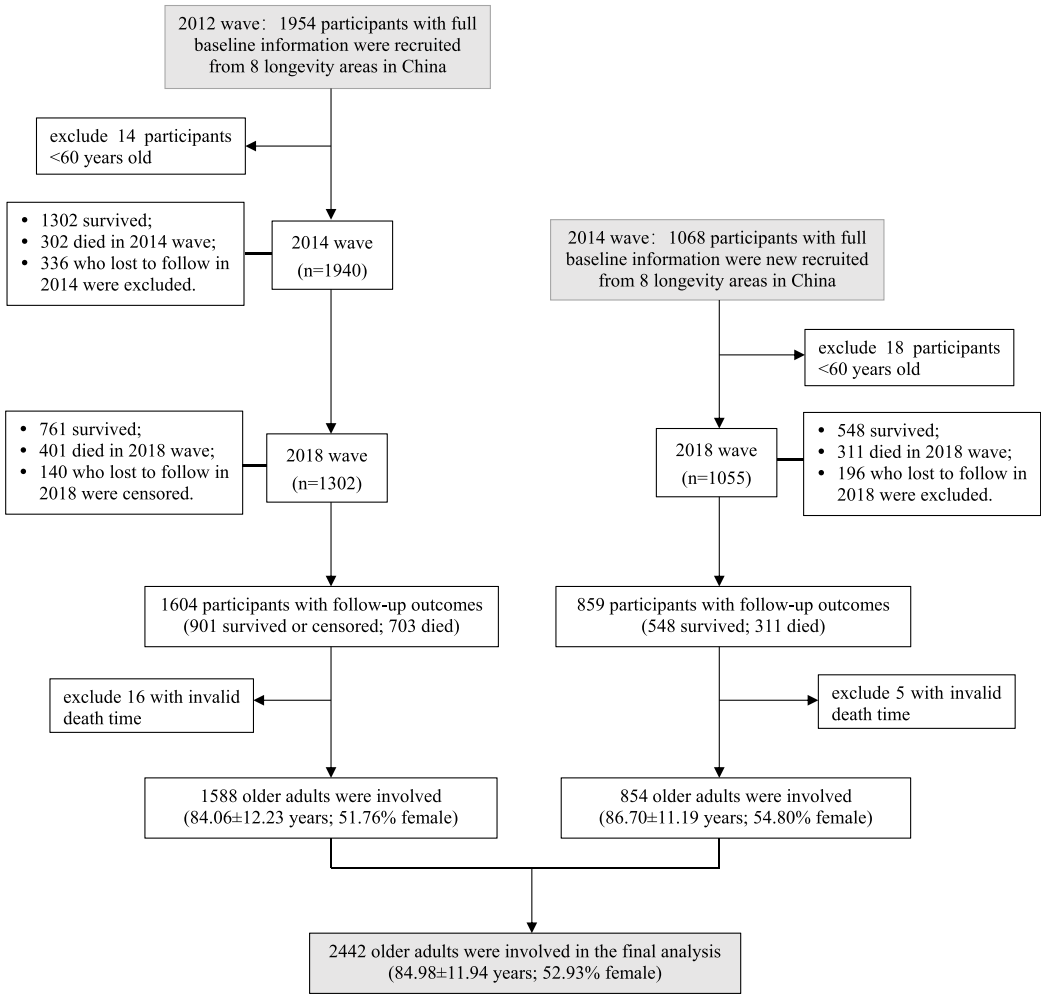

Fig. 1. Flowchart of participant recruitment and follow-up interviews.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Activities of daily living (ADLs) were evaluated using the 6-item Katz scale; participants with a total score <6 points were defined as having ADL impairment.[17] The Mini-Mental State Examination (MMSE)[18] was used to evaluate cognitive function; illiterate participants with a total MMSE score <18 or non-illiterate participants (≥1 year schooling) with a total score <24 were defined as having cognitive impairment.[19] Depression was investigated using a signal dichotomous question (In the past 2 weeks, did you feel sad or depressed?).

Chronic disease–related covariates: (1) Hypertension—participants with systolic blood pressures ≥140 mm Hg or diastolic blood pressures ≥90 mm Hg were defined as having hypertension. (2) Dyslipidemia—subjects with TC >5.17 mmol/L, TG >1.69 mmol/L, HDL <1.04 mmol/L, or LDL >3.36 mmol/L were defined as having dyslipidemia. (3) Pathoglycemia—defined as taking hypoglycemic drugs within the last 2 weeks or FPG ≥7.0 mmol/L. (4) Anemia—-men with HB <130 g/L and women with HB <120 g/L were defined as having anemia. (5) Vitamin D deficiency—Participants with 25 (OH)D <50 nmol/L were defined as having vitamin D deficiency. (6) Albumin, creatinine, and hs-CRP levels were included as continuous variables. (7) History of cerebrovascular disease (CVD) and chronic respiratory disease (CRD) were recorded using *International Classification of Diseases, 10th Revision*.

Statistical analysis

Descriptive data were presented as mean ± standard deviation, median (interquartile range), or numbers (percentages). Student's *t*-test, Wilcoxon rank-sum test, or Chi-squared test were used to compare the baseline characteristics. Kaplan–Meier curves were used to describe the survival probability across different limb strength groups. Three weighted Cox proportional hazards models were used to analyze the independent and joint association between limb strength and all-cause mortality. Each Cox model satisfied the proportional hazards assumption after using the Schoenfeld residuals test (*P*s > 0.05). Model 1 was not adjusted; Model 2 was adjusted for age (continuous variable); Model 3 was additionally adjusted for sex, ethnicity, education, marital status, living status, residence, smoking, drinking, BMI, WC, and CC; Model 4 was additionally adjusted for ADL, cognitive function, depression, hypertension, dyslipidemia, pathoglycemia, anemia, vitamin D deficiency, levels of creatinine, albumin, and hs-CRP, and history of CVD and CRD. Hazard ratios (HRs) and 95% confidence intervals (CIs) were documented in each model. Harrell's C-statistics was used to evaluate the accuracy of prediction in Model 4. As very few older people ($n = 86$) had only low LLS, we combined participants with low ULS only or low LLS only into one group. The combined associations of ULS and LLS with risk of mortality were examined

according to the following 3-level groups: (1) Group 1: normal limb strength, (2) Group 2: only low ULS or only low LLS, and (3) Group 3: low ULS + low LLS.

In subgroup analyses, we repeated the above analysis for two subgroups: age (60–79 vs ≥80 years) and sex (female vs male). We conducted four sensitivity analyses to test the robustness of the main results: (1) excluded 156 deaths in the first year after the follow-up survey, (2) excluded 267 participants with baseline MMSE score <5 to ensure the reliability of physical examinations, (3) excluded BMI from the fully adjusted model, and (4) added the eight regions of sample recruitment into the full adjusted model as a covariate. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). $P < 0.05$ (two tailed) was considered statistically significant.

Results

Demographic characteristics

The age of all participants at baseline ranged from 60 to 112 years, with a mean age of 84.98 ± 11.94 years, and 1290 (52.83%) were female. A total of 1568 (64.21%) participants had low ULS, 874 (35.79%) had low LLS, and 651 (26.66%) had both conditions. During a median follow-up period of 42.2 months, 993 (40.66%) participants died. Table 1 presents the characteristics of 2442 older adults across follow-up outcomes. Participants who had low limb strength were more likely to die (*Ps* < 0.001). Kaplan–Meier survival curves stratified by different limb strength groups were described in Supplementary Fig. 1.

Associations of ULS with all-cause mortality

Table 2 presented the association of low ULS with all-cause mortality. After adjusting for age (continuous variable), there was a significant association between low ULS and mortality risk (HR = 1.88, 95% CI = 1.57–2.25). After additionally adjusting for health status and clinical diseases (Model 4), low ULS was independently associated with higher mortality (HR = 1.51, 95% CI = 1.25–1.84). Similarly, a significant association between ULS and mortality was found in age-stratified subgroups and sex-stratified subgroups (*Ps* < 0.05).

Associations of LLS with all-cause mortality

Table 3 presented the association of low LLS with all-cause mortality. Low LLS was independently associated with higher mortality risk in the fully adjusted model (HR = 1.24, 95% CI = 1.05–1.47). The significant association between ULS and mortality was only found in men (HR = 1.36, 95% CI = 1.04–1.79) and the oldest-old subgroup (HR = 1.28, 95% CI = 1.07–1.51).

Combined associations of ULS and LLS with all-cause mortality

As Table 4 showed, participants with combined low ULS and low LLS had the highest risk of mortality than the normal limb strength group (HR = 2.06, 95% CI = 1.61–2.63). Both in the <80 years subgroup (HR = 2.26, 95% CI = 1.21–5.85) and the ≥80 years subgroup (HR = 1.93, 95% CI = 1.47–2.52), the association between combined limb strength weakness and mortality was significant after adjusting for all covariates. In addition, graded associations between limb strength with mortality were found in the total sample and subgroups (all *P*-trend <0.001). The C-statistic of the fully adjusted model was 0.801 (95% CI: 0.784–0.831) in all participants (Model 4) and decreased to 0.781 (95% CI: 0.755–0.806) when we deleted the variable of limb strength weakness. The change of C-statistic was statistically significant ($P < 0.001$), indicating the predictive value of limb weakness for mortality.

Sensitivity analyses

We found that exclusion of participants who died in the first follow-up year or who had low cognitive function did not appreciably attenuate the risk–mortality relation (Supplementary Tables 1 and 2). In addition, when we modified the strategy of adjusting covariates, the results in each subgroup were materially unchanged (Supplementary Tables 3 and 4).

Discussion

In this prospective cohort study, we found that both low ULS and low LLS were associated with the risk of death. Chinese community–dwelling older adults with combined low ULS and low LLS had the highest risk of all-cause mortality.

In the present study, low ULS was associated with higher risk of all-cause mortality (HR = 1.51, 95% CI = 1.25–1.84) after adjusting for age, sex, BMI, lifestyles, physical abilities, depression, cognitive function, and clinical biomarkers. Recently, numerous studies have reported a positive association between low ULS and increased risk of mortality or disease-related mortality in different settings.[7,20–23] In a national multicenter study in China, older inpatients with low HS had a 64% increased risk of 90-day mortality compared with those with normal HS.[24] In another UK Biobank study, both absolute grip strength and relative grip strength were confirmed predictors of mortality risk among community-based older adults.[25] Similarly, participants with low LLS had higher risk of mortality than their counterparts (HR = 1.24, 95% CI = 1.04–1.47), and consistent results were found in a few studies. Xue et al.[10] found that good knee function and high hip strength were related to lower mortality risk in community-living women aged 70–79 years. In Cooper's meta-analysis, the adjusted HR for mortality comparing the slowest with the fastest quarter of walking speed was 2.87.[6] In addition, we found that the association of LLS with mortality was not significant in females or younger older adults. Scholars suggested sex and age as potential sources of heterogeneity in the relationship between physical capabilities and mortality,[6,26] and inconsistent patterns were reported. Cooper et al.[6] found that the association between muscle strength and mortality was weaker in people aged ≤60 years than in older participants. Singh et al.[27] also found that in older people with peripheral arterial disease, leg strength predicted mortality in men but not in women. In contrast, in another prospective study, lower body performance tests had better predictive ability in women than in men.[28] This evidence suggested that age and sex should be taken into consideration when exploring the associations of muscle strength with health outcomes in older adults.

In the total sample, the prevalence of combined limb muscle weakness was 26.66%, and this proportion was 69.58% among the oldest-old. There was a cumulative effect of low ULS and low LLS on the risk of early death. Gao et al.'s[11] findings showed that the increased risk of death associated with low grip strength and low walking speed individually was 13% and 9%, respectively, which were lower than our results. The possible explanation was that the mean age of the subjects in our study was higher than in Gao's study. In another Spanish population of older adults aged ≥65 years, Amelia et al. confirmed that multiple strength measures were better predictors of the risk of health events than a single strength measurement.[29] Our findings added to the growing significance of combined muscle strength screening for early death prevention, especially among the oldest-old. Some mechanisms may explain the individual and joint associations of low ULS and

Table 1
Baseline characteristics of study participants across follow-up outcome groups ($N = 2442$).

Characteristics	Overall ($n = 2442$)	Death ($n = 993$)	Non-death ($n = 1449$)	*P*-value
Sociodemographics				
Age (years)	84.98 ± 11.94	92.23 ± 9.25	80.02 ± 11.01	<0.001
Female, *n* (%)	1290 (52.93)	593 (59.72)	697 (48.10)	<0.001
Han ethnic, *n* (%)	2157 (91.24)	880 (91.48)	1277 (91.08)	0.741
Rural, *n* (%)	1493 (61.14)	648 (65.26)	845 (58.32)	<0.001
Live alone, *n* (%)	544 (22.28)	220 (22.16)	324 (22.36)	0.905
<1 year schooling, *n* (%)	1527 (62.53)	753 (75.83)	774 (53.42)	<0.001
Have no spouse, *n* (%)	1367 (56.30)	721 (72.75)	646 (44.95)	<0.001
Health status				
BMI (kg/m^2)	21.64 ± 4.09	20.92 ± 4.52	22.15 ± 3.69	<0.001
Waist circumference (cm)	80.77 ± 10.91	79.48 ± 10.95	82.23 ± 10.74	0.003
Calf circumference (cm)	29.62 ± 5.21	27.95 ± 4.76	30.89 ± 5.16	<0.001
Smoking, *n* (%)	421 (17.25)	122 (12.31)	299 (20.63)	<0.001
Drinking, *n* (%)	393 (16.17)	125 (12.64)	268 (18.60)	<0.001
ADL impairment, *n* (%)	459 (18.79)	352 (35.45)	107 (7.38)	<0.001
Cognitive impairment, *n* (%)	871 (35.67)	492 (49.55)	379 (26.16)	<0.001
Depression, *n* (%)	374 (15.32)	189 (19.03)	185 (12.77)	<0.001
SBP (mm Hg)	141.81 ± 23.84	142.63 ± 24.61	141.24 ± 23.29	0.162
DBP (mm Hg)	80.45 ± 12.23	79.39 ± 12.74	81.16 ± 11.83	0.001
Hypertension, *n* (%)	1034 (42.34)	412 (41.49)	622 (42.93)	0.756
CVD history, *n* (%)	197 (8.07)	81 (8.16)	116 (8.01)	0.892
CRD history, *n* (%)	224 (9.17)	107 (10.78)	117 (8.07)	0.024
Biological indicators				
Fasting blood glucose (mmol/L)	4.6 (3.9, 5.4)	4.6 (4.0, 5.4)	4.6 (3.9, 5.4)	0.508
Pathoglycemia, *n* (%)	152 (9.57)	119 (11.98)	130 (8.97)	0.016
Hemoglobin (g/L)	125.99 ± 21.03	121.48 ± 21.07	130.53 ± 23.48	<0.001
Anemia, *n* (%)	1011 (43.92)	540 (54.38)	471 (35.98)	<0.001
Total cholesterol (mmol/L)	4.45 ± 0.97	4.29 ± 1.03	4.54 ± 0.96	<0.001
Triglycerides (mmol/L)	0.9 (0.7, 1.3)	0.8 (0.6, 1.2)	1.0 (0.7, 1.4)	<0.001
HDL-C (mmol/L)	1.3 (1.1, 1.5)	1.3 (1.0, 1.5)	1.3 (1.1, 1.56)	0.482
LDL-C (mmol/L)	2.55 ± 0.81	2.47 ± 0.84	2.61 ± 0.79	<0.001
Dyslipidemia, *n* (%)	1142 (46.76)	460 (46.32)	682 (47.07)	0.718
25 (OH)D (nmol/L)	38.7 (28.5, 52.7)	33.6 (25.1, 46.7)	43.3 (32.3, 56.3)	<0.001
Vitamin D deficiency, *n* (%)	1746 (71.50)	797(80.26)	949 (65.49)	<0.001
Albumin (g/L)	41.14 ± 4.55	39.70 ± 4.69	42.13 ± 4.17	<0.001
Creatinine (μmol/L)	77.5 (65.1, 91.8)	80.2 (67, 95.5)	75.1 (64.8, 89.8)	<0.001
hs-CRP (mg/L)	1.0 (0.4, 2.4)	1.1 (0.4, 3.1)	0.9(0.4, 2.1)	<0.001
Limb strength categories				
Normal limb strength, *n* (%)	788 (32.27)	134 (13.49)	654 (45.13)	<0.001
Low ULS + normal LLS, *n* (%)	917 (37.55)	381 (38.37)	536 (36.99)	
Low LLS + normal ULS, *n* (%)	86 (3.52)	36 (3.63)	50 (3.45)	
Low ULS + low ULS, *n* (%)	651 (26.66)	442 (44.51)	209 (14.42)	

25 (OH)D, 25-dihydroxyvitamin D; ADL, activities of daily living; BMI, body mass index; CRD, chronic respiratory disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LLS, lower limb strength; SBP, Systolic blood pressure; ULS, upper limb strength.

low LLS on all-cause mortality. According to the sarcopenia diagnosis consensus, combined upper and lower limb weakness was associated with more serious frailty and sarcopenia, which may partly explain early death. Besides, skeletal muscle mass is the main organ of body metabolism, and to some extent, low ULS and LLS reflect decreased skeletal muscle mass because of aging and malnutrition, which lead to a slower metabolic rate and reduced calorie consumption.[30] As is commonly known, falls are one of the leading causes of a higher risk of mortality among older adults,[31] and both upper and lower extremity strength are associated with the risk of falls, which may explain their joint association with mortality.

More significantly, we found the C-statistic of the fully adjusted model significantly decreased after excluding the variable of limb strength weakness. This indicated that limb muscle strength could be considered as a potential valuable predictor for mortality. Darryl et al.[7] also found that grip strength was confirmed to be a stronger predictor of all-cause and cardiovascular mortality than blood pressure. In addition, assessment of limb muscle strength is simple, non-invasive, radiation free, and low cost compared with muscle mass measurements and blood sampling. The four physical examination measures we applied in the present study could be performed using simple equipment and even independently. Thus, our study constructed a simple and doable mortality predictor with unique clinical implication. Our study has some strengths. The nationally representative sample of the older population in China and the availability of blood samples provided a unique opportunity to estimate the true association between limb muscle strength and all-cause mortality. Besides, the comprehensive information at baseline was beneficial in controlling the potential confounding bias on mortality.

Limitations

Several limitations should also be acknowledged. First, because the blood sample and handgrip data were only available among participants from eight longevity areas in the CLHLS, we could not obtain a large sample size of subjects at baseline. Specifically, only 6.67% of the older adults aged <80 years had low LLS in our study, and the association of limb muscle strength with mortality risk among middle older adults needs to be verified in future large samples. Second, similar to other observational studies, it is not possible to completely eliminate the influence of potential confounding factors. Third, participants in the present study were all

Table 2
Associations of low ULS with all-cause mortality ($N = 2442$).

Group		Participants	Deaths (%)	Model 1		Model 2		Model 3		Model 4	
				HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Overall	Normal	874	170 (19.45)	Ref	–	Ref	–	Ref	–	Ref	–
	Low ULS	1568	823 (52.49)	2.73 (2.41–3.11)	<0.001	1.88 (1.57–2.25)	<0.001	1.58 (1.31–1.92)	<0.001	1.51 (1.25–1.84)	<0.001
Male	Normal	495	83 (16.77)	Ref	–	Ref	–	Ref	–	Ref	–
	Low ULS	657	317 (52.75)	2.76 (2.21–3.41)	<0.001	1.91 (1.45–2.48)	<0.001	1.59 (1.19–2.11)	0.001	1.45 (1.07–1.95)	0.016
Female	Normal	379	87 (22.96)	Ref	–	Ref	–	Ref	–	Ref	–
	Low ULS	911	506 (55.54)	2.66 (2.25–3.12)	<0.001	1.80 (1.42–2.29)	<0.001	1.46 (1.12–1.88)	0.004	1.46 (1.12–1.91)	0.004
<80 years	Normal	566	51 (9.01)	Ref	–	Ref	–	Ref	–	Ref	–
	Low ULS	258	46 (17.83)	2.83 (1.68–3.64)	<0.001	1.73 (1.14–2.62)	0.009	1.71 (1.08–2.69)	0.022	1.53 (1.01–2.43)	0.005
≥80 years	Normal	308	119 (38.64)	Ref	–	Ref	–	Ref	–	Ref	–
	Low ULS	1310	777 (59.31)	2.59 (1.95–3.02)	<0.001	1.74 (1.43–2.12)	<0.001	1.52 (1.23–1.87)	<0.001	1.48 (1.22–1.92)	0.003

CI, confidence interval; HR, hazard ratio; ULS, upper limb strength.
Model 1: not adjusted. Model 2: adjusted for age (continuous variable). Model 3: additionally adjusted for sex (not in sex subgroup analyses), ethnicity, education, marital status, living status, residence, smoking, drinking, BMI, waist circumference, and calf circumference. Model 4: additionally adjusted for ADL, cognitive function, depression, hypertension, dyslipidemia, pathoglycemia, anemia, vitamin D deficiency, creatinine, albumin, hs-CRP, and history of CVD and CRD.

Table 3
Associations of low LLS with all-cause mortality ($N = 2442$).

Group		Participants	Deaths (%)	Model 1		Model 2		Model 3		Model 4	
				HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Overall	Normal	1705	170 (19.45)	Ref	–	Ref	–	Ref	–	Ref	–
	Low LLS	737	823 (52.49)	2.49 (2.18–2.85)	<0.001	1.41 (1.22–1.62)	<0.001	1.22 (1.05–1.42)	0.011	1.24 (1.05–1.47)	0.008
Male	Normal	923	83 (16.77)	Ref	–	Ref	–	Ref	–	Ref	–
	Low LLS	229	317 (52.75)	2.95 (2.35–3.64)	<0.001	1.73 (1.38–2.15)	<0.001	1.39 (1.08–1.81)	0.009	1.36 (1.04–1.79)	0.027
Female	Normal	782	87 (22.96)	Ref	–	Ref	–	Ref	–	Ref	–
	Low LLS	508	506 (55.54)	2.14 (1.81–2.54)	<0.001	1.31 (1.09–1.56)	0.003	1.14 (0.94–1.39)	0.167	1.20 (0.98–1.48)	0.073
<80 years	Normal	769	51 (9.01)	Ref	–	Ref	–	Ref	–	Ref	–
	Low LLS	55	46 (17.83)	2.55 (1.43–4.46)	0.003	1.83 (0.92–2.94)	0.078	1.47 (0.76–2.85)	0.245	1.45 (0.71–3.01)	0.309
≥80 years	Normal	936	119 (38.64)	Ref	–	Ref	–	Ref	–	Ref	–
	Low ULS	682	777 (59.31)	2.11 (1.85–2.39)	<0.001	1.42 (1.23–1.63)	<0.001	1.24 (1.06–1.45)	0.007	1.28 (1.07–1.51)	0.004

CI, confidence interval; HR, hazard ratio; LLS, lower limb strength.
Model 1: not adjusted. Model 2: adjusted for age (continuous variable). Model 3: additionally adjusted for sex (not in sex subgroup analyses), ethnicity, education, marital status, living status, residence, smoking, drinking, BMI, waist circumference, and calf circumference. Model 4: additionally adjusted for ADL, cognitive function, depression, hypertension, dyslipidemia, pathoglycemia, anemia, vitamin D deficiency, creatinine, albumin, hs-CRP, and history of CVD and CRD.

Table 4
Combined associations of low ULS and low LLS with all-cause mortality ($N = 2442$).

Group		Participants	Deaths (%)	Model 1		Model 2		Model 3		Model 4	
				HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Overall	Group 1	788	134 (17.01)	Ref	–	Ref	–	Ref	–	Ref	–
	Group 2	1003	417 (41.58)	2.98 (2.45–3.62)	<0.001	1.85 (1.51–2.28)	<0.001	1.72 (1.38–2.13)	<0.001	1.53 (1.23–1.91)	0.001
	Group 3	651	442 (67.90)	5.67 (4.63–6.94)	<0.001	2.44 (1.95–3.05)	<0.001	2.19 (1.73–2.79)	<0.001	2.06 (1.61–2.63)	<0.001
	P-trend				<0.001		<0.001		<0.001		<0.001
Male	Group 1	464	72 (15.52)	Ref	–	Ref	–	Ref	–	Ref	–
	Group 2	490	188 (38.37)	3.05 (2.33–4.02)	<0.001	1.83 (1.37–2.45)	<0.001	1.71 (1.25–2.32)	0.001	1.52 (1.11–2.08)	0.009
	Group 3	198	140 (70.71)	6.73 (4.96–9.12)	<0.001	2.89 (2.07–4.03)	<0.001	2.48 (1.72–3.57)	<0.001	2.29 (1.49–3.20)	<0.001
	P-trend				<0.001		<0.001		<0.001		<0.001
Female	Group 1	324	62 (19.14)	Ref	–	Ref	–	Ref	–	Ref	–
	Group 2	513	229 (44.64)	2.79 (2.11–3.69)	<0.001	1.79 (1.34–2.39)	<0.001	1.57 (1.16–2.13)	0.003	1.44 (1.06–1.97)	0.019
	Group 3	453	302 (66.67)	4.81 (3.63–6.36)	<0.001	2.21 (1.63–2.99)	<0.001	1.95 (1.42–2.68)	<0.001	1.81 (1.39–2.65)	<0.001
	P-trend				<0.001		<0.001		<0.001		<0.001
<80 years	Group 1	544	50 (9.19)	Ref	–	Ref	–	Ref	–	Ref	–
	Group 2	247	35 (14.17)	2.98 (1.21–4.76)	0.023	1.41 (0.91–2.21)	0.124	1.42 (0.89–2.27)	0.143	1.35 (0.83–2.21)	0.223
	Group 3	33	12 (36.36)	6.85 (5.29–8.65)	<0.001	2.89 (1.51–5.57)	0.001	2.62 (1.25–5.52)	0.011	2.26 (1.21–5.85)	0.015
	P-trend				<0.001		<0.001		<0.001		<0.001
≥80 years	Group 1	244	84 (34.43)	Ref	–	Ref	–	Ref	–	Ref	–
	Group 2	756	382 (50.53)	2.46 (1.23–3.94)	<0.001	1.68 (1.32–2.13)	<0.001	1.56 (1.22–2.01)	0.001	1.39 (1.08–1.78)	0.010
	Group 3	618	430 (69.58)	4.76 (3.39–6.67)	<0.001	2.27 (1.78–2.91)	<0.001	2.07 (1.59–2.69)	<0.001	1.93 (1.47–2.52)	<0.001
	P-trend				<0.001		<0.001		<0.001		<0.001

CI, confidence interval; HR, hazard ratio; LLS, lower limb strength; ULS, upper limb strength.
Group 1: normal limb strength; Group 2: only low ULS or only low LLS; Group 3: low ULS + low LLS.
Model 1: not adjusted. Model 2: adjusted for age (continuous variable). Model 3: additionally adjusted for sex (not in sex subgroup analyses), ethnicity, education, marital status, living status, residence, smoking, drinking, BMI, waist circumference, and calf circumference. Model 4: additionally adjusted for ADL, cognitive function, depression, hypertension, dyslipidemia, pathoglycemia, anemia, vitamin D deficiency, creatinine, albumin, hs-CRP, and history of CVD and CRD.

exclusively from China, and generalization of the findings to older people from other races should be done with caution.

Conclusions

Low ULS and low LLS were independently and synergistically associated with higher all-cause mortality risk among Chinese community–based older adults. Considering the high prevalence of limb muscle weakness among Chinese older adults, especially the oldest-old, it could be considered as a doable mortality predictor for community health care.

Author statements

Ethical approval

The study design was approved by the Ethics Committee of Beijing Hospital. The CLHLS was approved by the Ethics Committee of Peking University (No. IRB00001052-13074). All subjects (or guardians) provided written informed consent before participating in the survey.

Funding

This work was supported by National High Level Hospital Clinical Research Funding (Numbers: BJ-2022-133; BJ-2022-149) and National Key R&D Program of China (2021YFE0111800; 2020YFC2002700).

Competing interests

The authors declare no conflict of interest.

Author contributions

C.Z. and J.S. contributed to conceptualization. L.J. and P.Z. designed the research. C.Z. and Y.L. analyzed the study. L.Z. and G.F. interpreted the data. C.Z. and X.L. wrote the article. J.C., H.S., X.C, and P.Z. reviewed and edited the article. C.Z. and J.S contributed to supervision. All authors have read and agreed to the published version of the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.023.

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Public Health 220 (2023) 96–98

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Short Communication

Meeting the long-term health needs of Ukrainian refugees

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ARTICLE INFO

Article history:
Received 27 January 2023
Received in revised form
31 March 2023
Accepted 21 April 2023

ABSTRACT

Objectives: Since Russia's full-scale invasion of Ukraine on 24 February 2022, millions of people have fled the country. Most people have gone to the neighbouring countries of Poland, Slovakia, Hungary, Romania, and Moldova. This vulnerable population has significant healthcare needs. Among the most challenging to address will be chronic non-communicable diseases (NCDs), including mental disorders, as these require long-term, continuous care and access to medicines. Host country health systems are faced with the challenge of ensuring accessible and affordable care for NCDs and mental disorders to this population. Our objectives were to review host country health system experiences and identify priorities for research to inform sustainable health system responses to the health care needs of refugees from Ukraine.

Study Design: In-person conference workshop.

Methods: A workshop on this subject was held in November 2022 at the European Public Health Conference in Berlin.

Results: The workshop included participants from academia and non-governmental organisations, health practitioners, and World Health Organisation regional and country offices. This short communication reports the main conclusions from the workshop.

Conclusion: Addressing the challenges and research priorities identified will require international solidarity and co-operation.

By the end of May 2023, over 8.2 million refugees from Ukraine had been recorded across Europe. In the European Union, Poland and Germany have accepted the largest absolute numbers of refugees (approximately 1.6 and one million, respectively), whereas Estonia and Czechia host the largest share of refugees from Ukraine, relative to their populations (approximately 5% in both cases). More than 826,547 people from Ukraine have fled to the Republic of Moldova (hereafter Moldova). Out of this total, approximately 102,063 refugees (which represents some 4% of the population of Moldova) currently remain in the country as of January 2023, and more arrive each day.[1]

Those fleeing Ukraine have considerable healthcare needs.[2] Among them, chronic non-communicable diseases (NCDs), both physical and mental, will pose particular challenges, requiring continuous and long-term care, including access to medicines. They are drawn from a population with a high burden of NCDs, with approximately one-third of Ukrainian adults having hypertension and 7% with diabetes. Refugees are at increased risk of mental disorders because of what they have experienced on their journeys and the challenges arising from their new situations. Health authorities in destination countries face substantial logistical and financial challenges as they seek to provide affordable and appropriate care for the chronic healthcare needs of refugees. Yet, there is considerable uncertainty about the best way of achieving this.

This was the subject of a workshop co-hosted by the London School of Hygiene and Tropical Medicine's Centre for Global

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https://doi.org/10.1016/j.puhe.2023.04.015

Chronic Conditions and the European Observatory on Health Systems and Policies at the European Public Health Conference in Berlin on 11 November 2022. Its objectives were to (1) review the experiences of health systems as they sought to respond to the needs of refugees from Ukraine for care of chronic conditions and (2) identify priorities for research to inform sustainable health system responses to their needs. Here, we report the main conclusions from the workshop, including some of the main challenges facing host country health systems and research priorities.

Legal frameworks to support equitable health and health care for refugees

Displacement imposes a double burden on refugees; it increases their risks of illness and impedes their access to care, both exacerbated by loss of homes, family and social support, and livelihoods. Yet, with political will, these problems can be mitigated. A review of experiences of asylum seekers with different entitlements to health and social services in Germany over 30 years found that more inclusive responses, ensuring that they can realise access to health care, housing, employment, and family reunification, lead to better health and equity outcomes.[3] In 2001, the European Union (EU) developed a package of measures — the 'Temporary Protection Directive' — that could be implemented in response to mass displacement, and these have now been activated for Ukrainian refugees. In Germany, refugees have had the same entitlements as German citizens since June 2022, including full access to services, freedom of movement and (with few exceptions) choice of the place of residence, unless shelter in reception centres is temporarily needed. This avoids long-term encampment and reduces the risk of acquiring infectious diseases, including COVID-19, in crowded reception centres, as well as mental health burdens associated with housing in camps or camp-like accommodation.[4] Freedom of movement and entitlements to work also enhance labour market integration, thereby potentially helping to avoid the mental distress and depression that are sometimes associated with restricted labour market access.[5] Lack of restrictions on family reunification is also likely to unfold positive effects on mental health, as separation from closest family members negatively impacts refugee mental health.[6] Nevertheless, challenges remain. There is no systematic programme to identify the health needs of arriving refugees, including vaccinations, unless refugees from Ukraine seek shelter in reception centres. Interpretation services are ad hoc or not existent at all, especially in communities and schools, and other forms of support for navigating the system are underfunded.

Financing mechanisms to ensure sustainability of healthcare services for refugees

Healthcare coverage for refugees is insufficient in many European health systems,[7] often limited to emergency care, infectious diseases, and maternity services. This is a particular challenge where entitlement to other services is based on contributions, for example, to a social insurance fund. In these situations, refugees who are unemployed (in some cases, because they are not allowed to work) or have otherwise limited capacity to pay contributions become uninsured. Out-of-pocket payments create a barrier for all disadvantaged groups, and refugees are not an exception, with the cost of medicines a particular concern.[8] This calls for government investment in the extra capacity required, particularly in those countries that have absorbed large numbers of refugees relative to their populations, measures to remove administrative barriers that prevent these funds being deployed quickly, and absolute transparency on how funds are used, given the scope for the forms of abuse that many countries saw during the pandemic. Some middle-income countries that have absorbed large numbers of refugees, such as Moldova, have received external financial support to respond to their needs. However, more sustainable and comprehensive financing approaches must be put in place to avoid disparities in coverage between refugees and host populations. To ensure equitable financial contributions of EU member states to the public good of international protection within the EU, supranational funding mechanisms for health and social needs are urgently required. Scenarios for such mechanisms already exist[9] and could be used to further develop effective and equitable funding schemes beyond national silos.

Delivering continuous care for people with mental health disorders and other chronic NCDs

The care provided to those coming from Ukraine must take account of their particular needs, reflecting their pre-existing burden of disease and exposure to traumatic events. It is even more important than usual that service providers adopt people-centred approaches, taking account of language issues and incorporating a high degree of cultural competence while ensuring integration with other services and removing administrative barriers. One challenge will be access to the health records of refugees with chronic conditions, which is important to deliver continuity of care. Another will be the widespread underfunding of primary care in many countries, and especially community mental health services, made worse by shortages of health care workers trained in evidence-based treatment of mental health and NCDs. Health system responses may benefit from engaging the refugees themselves to support health care delivery, either as peer support networks or as health workers, for those with appropriate training. Resources should be invested in scale-up of evidence-based treatment approaches that have already been adapted for people in Ukraine affected by conflict and shown to be effective.[10]

Research priorities

The Russian invasion of Ukraine has caused the largest refugee crisis since the Second World War. But displacement of people globally is likely to increase in the future as a result of both man-made and natural disasters compounded by climate change. We must draw lessons from the Ukraine crisis to inform sustainable responses now but also to prepare for the future. The experiences of host countries in providing care for refugees from Ukraine have emphasised the importance of inclusive legal frameworks, timely mobilisation of public funds, and provision of people-centred primary care for mental health and NCDs. Still, key questions remain. We have yet to document comprehensively the self-reported day-to-day barriers experienced by refugees across Europe in accessing health care. One needs assessment of refugees from Ukraine aged $\geq$60 years in Moldova suggested that 26% were unable to access health services when required, including because they did not know where to go.[11] Similar needs assessments are required for refugees from Ukraine in other countries, especially for vulnerable groups. This evidence is vital to ensure that all barriers are considered in research and policy responses. As legal frameworks for granting entitlements to refugees from Ukraine vary across Europe, we should analyse the impact of different frameworks on health outcomes. For example, while the Temporary Protection Directive applies across the EU, its implementation may vary from country to country, variously affecting access to care for refugees and host populations.[12] We need to understand the overall costs to health systems of providing healthcare entitlements to refugees and the most cost-effective and sustainable ways of financing this

within and *across* individual countries. We also need to identify ways to improve the mobility and transferability of patient health records, something that should be easier with advances in digital health, to support continuity of care without compromising patient security and confidentiality. Narrative reports show the potential that electronic records have to improve monitoring and continuity of healthcare access for refugees and migrants, especially in border regions and with highly mobile populations. However, scientific evidence to support these reports and guide implementation is needed.[13] Finally, we must evaluate the feasibility, implementation, and effectiveness of different delivery approaches at the primary care and community levels, including the use of peer support groups. Importantly, all this research must involve those most affected – refugees themselves and local host populations – to ensure appropriate and acceptable responses. It must also be conducted using a 'whole-of-route' approach, involving collaboration and solidarity of countries across the region.

Author statements

Ethical approval

Ethical approval was not sought, as this is not a research study and no data were collected.

Funding

There was no funding for this work.

Competing interests

The authors have no competing interests to declare.

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Public Health 220 (2023) 120–126

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Themed Paper – Original Research

Mortality by road transport injury in Brazilian municipalities between 2000 and 2018

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ARTICLE INFO

Article history:
Received 25 January 2023
Accepted 22 April 2023

Keywords:
Injuries
Traffic
Mortality
Ecological studies
Global Burden of disease
Spatial analysis

ABSTRACT

Objectives: This study aimed to investigate patterns of mortality by road transport injury (RTI) in Brazilian municipalities, focused on deaths of motorcyclists, between 2000 and 2018, and their relation with population size and economic status.
Study design: This was an ecological epidemiological study with a descriptive and analytical nature.
Methods: The age-standardized RTI mortality rates were calculated for the Brazilian municipalities, referring to the 3-year periods of 2000/2002 (T1), 2009/2011 (T2), and 2016/2018 (T3). The rates were stratified according to macroregion and population size and were compared in terms of percentage variation from one 3-year period to another. The Moran Global and Local indices were used in the spatial point-pattern analysis of the rates. To verify the association with the gross domestic product (GDP) *per capita*, the Spearman correlation coefficient was applied.
Results: A decline in RTI mortality rates was found between 2000 and 2018, with the most significant declines observed in municipalities from the South and Southeast regions of Brazil. However, increases were observed among motorcyclists. Clusters of municipalities were detected, which presented high mortality rates among the motorcyclists in the Northeast region and in some states of the North and Midwest regions. The mortality rates showed a negative correlation with the GDP *per capita* of the Brazilian municipalities.
Conclusions: Although there were decreases in RTI mortality rates between 1990 and 2018, there was a significant increase in deaths among motorcyclists, especially in the Northeast, North, and Midwest regions of the country. Such differences can be explained by unequal growth in the size of the motorcycle fleet in those regions, by less law enforcement capability, and by the implementation of educational actions.

Introduction

According to the World Health Organization (WHO), 20–50 million people suffer injuries resulting from road transport injury (RTI) annually, and 1.3 million of those result in deaths.[1,2] The mortality rates are up to three times higher in low-income countries when compared with high-income countries.[2] The RTI causes economic losses to the victims and their families and society in

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https://doi.org/10.1016/j.puhe.2023.04.013
0033-3506/

general, and these costs—both direct and indirect—amount to 3% of the gross domestic product (GDP) in most countries.[3]

The causes of the RTI are multiple: socio-economic inequalities, poor road structure, differences in the distribution of the fleet of vehicles and a low-quality public transportation, problems in roadways, poor enforcement and application of the traffic laws, and vehicle safety.[4] At the individual level, behavioral aspects stand out: excessive speed, driving under the influence of alcohol, inadequate use or lack of use of the vehicles' safety features, disobeying traffic signs, and the violation of other norms established by traffic laws[5–7]

Brazil is ranked fifth in deaths by RTI worldwide,[8] with more than 40,000 deaths every year. The number of seriously injured people is estimated to be higher than 150,000 each year.[9] One study analyzing the RTI mortality rates between 1990 and 2019 identified a 43% decrease in these rates.[10] The mortality rate for pedestrians decreased by 77%; meanwhile, there was an increase of 53% in the indicator for motorcyclists, which rose from 7.3 to 11.7 deaths per 100,00 inhabitants in that period.[10] Another study identified stability in the RTI mortality rates in capital cities, an increase in small-scale municipalities, and great variability among states.[8]

In February 2020, the Swedish government and the WHO promoted the third Global Ministerial Conference on Traffic Safety, which resulted in the Stockholm Declaration,[11] reiterating the commitment with the UN Sustainable Development Goals (SDGs), with a 50% reduction in traffic deaths by 2030.[1] In this light, many countries that signed on to this agenda will continue to monitor the evolution of RTI morbidity–mortality.

Hence, the present study aimed to investigate the spatial point-pattern analysis of RTI mortality rates in Brazilian municipalities, focusing on deaths of motorcyclists between 2000 and 2018 and their relation with population size and municipal economic status.

Methods

Design of the study

This is an ecological epidemiologic study with a descriptive and analytical nature, which investigated the RTI mortality rates for Brazilian municipalities, referring to the 3-year periods of 2000–2002 (T1), 2009–2011 (T2), and 2016–2018 (T3).

Indicators and data sources

The calculation of the mortality rates included, for the numerator, the average of deaths and, for the denominator, the average population in each 3-year period. The number of municipal deaths was collected from the database of estimated deaths by the Institute for Health Metrics and Evaluation, from the University of Washington, in the context of the *Global Burden of Disease* (GBD) study, produced in partnership with the GBD Brazil.

Estimations of mortality were collected from the Mortality Information Systems (SIM) by municipality following the same methods used to estimate the state-level Brazil SIM estimates in GBD. A summary of data processing steps is included below. First, data were assigned a GBD cause using the listed International Classification of Diseases (ICD) code, and data with aggregated sex or age were split into detailed groups. Next, a correction for misclassification of dementia, Parkinson's disease, and atrial fibrillation and flutter was applied to the data. The data then underwent the process by which garbage codes (ICD codes that cannot be reliably assigned to a specific GBD cause, i.e. senility or back pain) were redistributed to real GBD causes. Finally, the data were smoothed to account for stochastic variation during a year in a process called noise reduction.[12,13]

The population numbers were taken from the population estimates by the Ministry of Health.[12] The rates were age standardized by the direct method using the standard population from the GBD study,[13] based on 100,000 inhabitants. Details about the methodology and the results of the GBD study can be checked in several publications.[12,13,15]

The economic index used in this study was the GDP *per capita* of the municipalities, taken from data from the Brazilian Institute of Geography and Statistics.[16] This indicator informs the average added value of each individual and of the goods and services produced in a given geographic space and time.[17–19]

Presentation and data analysis

The RTI mortality rates and subgroups (pedestrians, cyclists, motorcyclists, motor vehicles, and other RTIs) were presented in choropleth maps and tabled. Aggregate data analyses were also conducted according to Brazilian macroregions and population size ($\leq$50,000 inhabitants; 50,000–300,000; >300,000). The population size strata were defined after conducting an exploratory analysis of the data based on the evidence of increases in mortality rates in less populated municipalities and drops in rates in more populous municipalities, as evidenced by another scientific publication;[8] 95% confidence intervals (95% CIs) were calculated according to the method set forth by the Centers for Disease Control and Prevention.[20]

Percentages of change in mortality rates among the 3-year periods are shown by comparing the relative differences among T1/T2, T2/T3, and T1/T3.

The spatial point-pattern analysis of the mortality rates was based on the calculation of the Moran Global Index, which can evaluate the spatial interdependency relationship among all areas in Brazil and express it through a single value for the entire country.[21] To detect clusters of the risk of death by RTI, the Univariate Local Moran index (LISA) was applied. Such an analysis allows for the classification of the municipalities according to the significance of the local indices of spatial association as low–low and high–high.[21] These clusters determine a positive association; in other words, the municipalities included have neighbors with similar RTI values.

To verify the association of the municipal mortality rates of motorcyclists, with the average *per capita* GDP, our study applied the Spearman correlation coefficient, which verifies if the intensity of the relationship between two variables can be described using a monotonic function.[22]

The data presentation and analysis were conducted using the R Studio[23] software with the aid of the *Rgeoda* package.

Ethical aspects

This study was conducted according to that set forth in Resolution 466/12 from the National Health Council and integrates the project "Inequalities in indicators of non-communicable diseases, violence, and their risk factors in small geographic areas," approved by the Research Ethics Committee from Universidade Federal de Minas Gerais (decision number 3,258,076).

Results

Between 2000 and 2018, 872,046 deaths by RTI were registered in Brazil (23.5 deaths/100,000 inhabitants, on average). In T1, the mortality rate was 24.1 deaths/100,000 inhabitants in Brazilian municipalities (5561 municipalities). In T2, the observed rate was 24.6/100,000 inhabitants (5564 municipalities), and in T3, 21.2 deaths/100,000 inhabitants (5564 municipalities). Throughout the entire

period, in 29.3% of the deaths, the victim was riding a motorcycle (n = 256,038 deaths and 6.8 deaths/100,000 inhabitants on average).

Table 1 shows the deaths by RTI, according to the victim's region of residency, in the 3-year periods analyzed in this study. A decrease in RTI mortality was observed in every region. A further decline was found in the South and Southeast in 2000/2001/2002 and 2016/2017/2018: −28.5% and −28%. The decrease in pedestrian mortality rates was more evident. Considering the period from T1 to T3, these rates ranged from −48% in the North to −60.8% in the South. The drop in the category of motor vehicles ranged from −6.5% in the Southeast to −19.2% in the Midwest. "Other Motor Vehicles" had low rates, and the decline ranged from −27.4% in the Northeast to −39.1% in the South. Concerning the cyclists, the decline ranged from −6.4% in the Southeast to −25.5% in the South. Meanwhile, among motorcyclists, progressive increases were found, resulting in higher rates in T3, especially in the Northeast (9.5/100,000 inhabitants), Midwest (8.1/100,000 inhabitants), North (7.5/100,000 inhabitants), South (6.2/100,000 inhabitants), and Southeast (4.9/100,000), with a 72.3% increase between T1 and T3; 45.7%, 49.2%, 16.8%, and 21.5%, respectively.

Fig. 1A shows the evolution of the total RTI mortality rates in the 3-year periods of T1, T2, and T3 in Brazilian municipalities. For geographic reasons, the state of Amazonas showed low mortality rates in the three periods. Between T1 and T2, the mortality rates showed a slight oscillation in Brazil, whereas in T3, they showed a decrease, especially in the municipalities of the South and Southeast. The municipalities from the Northeast and Midwest had the highest rates in all the periods.

Fig. 1B shows the evolution in the distribution of motorcyclists' mortality in Brazilian municipalities. A sharp increase was observed in the rates between T1 and T2. For the remaining subgroups, Figs. S1–S4 show the distribution of the mortality rates among Brazilian municipalities in the three periods.

Table S1 shows the value of the Moran Global Index for all traffic causes studied in each of the three periods, considering the Brazilian municipalities. All the observed indices proved to be positive and showed a *P*-value <0.0001. For all the RTIs, as well as in the case of pedestrians, cyclists, and other RTIs, the spatial pattern remained stable throughout the three periods. For motorcyclists, however, the Moran Global Index showed a significant increase from 0.39 (T1) to 0.49 (T3), indicating that over time, the municipalities with low (high) mortality tend to become increasingly closer to neighbors with the same characteristics. The opposite behavior can be observed in RTIs involving motor vehicles, in which a decline in the spatial pattern can be detected between T1 and T3.

The local spatial pattern associated with the mortality of motorcyclists is shown in Fig. 2. In that figure, the Brazilian municipalities are classified into two clusters: high–high (red) and low–low (blue). Throughout the three periods, we can notice an increase in the number of municipalities in high–high and low–low clusters. This is in line with the information in Table 2 that this cause of death shows a spatial pattern of mortality that increases over the years. Concerning the high–high pattern, the municipalities are more concentrated in the Northeast and Midwest. The states of Roraima and Santa Catarina show decreases in this pattern, whereas in the Southeast, the state of Espírito Santo had municipalities with that pattern. The low–low pattern is more commonly observed in the states of the North, Southeast, and South regions. The state of Bahia stands out for its reduction in that pattern over the years.

Table 2 presents the variation in the mortality rates of motorcyclists per triennium and according to population size. In general, the

Table 1
Age-standardized mortality rates by groups of road transport injury (RTI) and subgroups (pedestrians, cyclists, motorcyclists, motor vehicle, and other LTAs), per 100,000 inhabitants, together with respective 95% confidence intervals (95% CI), for the 3-year periods of T1 (2000–2002), T2 (2009–2011), and T3 (2016–2018) and percentage variation.

Cause	Region	Three-year periods			Percentage variation		
		T1: 2000 to 2022	T2: 2009 to 2011	T3: 2016 to 2018	T1-T2	T2-T3	T1-T3
Road injuries	Midwest	30.3 (29.2–31.3)	29.6 (28.7–30.5)	23.5 (22.8–24.3)	−2.2	−20.5	−22.2
	Northeast	25.1 (24.6–25.6)	25.1 (24.6–25.5)	22.5 (22.1–22.9)	−0.2	−10.3	−10.5
	North	25.2 (24.2–26.2)	24.1 (23.2–24.9)	20.5 (19.8–21.2)	−4.6	−14.9	−18.9
	Southeast	21.7 (21.3–22)	20.2 (19.9–20.5)	15.6 (15.4–15.9)	−6.8	−22.7	−28.0
	South	27.9 (27.2–28.5)	26.3 (25.7–26.9)	19.9 (19.4–20.4)	−5.7	−24.2	−28.5
Pedestrian road injuries	Midwest	12.2 (11.4–12.9)	8.1 (7.6–8.7)	5.3 (4.9–5.6)	−33.1	−35.6	−56.9
	Northeast	10.9 (10.6–11.2)	7.9 (7.7–8.2)	5.5 (5.3–5.7)	−27.2	−30.6	−49.5
	North	12.4 (11.7–13.2)	9 (8.5–9.6)	6.5 (6–6.9)	−27.4	−28.6	−48.1
	Southeast	10.8 (10.6–11.1)	6.9 (6.7–7.1)	4.5 (4.3–4.6)	−36.2	−35.6	−58.9
	South	11.1 (10.7–11.5)	7.2 (6.8–7.5)	4.3 (4.1–4.6)	−35.5	−39.2	−60.8
Cyclist road injuries	Midwest	1.3 (1.1–1.5)	1.5 (1.3–1.7)	1.2 (1–1.4)	14.7	−20.8	−9.2
	Northeast	0.8 (0.8–0.9)	0.9 (0.8–1)	0.8 (0.7–0.9)	4.9	−11.4	−7.0
	North	1 (0.8–1.2)	1 (0.9–1.2)	0.9 (0.7–1)	7.7	−14.1	−7.5
	Southeast	0.7 (0.6–0.8)	0.8 (0.8–0.9)	0.7 (0.6–0.7)	20.7	−22.5	−6.4
	South	1.3 (1.1–1.4)	1.3 (1.2–1.5)	1 (0.9–1.1)	2.6	−27.4	−25.5
Motorcyclist road injuries	Midwest	5.6 (5.2–6)	9 (8.6–9.5)	8.1 (7.7–8.5)	62.3	−10.2	45.7
	Northeast	5.5 (5.3–5.7)	8.7 (8.4–8.9)	9.5 (9.2–9.7)	57.7	9.2	72.3
	North	5.1 (4.6–5.5)	7.6 (7.2–8)	7.5 (7.1–7.9)	49.9	−0.5	49.2
	Southeast	4.1 (3.9–4.2)	5.7 (5.5–5.8)	4.9 (4.8–5.1)	40.2	−13.4	21.5
	South	5.3 (5–5.6)	7.7 (7.3–8)	6.2 (5.9–6.5)	44.7	−19.3	16.8
Motor vehicle road injuries	Midwest	10.6 (10–11.3)	10.4 (9.9–10.9)	8.6 (8.1–9)	−2.1	−17.4	−19.2
	Northeast	7.4 (7.1–7.6)	7.1 (6.9–7.4)	6.4 (6.2–6.6)	−2.9	−11.0	−13.6
	North	6.3 (5.8–6.7)	6 (5.6–6.4)	5.2 (4.9–5.6)	−4.5	−12.5	−16.4
	Southeast	5.7 (5.6–5.9)	6.5 (6.3–6.6)	5.4 (5.2–5.5)	12.9	−17.2	−6.5
	South	9.8 (9.4–10.2)	9.8 (9.4–10.2)	8.2 (7.9–8.5)	0.1	−16.6	−16.5
Other road injuries	Midwest	0.6 (0.4–0.7)	0.5 (0.4–0.6)	0.4 (0.3–0.5)	−14.5	−22.1	−33.4
	Northeast	0.5 (0.4–0.6)	0.4 (0.4–0.5)	0.4 (0.3–0.4)	−12.7	−16.9	−27.4
	North	0.5 (0.3–0.6)	0.4 (0.3–0.5)	0.3 (0.2–0.4)	−15.8	−18.4	−31.2
	Southeast	0.4 (0.3–0.4)	0.3 (0.3–0.3)	0.2 (0.2–0.3)	−19.2	−22.0	−37.0
	South	0.4 (0.3–0.5)	0.3 (0.3–0.4)	0.2 (0.2–0.3)	−17.3	−26.3	−39.1

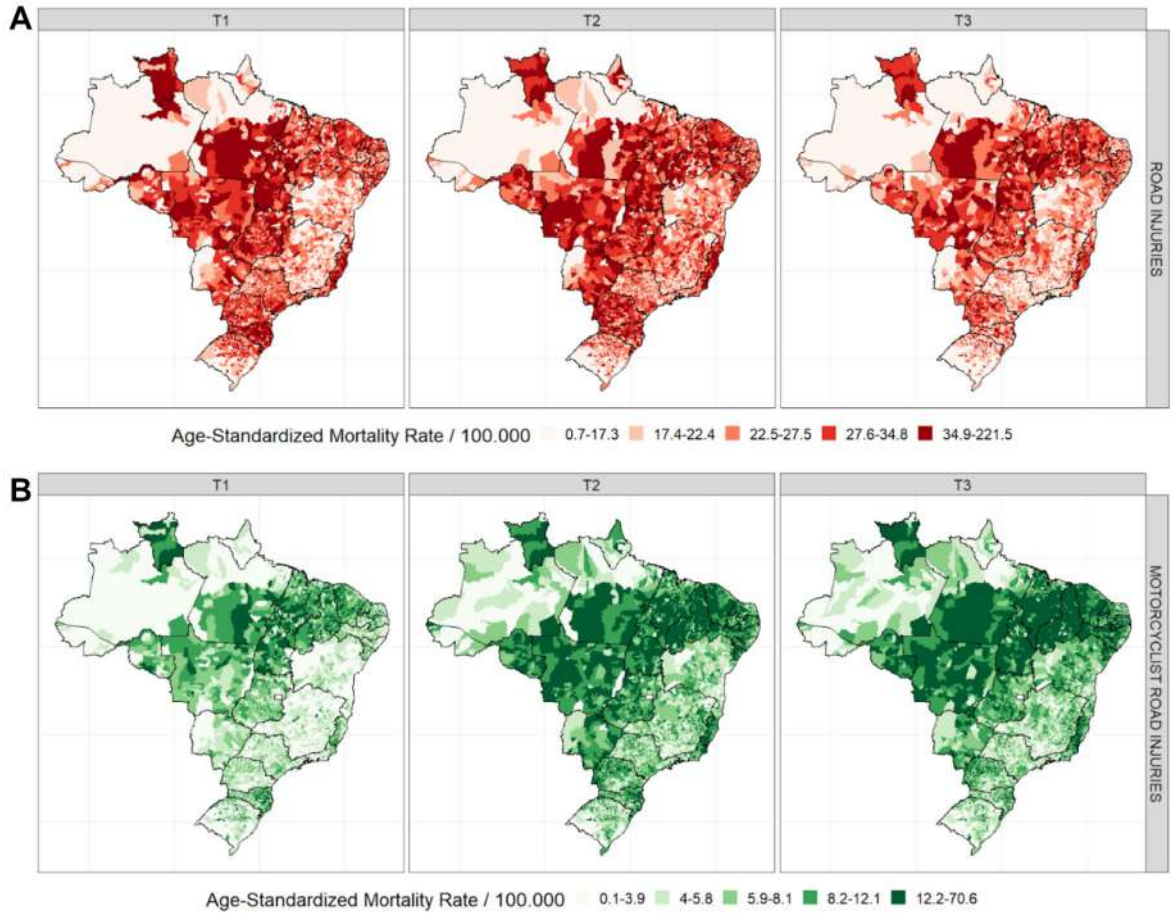

Fig. 1. (A) Age-standardized mortality rates according to the entire group of road injury, per 100,000 inhabitants in the three periods of T1 (2000–2002), T2 (2009–2011), and T3 (2016–2018). (B) Age-standardized mortality rates of motorcyclists per 100,000 inhabitants, in the three periods of T1 (2000–2002), T2 (2009–2011), and T3 (2016–2018).

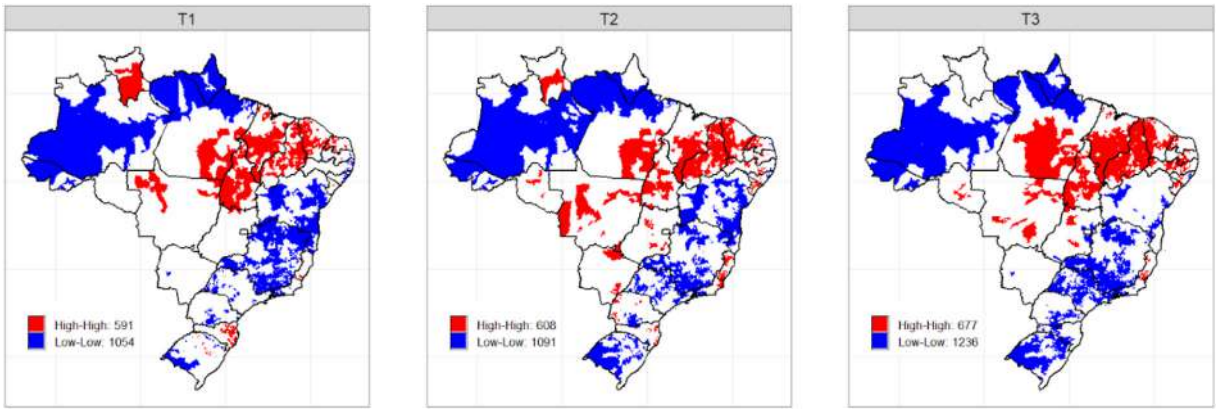

Fig. 2. Local spatial dependence (LISA) of the municipal mortality rates of motorcyclists, Brazil, in the three periods of T1 (2000–2002), T2 (2009–2011), and T3 (2016–2018).

rates were higher in smaller municipalities and lower in larger municipalities. In the Midwest region, the rates in municipalities "≤50,000 inhabitants" increased 64.4% between T1/T3. The increase was lower in the "50 to 300.000 inhabitants "(54.1%) and was 24.6% in ">300,000 inhabitants" In the Northeast, the increase in mortality for municipalities "≤50,000" varied 89.5% between T1/T3, which was the highest change percentage observed. In the North region, the larger the size of the municipalities, the bigger the percentage observed in the mortality rates between T1/T3. In the Southeast, the smaller municipalities had an expressive increase between T1/T3 (48.5%) when compared with municipalities "50 to 300.000 inhabitants" (18.5) and ">300,000 inhabitants" (10.6), where there was the lowest increase in motorcyclist mortality between T1/T3. In the South, the municipalities with "50 to 300,000 inhabitants" had the largest change in percentage of mortality rates between T1/T3 (20.1%).

Fig. 3 shows the correlation between the logarithm of the average GDP *per capita* in T3 with the mortality rate of motorcyclists in the same 3-year period stratified by regions, considering

Table 2
Age-standardized mortality rates for motorcyclists per 100,000 inhabitants, with 95% confidence intervals (95% CI), according to Brazilian macroregions and population size, in the three periods of T1 (2000–2002), T2 (2009–2011), and T3 (2016–2018), and percentage variation.

Region	Population size (inhabitants)	Three-year periods			Percentage variation		
		T1	T2	T3	T1-T2	T2-T3	T1-T3
Midwest	Less or equal to 50,000	6.5 (5.8–7.3)	11.2 (10.3–12.1)	10.8 (9.9–11.6)	71.2	−3.9	64.4
	Above 50,000 up to 300,000	6 (5.1–7)	9.8 (8.8–10.9)	9.3 (8.4–10.2)	63.8	−5.9	54.1
	Above 300,000	4.4 (3.9–5)	6.9 (6.3–7.6)	5.5 (5–6.1)	56.1	−20.2	24.6
Northeast	Less or equal to 50,000	6.6 (6.3–7)	11 (10.5–11.4)	12.6 (12.1–13)	65.4	14.5	89.5
	Above 50,000 up to 300,000	5.6 (5.2–6)	8.9 (8.4–9.4)	9.6 (9.1–10)	58.1	7.6	70.1
	Above 300,000	3.4 (3.1–3.8)	5.2 (4.8–5.5)	4.9 (4.5–5.2)	50.4	−5.8	41.6
North	Less or equal to 50,000	6.3 (5.6–7.1)	9.2 (8.4–10)	9.4 (8.6–10.2)	45.0	2.3	48.3
	Above 50,000 up to 300,000	5.7 (4.9–6.5)	9.3 (8.4–10.1)	8.9 (8.1–9.6)	62.3	−4.2	55.4
	Above 300,000	2.9 (2.3–3.4)	4.5 (3.9–5)	4.8 (4.2–5.3)	57.2	6.0	66.5
Southeast	Less or equal to 50,000	4.5 (4.2–4.8)	7.3 (6.9–7.7)	6.7 (6.4–7.1)	61.9	−8.3	48.5
	Above 50,000 up to 300,000	4.7 (4.4–5)	6.2 (5.9–6.5)	5.6 (5.3–5.8)	32.4	−10.6	18.5
	Above 300,000	3.5 (3.3–3.7)	4.7 (4.5–4.9)	3.9 (3.7–4)	34.9	−18.0	10.6
South	Less or equal to 50,000	6.3 (5.9–6.8)	8.9 (8.4–9.4)	7.4 (6.9–7.9)	40.6	−16.3	17.7
	Above 50,000 up to 300,000	5 (4.6–5.5)	7.7 (7.2–8.2)	6 (5.6–6.5)	53.6	−21.8	20.1
	Above 300,000	3.9 (3.5–4.4)	5.7 (5.1–6.2)	4.7 (4.2–5.1)	43.7	−17.7	18.2

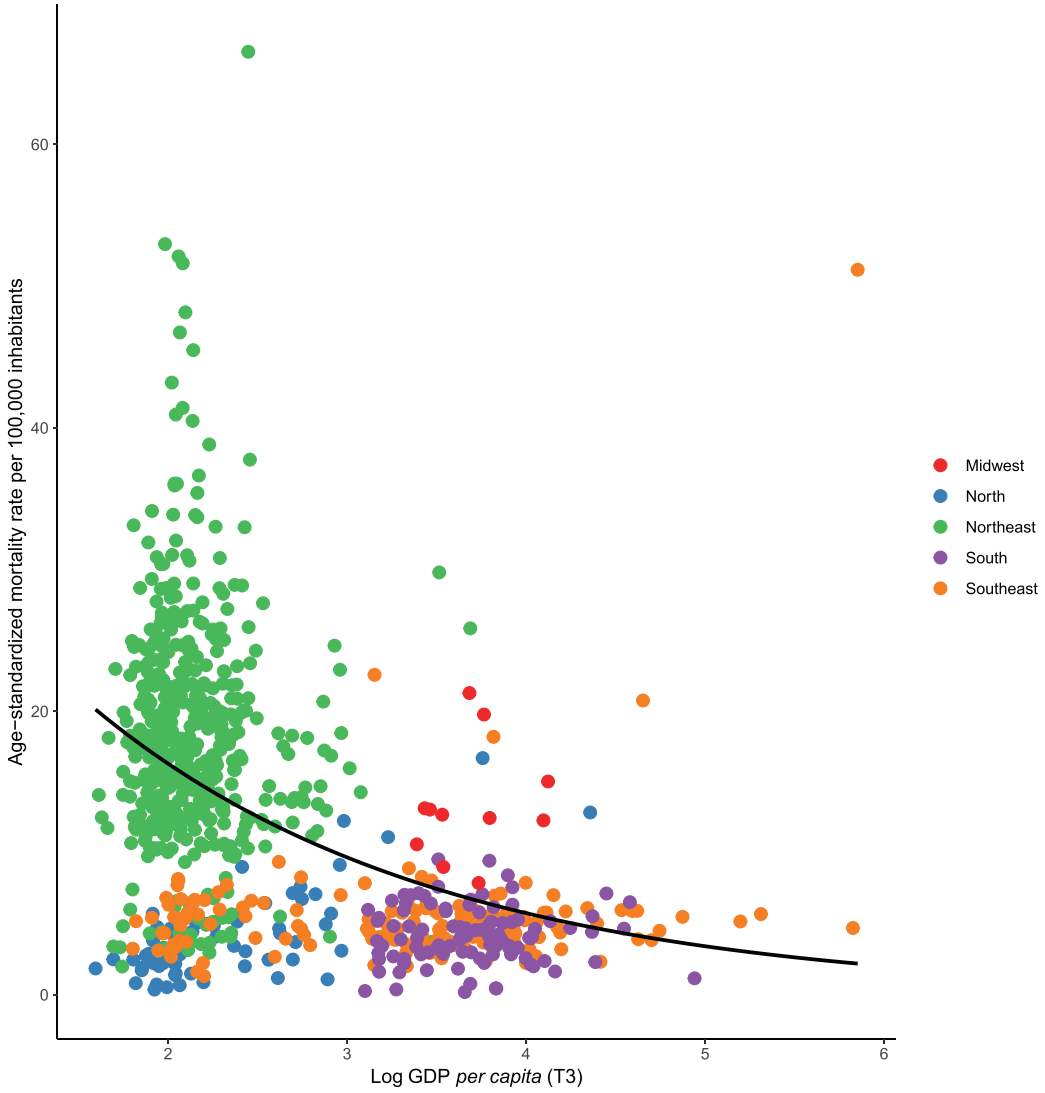

Fig. 3. Dispersion graph and correlation analysis between the logarithm of the average gross domestic product per capita in T3 (2016–2018) and the mortality rates of motorcyclists in the LISA-significant municipality referring to the same 3-year period according to macroregions. PIB, produto interno bruto.

municipalities, which were conjointly significant in the LISA evaluated for mortality rates in T3 (Fig. 3) and in the LISA evaluated for the GDP (Fig. S5). The calculated Spearman correlation coefficient was $r_s = -0.49$ (value of $P < 2.2e^{-16}$), and the solid line represents a logarithmic smoothing indicating that as the GDP increases, the mortality rate decreases.

Discussion

A decrease was observed in the RTI mortality rates between 2000 and 2018 for the total RTIs per municipality in Brazil; the most significant declines were observed in the South and Southeast. However, progressive increases were found among motorcyclists, resulting in higher rates in the third triennium. Our study indicated clusters of municipalities with high rates of mortality among motorcyclists from the Northeast and from some states from the North and Midwest regions. The mortality rates were higher in smaller municipalities and showed a negative correlation with the GDP *per capita*.

The sharpest declines in RTI mortality rates occurred in the South and Southeast regions, and the result can be attributed to a better implementation of the National Traffic Legislation, with enforcement measures directed to the control of speeding and driving under the influence of alcohol.[13] It is also important to mention the improvements in the road system, mandatory safety items (seat belts and child seats), and Anti-lock Braking System (ABS) brakes and the increase in educational actions.[3,18]

Studies have indicated differences in the profile of risks of injuries by RTI according to region and population size. A decrease in deaths was observed in the Southeast and South regions of the country and in large municipalities, whereas an increase was found in the Northeast and Midwest regions and small countryside municipalities.[3] Such differences can be explained by the decentralization of traffic law enforcement, which passed from the state level to the municipal level, but unequally in recent decades. The most affected states are in the Northeast and North regions, which have a large number of poor municipalities with less capacity to regulate traffic.

Different tendencies in mortality rates were observed according to the type and means of transportation. The reduction in deaths of pedestrians and motor vehicle occupants is coherent with the international trend[7] and may be related to traffic control measures, use of seat belts, child safety equipment, improvements in street signs and in the safety of the vehicles, and traffic education actions as well.[3,20]

The growth in mortality rates of motorcyclists during the period, especially after 2000, was also described in other studies conducted in Brazil[13,21–23] and may well be associated with the growth of the fleet, especially in states of the Northeast region, where there has been a 1400% increase in the annual sales of motorcycles between 1991 and 2008.[24,25] Such an increase may be a result of the economic growth between 2004 and 2014. Motorcycles have become a kind of vehicle incorporated into urban and rural work throughout the country.[3,22] In the countryside areas, such means of transportation have substituted, inclusively, non-motorized means of transportation, such as bicycles and animals.[24] The tax incentives for the production of motorcycles, easy access to and acquisition of motorcycles,[25] and the degradation of public transportation were elements that induced the increase in the fleet of motorcycles.[8]

The increase in fleet size has not been followed by measures of traffic safety. The vulnerability due to the exposure of the motorcyclists' body adds up to their risk-taking behavior, considerably increasing the risk of injuries and deaths. The National Health Survey (2019) showed that in the North and Northeast regions, helmet use is much less frequent than in the other regions. Wearing a helmet reduces the risk of death by 40% and the risk of injuries by 70%.[26] Moreover, the North and Northeast regions have the lowest percentages of municipalities included in the National Traffic System. Consequently, they have less capability to regulate and receive less investments in road signs and road maintenance.

Other public policies implemented in the country add up to the Brazilian Traffic Law (CTB, in Portuguese), contributing to a reduction in RTI mortality rates, such as the Dry Law[26] and the New Dry Law[27] from 2008 to 2012, which allowed for an increase in the surveillance of drivers under the influence of alcohol; the implementation of the Mobile Urgent Care Services (SAMU, in Portuguese) in 2004,[28] which had a highly positive impact on addressing emergencies, as well as the implementation of the Life in Traffic Project in 2010 by the Brazilian Ministry of Health, the Pan American Health Organization, and the World Health Organization (WHO).[29]

Regardless of the progress in the country, there is still much work to be done by the Brazilian government and society in terms of making the levels of RTI mortality rates drop to the levels observed in European countries.[1] However, drawbacks have been noticed in traffic laws in Brazil. In 2020, there was a change in the CTB, which allows for a wider margin of violations before the driver's license is suspended, and a longer validity of the document. Furthermore, the changes allowed for the automatic conversion of traffic violation fines into warnings in the case of less severe violations.[27] Such measures compromise driving safety. Other actions by the government, in terms of discrediting the enforcement of speeding laws or the proposal to revoke the need for child car seats for children up to 7 years of age,[28–32] may result in an increase in the risk of injuries and deaths in traffic.

The results of the GBD are important to standardize methods, enabling a comparison between states and for the analysis of temporal evolution, thereby supporting a more trustworthy understanding of the magnitude of health problems in Brazil and the planning of public health actions. In Brazil, the estimates from the GBD study are based on data from the SIM and may have been affected by underreporting and by the proportion of indeterminate external causes, although those indicators have been improved in recent decades.[13–15]

The results verified in this study showed a decrease in RTI mortality rates between 1990 and 2018 but with an increase in the deaths of motorcyclists. There are regional inequalities, inequalities in terms of population size and socio-economic characteristics of the municipalities, as well as discrepancies in terms of the different conditions of the victims. The loosening of regulatory measures in traffic laws may even further compromise the possibility of achieving the established SDG goals.

Author statements

Acknowledgments

M.D.C. thanks the National Council for Scientific and Technological Development (CNPq) for the productivity grant.

Ethical approval

This study was conducted according the norms the National Health Council and integrates the project "Inequalities in indicators of non-communicable diseases, violence, and their risk factors in small geographic areas," approved by the Research Ethics Committee from Universidade Federal de Minas Gerais (decision number 3,258,076).

Funding

This study was funded by the following projects: (1) Pan American Health Organization, Brazil [Letter of Agreement SCON2021-00288]; (2) National Health Fund from Ministry of Health, Brazil [grant number 148/2018].

Competing interests

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.013.

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Public Health 220 (2023) 72–79

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Online songwriting reduces loneliness and postnatal depression and enhances social connectedness in women with young babies: randomised controlled trial

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ARTICLE INFO

Article history:
Received 15 December 2022
Received in revised form
12 April 2023
Accepted 21 April 2023

Keywords:
Loneliness
Music
Perinatal
Postnatal depression
Social connectedness
Songwriting

ABSTRACT

Objective: Loneliness is a public health challenge associated with postnatal depression (PND). This study developed and tested an online songwriting intervention, with the aim of reducing loneliness and symptoms of PND and enhancing social connectedness among women with young babies.
Study design: This was a two-armed non-blinded randomised controlled trial (RCT, ISRCTN17647261).
Methods: Randomisation was conducted in Excel using a 1:1 allocation, with participants ($N = 89$) allocated to an online 6-week songwriting intervention (*Songs from Home*) or to waitlist control. Inclusion criteria were women aged ≥18 years, with a baby ≤9 months old, reporting loneliness (4+ on UCLA 3-Item Loneliness Scale) and symptoms of PND (10+ on Edinburgh Postnatal Depression Scale [EPDS]). Loneliness (UCLA-3) was measured at baseline, after each intervention session and at 4-week follow-up. The secondary measures of PND (EPDS) and social connectedness (Social Connectedness Revised 15-item Scale [SC-15]) were measured at baseline, postintervention and at 4-week follow-up (Week 10). Factorial mixed analyses of variance with planned custom contrasts were conducted for each outcome variable comparing the intervention and control groups over time and across baseline, Weeks 1–6 and the follow-up at Week 10 for each outcome variable.
Results: Compared with waitlist control, the intervention group reported significantly lower scores postintervention and at follow-up for loneliness ($P < 0.001$, $\eta^2_P = 0.098$) and PND ($P < 0.001$, $\eta^2_P = 0.174$) and significantly higher scores at follow-up for social connectedness ($P < 0.001$, $\eta^2_P = 0.173$).
Conclusions: A 6-week online songwriting intervention for women with young babies can reduce loneliness and symptoms of PND and increase social connectedness.

Introduction

Loneliness is associated with physical and mental health problems, including mortality.[1,2] It affects one-third of people in industrialised countries, making it a significant public health problem.[3] Loneliness is different from social isolation and arises when an individual feels dissatisfied with their social relationships.[4] In the United Kingdom – both before and during the COVID-19 pandemic – some groups have a higher risk of loneliness, including young adults and women.[5] Loneliness has been suggested to be the 'opposite' of social connectedness, 'a subjective psychological bond that people feel in relation to individuals and groups of others'[6] that incorporates caring about others, feeling cared for and belonging.[7]

Crucially, social factors are known to be a key predictor of the perinatal mental illness postnatal depression (PND). UK health records indicate that more than one in 10 women have a depression diagnosis or depressive symptoms in the year after giving birth, with more than one in eight receiving antidepressant medication.[8] PND is debilitating for those experiencing symptoms and has repercussions for fathers,[9] mother–baby bonds,[10] and children's social-emotional development.[11] PND requires attention because suicide is the leading cause of mortality in the first year after giving birth.[12] Low or lacking social support postnatally is a risk factor for PND,[13] and there are identified links between functional and informal social support and lower incidence of PND.[14] Importantly, social support – or lack

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https://doi.org/10.1016/j.puhe.2023.04.017

thereof – also links with *experiences* of loneliness among women with PND.[15] Luoma et al., for example, demonstrated that 34–38% of a sample of mothers reported loneliness and that maternal loneliness was associated with the presence of depressive symptoms.[16] A recent meta-synthesis confirmed that loneliness appears to play an important role in the experience of perinatal depression.[17] Generally, it is well established that loneliness is linked with depression and poorer mental health outcomes.[18]

There can be challenges with detection and treatment for PND,[19] and interventions targeting loneliness are disproportionally designed for, and tested with, older adults.[20,21] Loneliness in depression has been identified as a potential target for the development and testing of interventions[18] but there is a significant gap in how to reduce loneliness among people with perinatal mental illness. This study therefore focused on the development and testing of a songwriting intervention to tackle loneliness and enhance social connections among women with PND. Built from the above evidence base, the study was underpinned by four drivers. First, social support may prevent or reduce PND. Second, people with PND can feel lonely, which is, in turn, associated with poorer mental health outcomes. Third, there is a lack of psychosocial interventions that are specifically designed to build social connections and reduce loneliness among people with PND and that are delivered online. Online delivery may address issues of access and equity recognising that there can be financial, social, practical or health barriers to in-person interventions. Fourth, previous research has demonstrated that in-person group singing can speed up recovery from PND[22] as well as support connections with other mothers and enhance mother–baby closeness.[23,24] While the COVID-19 pandemic catalysed research into the efficacy of online singing groups for PND,[25] evidence in this field remains in its infancy, and further studies are required. Songwriting has been previously investigated in a variety of clinical settings, including for addressing emotional or psychological challenges and facilitating the telling or sharing of stories.[26] It was selected in this study as a process previously used in perinatal contexts,[27,28] including to support social connections,[29] that could be particularly suited to the online context because of the potential for different creative processes that can be both synchronous and asynchronous (see 'The intervention' section). More widely, music has been reported to support social connectedness[30] and social bonding,[31] but little is known about the potential for online songwriting to support perinatal loneliness and depression.

Three hypotheses were therefore tested regarding scores among an online intervention (songwriting) group compared with a control group.

H1. significantly larger decrease in self-reported loneliness scores over time

H2. significantly larger decrease in self-reported PND scores over time

H3. significantly larger increase in self-reported social connectedness scores over time

The intervention

The *Songs from Home* songwriting intervention included free weekly online songwriting sessions in groups of 9–12 people. Following previous research,[22] the intervention lasted 6 weeks. The development of the intervention was supported by Personal and Public Involvement (PPI), undertaken via two online focus groups in which participants discussed experiences of motherhood, existing resources and support, and key features and success markers of a potential online songwriting programme. Focus groups information informed (1) activity description in publicity materials (e.g. to be inclusive and welcome all levels of musical experience), (2) content of the sessions (e.g. some activities for mothers and some for babies, have a workspace between sessions), (3) the goals of the sessions (e.g. a sense of achievement), (4) the social aspects of online work (e.g. including time for conversation) and (5) timing, frequency and duration of sessions (e.g. weekly, hour-long sessions).

Informed by the PPI stage, each intervention session included a 60-min synchronous online workshop hosted via Zoom, led by one of two professional music workshop leaders and supported by one of two musically trained research assistants. Participants also had access to an asynchronous workspace hosted online through Trello.com. The workshops included a welcome and warm-up, facilitated songwriting composition through discussion of ideas, refinement of lyrics and creation of melody, and group singing of songs. No musical style was specified, and leaders and assistants accompanied songs using instruments such as violin or ukulele. Women attended with and without their babies. Following the co-construction phase, the leaders articulated four session goals: to create feelings of comfort and safety; to facilitate achievement; to support participants' connection with their children and their own musical selves; and to adapt to individuals by being responsive to their needs, cultural backgrounds and identities. These goals were addressed using fundamental principles or techniques. For example, in working toward feelings of comfort and safety, the music leaders ensured that participants frequently had control of the specifics of the content and that there were a variety of approaches to song creation to allow for varying levels of confidence and prior experience.[32]

In line with this approach, there were several ways in which the lyrics and melodies were developed and recorded. Here we provide two examples of possible creative processes, with more information provided elsewhere.[32] Some songs were developed quickly, and others were worked on over several weeks. Those developed more quickly – which typically happened near the beginning of sessions – were designed to be small creative tasks that should be straightforward to contribute to and celebrate the participants' creativity. Several techniques were used for each stage. For example, to facilitate a collaborative route to choosing ideas to focus on in a song, the music leader created a graphic of a wiggly line on the Zoom whiteboard, with the idea of the peaks and troughs of a parenting day. The participants could contribute ideas either by writing them on the line or in the Zoom chat option or by suggesting them verbally. Once several ideas had been shared, the music leader asked the participants what topic jumped out to them, and this formed the basis for the song.

The larger songwriting tasks were spread over several weeks, and everyone was offered a chance to contribute in their preferred way in every session. The leaders began the process by discussing a proposed topic as a group. Ideas could be noted on a group whiteboard, through the Zoom chat function, or verbally with a research assistant noting in the chat what was being said. A week later – so that there would be less individual association with ideas and more of a sense of shared ownership – lyric writing would begin. For this, the music leader would ask participants in turn what phrases from the discussion resonated with them, and then as a group, they would edit the ideas into lyrical phrases. In a later session, they worked on the melody. The leaders capitalised on the online context and used the mute function to encourage some unselfconscious creativity. The music leader shared the first few lines of lyrics on the screen and played a chord progression round and round on a ukulele, asking the participants to sing the first line (on mute) however they felt it should go and to try it in several different ways if they wanted to. The music leader then asked for

volunteers to sing their ideas. She always accepted the first idea and found that once someone had sung the first section, other participants seemed more confident either to sing the next section or to edit and add to it. In the following session, the music leader would sing the song back, fully formed, and ready for the group to sing together. Participants were sent recordings of two or three of the created songs, recorded by the music leaders, following the 6-week intervention.

Methods

Design

A two-armed, non-blinded randomised controlled trial (RCT) with a non-intervention waitlist control group was registered with the ISRCTN registry (ISRCTN17647261, first registration 15/09/2021) and run from 17 September 2021 to January 2022. The intervention was offered in separate groups to optimise group sizes, and those in the waitlist control group offered the same non-measured intervention following their involvement in the trial. Two 6-week intervention groups ran from September to November 2021, with follow-up in December 2021, and two further 6-week groups ran from November to December 2021, with follow-up in January 2022 when the trial concluded as planned. No adverse events were reported. The mean attendance was 3.91 sessions (median = 4.00, standard deviation [SD] = 1.44) out of six.

Outcome variables

Demographic data were collected at baseline. The primary outcome variable was the UCLA 3-Item Loneliness Scale (UCLA-3), frequently used in loneliness interventions.[33] This short 3-item scale was administered via an online questionnaire at eight points (and at equivalent time points for the control group): at baseline (2 weeks before intervention start), immediately following each of the six synchronous online sessions and at follow-up 4 weeks after the end of the intervention. The secondary outcome variables included measures of social connectedness (Social Connectedness Revised 15-item Scale [SC-15][34]) and PND symptoms (Edinburgh Postnatal Depression Scale [EPDS][35]). Data on secondary outcomes were collected via an online questionnaire at baseline (2 weeks before intervention start), immediately following the final synchronous session and at 4-week follow-up. All data were collected through Microsoft Forms and Qualtrics.

Participants

All procedures involving human participants were approved by the Conservatoires UK Research Ethics Committee on 5 March 2021 [CUK/RCCSD/2020-21/5] and amended on 2 August 2021 [CUK/SF/2020-21/5/2]. Written informed consent was obtained online from all participants. Recruitment was conducted through the project's organisational partner Happity through their established communication channels (Web site, emailed newsletters and social media), as well as through online advertising via the research team. As such, the study makes use of a community rather than a clinical sample.

PPI focus groups

Fourteen mothers from across the United Kingdom, aged >18 years, participated in the focus group. They all had experience of motherhood, self-reported loneliness and/or self-reported symptoms of PND in the last 3 years. Their most recent baby was between 9 months and at most 3 years old.

Randomised controlled trial

Participants registered their interest for the project and underwent a screening process. Eligibility criteria were people identifying as women, aged ≥18 years, with a baby aged ≤9 months, experiencing some loneliness (scoring 4+ on UCLA-3), and reporting symptoms of PND (scoring 10+ on EPDS). Once fully consented, eligible participants were randomly allocated to either the intervention or control group. Randomisation was conducted in Excel using a 1:1 allocation and random number generation and custom sort functions, stratified by loneliness scores (UCLA), PND scores (EPDS) and age of baby. Independent samples *t*-tests conducted before the randomisation groupings were implemented confirmed no significant differences or meaningful effect sizes between groups across these variables. Randomisations, enrolment and assignment of participants to the intervention/control group were conducted by the authors, independently of the workshop leaders and research assistants who led and attended the workshops.

A meta-analysis of previous research examining loneliness interventions[33] demonstrated a small effect of 0.198 among RCTs (with a larger effect of 0.459 in controlled studies using non-randomised group allocation). Power analysis (assuming two groups with measures at eight points and measure correlation of 0.7[33]) indicated a minimum of 68 participants divided across the intervention and control groups to determine the significance of an effect of similar size. Ninety-four participants were recruited and consented in two waves of recruitment (September 2021 and November 2021; see Fig. 1). Five participants consented but took no further part in the study, leaving a total of 89 participants. The mean UCLA score at baseline was 7.55 (SD = 1.22, range = 6–9; intervention mean = 7.53 [SD = 1.24]; control mean = 7.30 [*SD* = 1.29]), the mean EPDS score at baseline was 16.51 (SD = 3.56, range = 10–24; intervention mean = 16.97 [SD = 3.74]; control mean = 15.63 [*SD* = 3.31]), and the mean social connectedness score at baseline was 51.55 (SD = 11.28, range = 31–76; intervention mean = 50.97 [SD = 12.47]; control mean = 53.73 [SD = 10.42]).

Seventy-eight participants provided data at Week 6, and 62 participants provided data at Week 10 (see Fig. 1). Where individual loneliness (UCLA) scores were missing across the Week 1–6 (but not baseline or Week 10) data from participants who provided preceding and subsequent scores, the *last observation carried forward* method was used to input a missing value. If there was a difference of two or more points to the next recorded value the mean value of the last and next observations was inserted. This affected the scores of 19 of the participants and allowed them to be included in the analyses. The total cohort reported a mean age of 35.39 years (median = 35, SD = 3.74, range 26–45 years) and had a median household gross income of £52,000 to £75,999. Participants lived in the United Kingdom, primarily in London and the south of England, were highly educated (93% having undertaken higher education), 67% were White and 76% were married or in a civil partnership. Sixteen percent of participants reported taking medication for mood, and 24% reported having talking therapy. Full demographic details are presented in Table 1.

Analysis

Baseline measures and demographics were compared between intervention and control groups using independent samples *t*-tests for continuous variables (age, number of children, EPDS, UCLA-3, SC-15) and Chi-squared tests for categorical variables (relationship status, use of medication, talking therapy, level of education, region, income). No significant differences were found; thus, covariates were not included in subsequent models. Factorial mixed

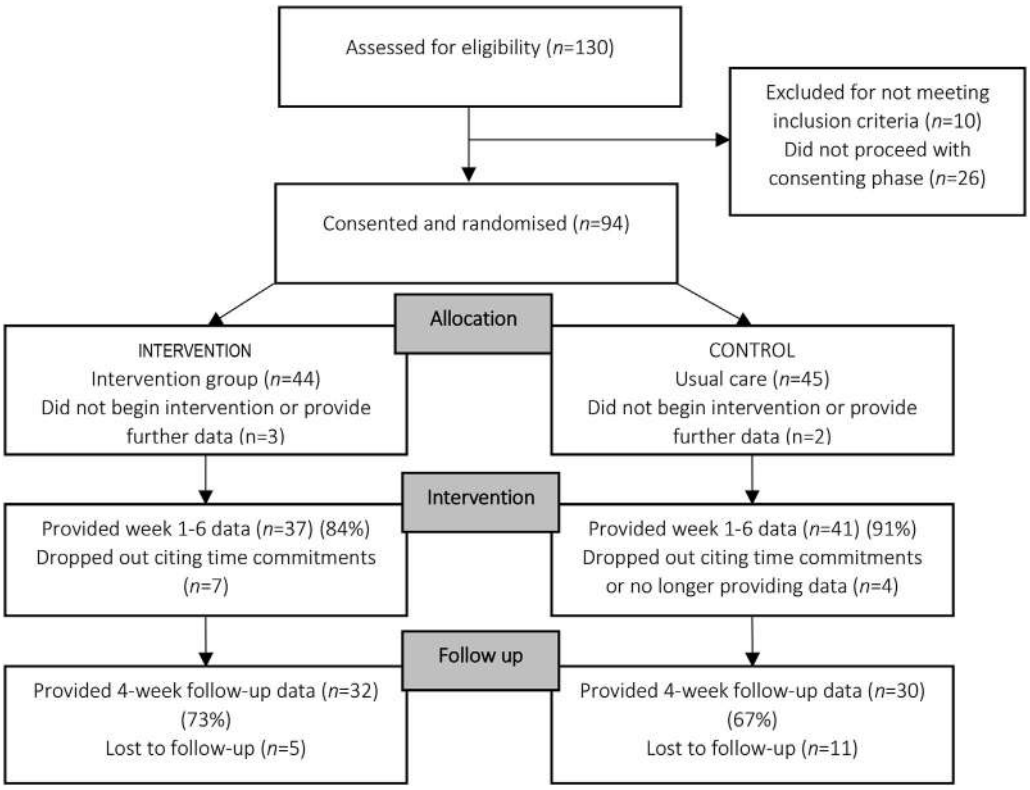

Fig. 1. Participant flowchart.

analyses of variance (ANOVAs) were conducted for each of the three outcome variables. Each ANOVA was followed by a custom planned contrast in which a repeated comparison was conducted within each of the control and intervention groups comparing baseline with Week 6 and Week 6 with Week 10, as well as comparisons of the intervention/control pairing at each time point. This resulted in seven total comparisons each for the EPDS and SC-15 and 12 comparisons for the UCLA-3. Effect sizes were calculated using partial eta squared. Tests of homogeneity and sphericity were conducted and, where the latter were violated, Greenhouse-Geisser corrections applied (indicated below). Analyses were conducted using JASP (v. 0.16.1).

Results

Hypothesis 1

A 2 × 8 mixed ANOVA was conducted comparing the intervention and control groups across baseline, Weeks 1–6 and the follow-up at Week 10 ($n = 62$ provided data at all time points; see Fig. 1). Sphericity was violated; thus, a Greenhouse-Geisser correction applied. A moderate and significant interaction effect between loneliness and treatment group was found ($F_{5.554,333.248} = 6.504$, $P < 0.001$, $\eta^2_P = 0.098$) in which loneliness scores were found to fall significantly lower within the intervention group compared with the control group, thus supporting the hypothesis. A large and significant main effect of time on loneliness was found ($F_{5.554,333.248} = 13.106$, $P < 0.001$, $\eta^2_P = 0.179$) in which loneliness scores fell overall (see Table 2 and Fig. 2). The main effect of treatment group was also significant with a moderate effect size ($F_{1,60} = 4.416$, $P < 0.05$, $\eta^2_P = 0.069$).

The planned custom contrasts revealed that group differences in loneliness scores first significantly differed following 3 weeks of the intervention, with the peak difference appearing at Week 4 after which differences stabilised (see Table 2 and Fig. 2). Both intervention and control groups saw significantly lower scores ($t = 8.500$, $P < 0.001$; $t = 2.235$, $P < 0.05$) at Week 6 compared with baseline, with the intervention group dropping a total 1.72 points on the 7-point scale (a 38% relative and 25% absolute drop) and the control group dropping 0.47 points (a 10% relative and 7% absolute drop), 0.40 of which fell between baseline and Week 1. No significant differences were seen between Week 6 and follow-up at Week 10.

Hypothesis 2

A 2 × 3 mixed ANOVA was conducted comparing the intervention and control groups across baseline, Week 6 and the follow-up at Week 10 ($n = 60$ provided data at all time points). Sphericity was violated; thus a Greenhouse-Geisser correction applied. A large and significant interaction effect between PND and treatment group was found ($F_{1.665,96.596} = 12.231$, $P < 0.001$, $\eta^2_P = 0.174$) in which PND scores were found to fall significantly lower within the intervention group compared with the control group, thus supporting the hypothesis. A large and significant main effect of time on PND was found ($F_{1.665,96.596} = 30.438$, $P < 0.001$, $\eta^2_P = 0.344$) in which PND scores fell overall (see Table 3 and Fig. 2). The main effect of treatment group was not significant.

The planned custom contrasts revealed that group differences in PND scores did not significantly differ at baseline but were significantly lower among the intervention group at Weeks 6 and 10 (see Table 3 and Fig. 2). Both intervention and control groups saw significantly lower scores ($t = 7.124$, $P < 0.001$; $t = 2.229$, $P < 0.05$) at Week 6 compared with baseline, with the intervention group dropping a total 5.44 points on the 31-point scale (a 32% relative and 18% absolute drop) and the control group dropping 1.70 points

Table 1
Participant demographics ($N = 89$).

Variable	Category	Count			Percent (of 44, 45, 89)		
		Int.	Control	Total	Int.	Control	Total
Number of children	1	28	23	51	64%	51%	57%
	2	12	21	33	27%	47%	37%
	3	3	1	4	7%	2%	5%
	4	1	0	1	2%	0%	1%
Relationship status	Single	8	6	14	18%	13%	16%
	Married/civil partnership	34	34	68	77%	76%	76%
	Separated/divorced	0	1	1	0%	2%	1%
	Prefer not to say	2	4	6	5%	9%	7%
Live with partner?	Yes	41	41	82	93%	91%	92%
Taking medication for mood?	No	38	35	73	86%	78%	82%
	Yes	4	10	14	9%	22%	16%
	Prefer not to say	2	0	2	5%	0%	2%
Having a talking therapy?	No	33	34	67	75%	76%	75%
	Yes	10	11	21	23%	24%	24%
	Prefer not to say	1	0	1	2%	0%	1%
Level of education/qualification	Secondary (e.g. high school)	2	3	5	5%	7%	6%
	Tertiary/higher/further	26	22	48	59%	49%	54%
	Advanced (e.g. masters, doctorate)	16	19	35	36%	42%	39%
	Prefer not to say	0	1	1	0%	2%	1%
Region	North England	5	10	15	11%	22%	17%
	London	27	19	46	61%	42%	51%
	South England	10	14	24	23%	31%	27%
	Scotland	2	2	4	5%	4%	5%
Household gross income	Up to £5199	1	0	1	2%	0%	1%
	£5200 and up to £10,399	0	1	1	0%	2%	1%
	£15,600 and up to £20,799	0	1	1	0%	2%	1%
	£20,800 and up to £25,999	0	2	2	0%	4%	2%
	£26,000 and up to £31,199	2	2	4	5%	4%	5%
	£31,200 and up to £36,399	0	1	1	0%	2%	1%
	£36,400 and up to £41,599	2	2	4	5%	4%	5%
	£41,600 and up to £46,799	3	4	7	7%	9%	8%
	£46,800 and up to £51,999	2	3	5	5%	7%	6%
	£52,000 and up to £75,999	11	10	21	25%	22%	24%
	£76,000 and above	13	12	25	30%	27%	28%
	Prefer not to say	10	7	17	23%	16%	19%
Ethnicity	Arab	1	0	1	2%	0%	1%
	Asian	2	5	7	5%	11%	8%
	Black	4	1	5	9%	2%	6%
	White	29	31	60	66%	69%	67%
	Mixed	5	6	11	11%	13%	12%
	Other	3	1	4	7%	2%	5%
	Prefer not to say	0	1	1	0%	2%	1%

(an 11% relative and 5% absolute drop). No significant differences were seen between Week 6 and follow-up at Week 10 in either group.

Table 2
Descriptives and pairwise comparisons for the Loneliness (UCLA-3) scores.

Loneliness (UCLA-3)	Treatment	Mean	SD	Difference	t	P
Baseline	Control	7.30	1.29	0.23	0.659	0.511
	Intervention	7.53	1.24			
Week 1	Control	6.90	1.40	0.07	0.196	0.845
	Intervention	6.97	1.36			
Week 2	Control	7.00	1.29	−0.38	−1.069	0.287
	Intervention	6.63	1.31			
Week 3	Control	7.10	1.24	**−0.82**	**−2.334**	**0.021**
	Intervention	6.28	1.35			
Week 4	Control	7.00	1.49	**−1.09**	**−3.119**	**0.002**
	Intervention	5.91	1.42			
Week 5	Control	6.93	1.26	**−0.90**	**−2.572**	**0.011**
	Intervention	6.03	1.35			
Week 6	Control	6.83	1.46	**−1.02**	**−2.911**	**0.004**
	Intervention	5.81	1.80			
Week 10	Control	6.83	1.32	**−1.02**	**−2.911**	**0.004**
	Intervention	5.81	1.38			

EPDS, Edinburgh Postnatal Depression Scale; SD, standard deviation. Figures in bold indicate significance at $P < 0.05$.

Hypothesis 3

A 2 × 3 mixed ANOVA was conducted comparing the intervention and control groups across baseline, Week 6 and the follow-up at Week 10 ($n = 59$ provided data at all time points). A large and significant interaction effect between social connectedness and treatment group was found ($F_{2,114} = 11.949$, $P < 0.001$, $\eta^2_P = 0.173$) in which social connectedness scores were found to rise significantly higher within the intervention group compared with the control group, thus supporting the hypothesis. No significant main effects of social connectedness or treatment group were seen (see Table 3 and Fig. 2).

The planned custom contrasts revealed that group differences in social connectedness scores did not significantly differ at baseline or at Week 6 but were significantly higher among the intervention group at Week 10 (see Table 3 and Fig. 2). Only the intervention group saw a significant difference in scores ($t = -3.685$, $P < 0.001$) at Week 6 compared with baseline, with the intervention group increasing by 5.20 points on the 76-point scale (a 14% relative and 7% absolute increase). No significant differences were seen between Week 6 and follow-up at Week 10 in either group.

To confirm general effects with a larger sample, mixed ANOVAs were conducted among the participants ($n = 78$ UCLA; $n = 76$ EPDS; $n = 75$ SC-15) who had provided baseline and Week 1–6 data only.

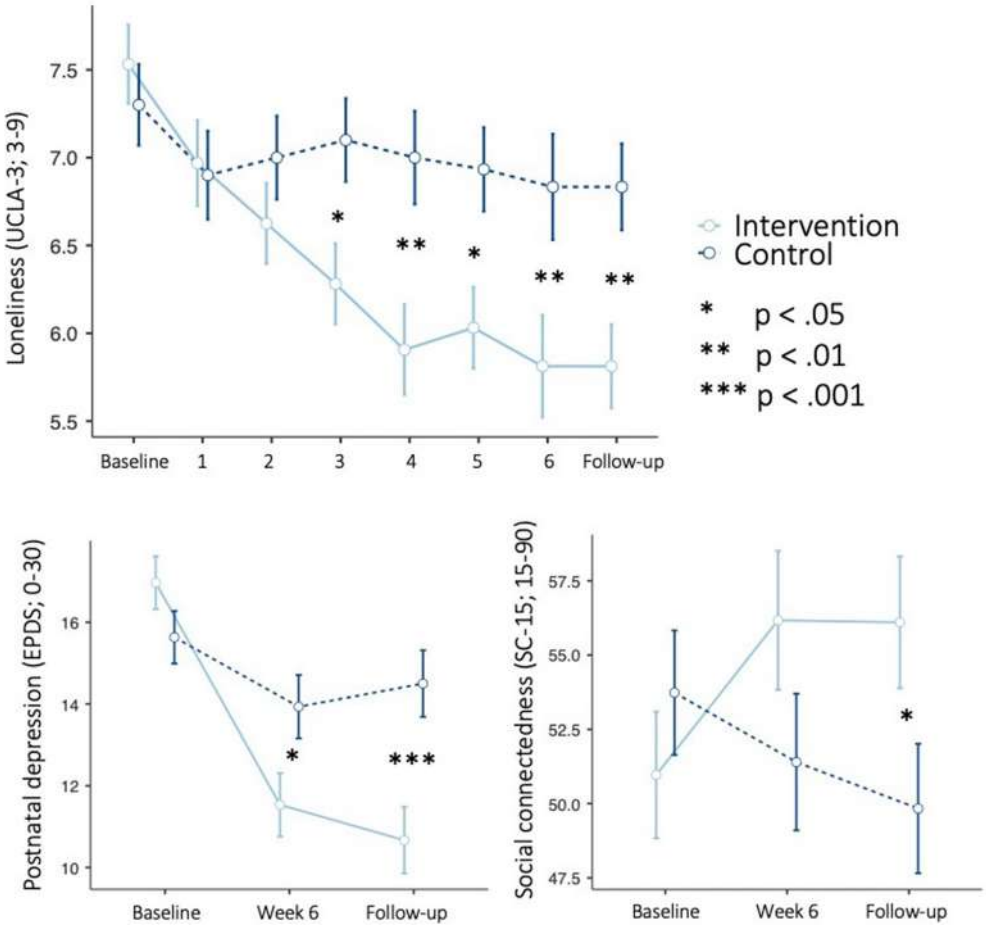

Fig. 2. Differences between intervention and control groups on the three outcome variables (error bars show ±1 standard error).

No differences in descriptive trends or the significance or size of main, interaction, or contrast effects were observed that would alter the above interpretations of the hypotheses.

Discussion

All three hypotheses were supported by the data with moderate-to-large effects. These findings provide evidence that an online songwriting intervention can reduce postnatal loneliness. They reinforce existing evidence that music can reduce loneliness[36] and support social connectedness[30] as well as support perceived mother–infant closeness[24] and bonding.[37]

As illustrated in Fig. 2, the intervention and control group significantly deviated in loneliness scores at Week 3 of the intervention, with the difference peaking at Week 4 and then stabilising through until follow-up. It is possible that the drop in loneliness seen in the control group between baseline and Week 1 was an effect of being part of a research project and contributing to a sense of 'sisterhood' that has been identified in other research.[38] In the intervention group, the beneficial effect on loneliness was maintained for at least the 4-week follow-up period. It should be noted that loneliness scores remained relatively high in the intervention group (mean 5.81) although, importantly, postintervention scores dropped below the cutoff of 6 identified in other research as indicative of being lonely.[39] The intervention also increased social connectedness scores, suggesting that participants also experienced feeling more connected to others, an important 'opposite of loneliness',[7] although the effect on social connectedness was weaker than that for loneliness and PND and took longer to appear.

Alongside these effects, the intervention reduced symptoms of PND among participants in the intervention group. In this group, EPDS scores had reduced to below the cutoff of 12/13 suggested for 'major' depression[40] by the end of the 6-week songwriting programme and reduced further by follow-up. This lends support to existing research showing that a group singing intervention can speed up recovery from moderate–severe symptoms of PND[22] and

Table 3
Descriptives and pairwise comparisons for the PND (EPDS) and Social Connectedness (SC-15) scores.

Outcome	Treatment	Mean	SD	Difference	*t*	*P*
PND						
Baseline	Control	15.63	3.31	1.34	1.261	0.210
	Intervention	16.97	3.74			
Week 6	Control	13.93	3.72	**−2.40**	**−2.270**	**0.025**
	Intervention	11.53	4.70			
Week 10	Control	14.50	4.69	**−3.83**	**−3.626**	**<0.001**
	Intervention	10.67	4.21			
Social connectedness						
Baseline	Control	53.73	10.42	−2.76	−0.885	0.379
	Intervention	50.97	12.47			
Week 6	Control	51.40	11.08	4.77	1.526	0.131
	Intervention	56.17	14.00			
Week 10	Control	49.83	9.74	**6.27**	**2.005**	**0.049**
	Intervention	56.10	13.85			

EPDS, Edinburgh Postnatal Depression Scale; PND, postnatal depression; SD, standard deviation. Figures in bold indicate significance at $P < 0.05$.

more widely that music can support perinatal mental health.[41] Looking across the outcome measures in this study, we know that higher loneliness is associated with more severe mental health symptoms[42] and that there is some evidence that greater loneliness predicts poorer depression outcome.[18] It is possible that a two-way effect may operate with songwriting, whereby the intervention increases social connectedness and reduces loneliness (risk factors for PND[13]), thereby helping to reduce symptoms of PND, and/or the intervention reduces symptoms of PND and therefore reduces the loneliness that people with this illness have reported.[14]

This RCT was not blinded, given the participatory nature of the intervention. It also relied on self-reports of primary and secondary outcomes. It is therefore possible that effects were driven by some combination of acquiescence bias and researcher effects, although the consistency of follow-up scores suggests a degree of internal validity. Of note is also the relatively large number of participants lost to drop out ($n = 11$ during the intervention and a further $n = 16$ lost at follow-up, see Fig. 1). When reported, dropout reasons included time commitments and scheduling conflicts. It is possible that the online mode of delivery also influenced attrition rates, with participants reporting varying views on the acceptability and desirability of songwriting online.[32] Research at the start of the COVID-19 pandemic (May 2020) revealed that people engaged in virtual music groups reported significantly lower group identification and psychological needs satisfaction than people in face-to-face music groups, although scores remained high in both groups.[43] Other studies have also recognised the complexity of online music provision, which is likely to have both benefits and limitations.[44,45] Finally, the research is limited by the lack of diversity in some aspects of the sample; most participants lived in London or the South of England, were highly educated and had relatively high household income.

Future research replicating this trial with a larger and more diverse sample, including fathers and partners, will be important. Although the online setting offers some advantages in terms of accessibility, workshop leaders reported some participants experiencing discomfort when working creatively online on the sensitive topic of parenthood. Additional research is needed to investigate the acceptability of online songwriting for this population and to scrutinise whether there are differences in effects when comparing online with in-person settings. Finally, future research is needed to investigate the mechanisms behind the effects reported here, including qualitative work to capture experiences and perceptions of the intervention in relation to mental health.

Conclusions

This study demonstrates that a 6-week online songwriting intervention for women with young babies can reduce loneliness and symptoms of PND and increase social connectedness. Given that loneliness detrimentally affects both physical and mental health[18] and that PND can lead to lasting adverse parent and child outcomes,[46] the results of this study may have relevance for the management of postnatal loneliness and PND.

Author statements

Acknowledgements

The authors acknowledge Rosie Adediran, Inês Delgado, Penny Osmond, Ananya Panwar, Emily Tredget (Happity), Sunita Sharma (Chelsea and Westminster Hospital NHS Foundation Trust) and the study participants.

Ethical approval

All procedures involving human participants were approved by the Conservatoires UK Research Ethics Committee on 5 March 2021 [CUK/RCCSD/2020-21/5] and amended on 2 August 2021 [CUK/SF/2020-21/5/2]. Written informed consent was obtained online from all participants.

Funding

This project was funded by the Loneliness & Social Isolation in Mental Health Research Network, which was funded by UK Research and Innovation (Grant reference: ES/S004440/1) and their support is gratefully acknowledged. Any views expressed here are those of the project investigators and do not necessarily represent the views of the Loneliness & Social Isolation in Mental Health Research Network or UKRI. The funding body had no role in the design of the study, collection, analysis and interpretation of data, or in writing the article.

Data availability

The dataset for the outcome measures is freely available at https://doi.org/10.24379/RCM.00002326.

Competing interests

The authors declare that they have no competing interests.

Author contributions

R.P. formulated the research question, designed and carried out the study and led the writing of the article. N.S. formulated the research question, designed and carried out the study and wrote the article. G.W. formulated the research question, designed and carried out the study, conducted the analyses and wrote the article.

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Public Health 220 (2023) 148–154

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Physical activity and long COVID: findings from the Prospective Study About Mental and Physical Health in Adults cohort

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ARTICLE INFO

Article history:
Received 21 February 2023
Received in revised form
2 May 2023
Accepted 10 May 2023

Keywords:
Physical activity
Long COVID
COVID-19
Cohort
Symptoms

ABSTRACT

Objectives: The study investigated the longitudinal association between physical activity and the risk of long COVID in patients who recovered from COVID-19 infection.
Study design: We analyzed longitudinal data of the Prospective Study About Mental and Physical Health cohort, a prospective cohort study with adults living in Southern Brazil.
Methods: Participants responded to an online, self-administered questionnaire in June 2020 (wave 1) and June 2022 (wave 4). Only participants who self-reported a positive test for COVID-19 were included. Physical activity was assessed before (wave 1, retrospectively) and during the pandemic (wave 1). Long COVID was assessed in wave 4 and defined as any post-COVID-19 symptoms that persisted for at least 3 months after infection.
Results: A total of 237 participants (75.1% women; mean age [standard deviation]: 37.1 [12.3]) were included in this study. The prevalence of physical inactivity in baseline was 71.7%, whereas 76.4% were classified with long COVID in wave 4. In the multivariate analysis, physical activity during the pandemic was associated with a reduced likelihood of long COVID (prevalence ratio [PR]: 0.83; 95% confidence interval [CI]: 0.69–0.99) and a reduced duration of long COVID symptoms (odds ratio: 0.44; 95% CI: 0.26–0.75). Participants who remained physically active from before to during the pandemic were less likely to report long COVID (PR: 0.74; 95% CI: 0.58–0.95), fatigue (PR: 0.49; 95% CI: 0.32–0.76), neurological complications (PR: 0.47; 95% CI: 0.27–0.80), cough (PR: 0.40; 95% CI: 0.22–0.71), and loss of sense of smell or taste (PR: 0.43; 95% CI: 0.21–0.87) as symptom-specific long COVID.
Conclusion: Physical activity practice was associated with reduced risk of long COVID in adults.

Introduction

More than 671 million have been diagnosed with COVID-19 since March 2020.[1] However, the World Health Organization has noticed that many survivors may suffer from a long, persistent form of the disease known as long COVID.[2] Long COVID condition refers to patients with probable or confirmed SARS-CoV-2 infection whose symptoms persisted for at least 3 months.[3] Recent estimates suggested a prevalence as high as 75% of long COVID in the general population. The most common symptomology is fatigue, followed by respiratory and neurological complications.[4] Identifying protective mechanisms to reduce the risk of this condition is an

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https://doi.org/10.1016/j.puhe.2023.05.011
0033-3506/

emerging priority in public health to reduce the projected burden of long COVID.

Physical activity is associated with reduced risk of infection, hospitalization, and mortality related to COVID-19.[5,6] However, the levels of physical activity were drastically disrupted during social distancing restrictions.[7–9] A body of evidence demonstrates the deleterious impact of physical inactivity on cardiovascular, muscular, respiratory, neurological, and immune systems, which are all affected by COVID-19 infection.[10,11] Previous studies have suggested an association between physical inactivity and the risk of long COVID.[12,13] Although these investigations suggested a higher prevalence of long COVID-19 in physically inactive adults, the association between different trajectories of physical activity from before to during the pandemic is scanty. Therefore, this study aimed to investigate the longitudinal association between physical activity and the risk of long COVID.

Methods

Study design

We analyzed data from the Prospective Study About Mental and Physical Health (PAMPA) cohort, a prospective study that evaluates the effects of the COVID-19 pandemic on health parameters in Southern Brazil. The ethics board approved the study from the Physical Education Faculty (Universidade Federal de Pelotas, Brazil; CAAE: 31906920.7.0000.5313). More details about study design and recruitment can be found elsewhere.[14]

Participants recruitment and sample

Adults (aged ≥18 years) living in the Rio Grande do Sul state were recruited by a four-arm approach aiming to reach participants in all state regions. Researchers spread the questionnaire's weblink via (1) messages to their personal and professional contacts over the state, (2) social media campaigns, (3) local media and state agencies, and (4) universities' staff and students.[14] For this study, we used data from wave 1 (assessed in June and July 2020) and wave 4 (assessed in June and July 2022), as we first included questions on persistent symptoms after COVID-19 infection in the latest wave. Wave 1 assessed two periods: before (retrospectively) and during the first months of the pandemic (present). A total of 2239 participants were recruited in wave 1, and 462 participants were followed up in wave 4. Overall, 237 participants reported a positive COVID-19 test and were included in the study (Fig. 1).

Outcome

Participants who reported a positive test for COVID-19 were asked to indicate for how long they had COVID-related symptoms. A list of symptoms was displayed (e.g. fatigue, cough, headache), and for each one, there were the following answering options: (1) did not have, (2) 3 months, (3) 6 months, (4) 12 months, (5) 15 months, and (6) ≥18 months. Based on this information, two outcome variables were built, as follows: (1) presence of general long COVID symptoms (any COVID-related symptoms that lasted at least 3 months) and (2) duration of long COVID symptoms (<6 months, >6 and <12 months, and 12 or more months). We also analyzed the association between physical activity and the presence of each persistent symptom, henceforward referred to as symptom-specific long COVID. Only symptoms with a prevalence ≥20% were analyzed for analysis purposes. Memory and concentration problems, irritability, depression, and anxiety were grouped as neurological complications in these analyses.

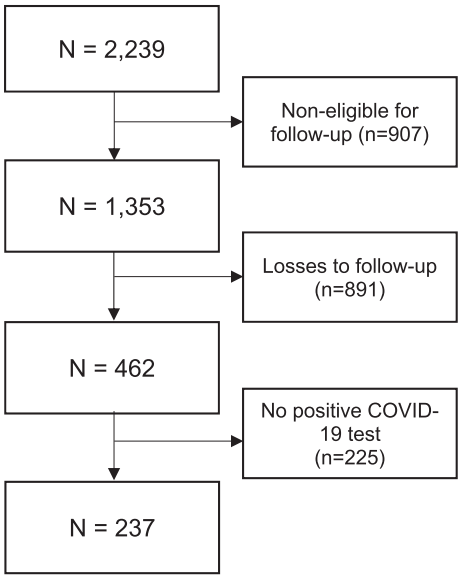

Fig. 1. Study sampling process.

Exposure

Physical activity was assessed on wave 1, with two-time references: before (retrospectively) and during the pandemic (at survey's week). Participants were asked if they engaged in regular physical activities before the pandemic and in the last 7 days. Those who answered yes were asked about the frequency (days per week) and time (minutes per day) the activities lasted.[15] Two main exposure variables were built. Participants were considered inactive if they engaged in <150 min/week and active if they engaged in ≥150 min/week.13 The trajectory of physical activity from before (retrospectively) to during wave 1 (baseline) was examined using a four-category variable that classified participants based on their physical activity status in both periods as follows: remained inactive, became inactive, remained active, or became active.

Potential confounders

Sex, age, educational level, ethnicity, marital status, comorbidities, body mass index (BMI), pandemic routine behavior (stayed at home always, left home to essentials only, left home all days), family income, and vaccination status (unvaccinated, one to four doses) were used as possible confounders. Self-reported weight and height were assessed to calculate BMI, which was categorized as follows: normal (<25 kg/m^2), overweight (≥25 and <30 kg/m^2), and obese (≥30 kg/m^2). Participants reported their daily routine during wave 1 and were categorized as follows: stayed at home always, left home to essentials only, and left home all days. Negative economic impact of COVID-19 was assessed, with participants reporting whether monthly income decreased from before to during the social distancing restrictions (wave 1). Finally, participants were asked about the number of vaccine doses they took until wave 4 (June 2022).

Data analyses

Descriptive data are presented as total and relative frequencies. A Chi-square test was used to check for associations between outcomes and exposures, and when necessary, the Fisher exact test was used. Robust Poisson regression models were used to evaluate

the association between physical activity assessed in wave 1 and the presence of general and specific long COVID symptoms 2 years later in wave 4. Data are presented as prevalence ratio (PR) with their respective 95% confidence interval (95% CI). Ordinal logistic regression models were used for the association between physical activity and duration of general and specific long COVID symptoms, with data presented as odds ratio (OR) with their respective 95% CI. Because of our low follow-up rate (51.3%), we conducted inverse probability weights models for successful follow-up for general and specific long COVID symptom and physical activity variables. This method is used in situations with unequal selection probabilities to avoid censoring or non-response bias.[16] All models were adjusted for age, sex, education, ethnicity, income, presence of comorbidities, and vaccination status. In addition, we used structural equation modeling to examine the possible mediation role of income and education in the association between physical activity and the long COVID.[17]

Results

We included 237 participants with a mean age of 37.1 ± 12.3 years, with most being women, White, and with at least one university degree (Table 1). The prevalence of physical inactivity increased from before (49.8%) to during (71.7%) the pandemic (wave 1). Three in four participants had general long COVID (76.4%; 95% CI: 70.5%, 81.4%). The most common symptomatology was fatigue (53.2%), followed by neurological complications (40.1%), cough (39.7%), headache (35.9%), and loss of sense of smell or taste (27.8%). Symptoms lasted from 3 to 6 months in 38.5% and more than 6 months in 37.5% of the included participants.

Participants who reported being physically active during the pandemic showed a lower likelihood of general long COVID as well as fatigue, neurological complications, and cough as symptom-specific long COVID (Table 2). Participants who were active before the pandemic showed a lower likelihood of fatigue, neurological complications, and headache as symptom-specific long COVID. Structural equation modeling indicated that income ($P = 0.834$ for indirect effect) and education ($P = 0.849$ for indirect effect) do not mediate the association between physical activity and the likelihood of long COVID.

We also investigated the association between changes in physical activity status and long COVID, as described in Table 3. Participants who were physically active before and during the pandemic showed a lower probability of long COVID than those who remained physically inactive. This protective association was also observed for persistent fatigue, neurological complications, cough, loss of sense of smell or taste, and headache. In addition, those who became active showed a lower likelihood of neurological

Table 1
Characteristics of the included participants (N = 237).

Variables	Overall, *n* (%)	Long COVID, *n* (%)		*P*-value
		No (*n* = 56)	Yes (*n* = 181)	
Sex				0.074[a]
Male	59 (24.9)	19 (33.9)	40 (22.1)	
Female	178 (75.1)	37 (66.1)	141 (77.9)	
Age in years				0.937[b]
18–30	92 (38.8)	23 (41.1)	69 (38.1)	
31–59	131 (55.3)	30 (53.6)	101 (55.8)	
≥60	14 (5.9)	3 (5.4)	11 (6.1)	
Skin color				0.086[b]
White	213 (89.9)	46 (82.1)	167 (92.3)	
Mixed	14 (5.9)	6 (10.7)	8 (4.4)	
Black	10 (4.2)	4 (7.1)	6 (3.3)	
Highest education achievement				0.632[a]
High school or less	66 (27.8)	17 (30.4)	49 (27.1)	
University degree or higher	171 (72.2)	39 (69.6)	132 (72.9)	
Conjugal situation				0.387[a]
Living with partner	158 (66.7)	40 (71.4)	118 (65.2)	
Living alone	79 (33.3)	16 (28.6)	63 (34.8)	
Daily routine during pandemic				0.161[b]
Stayed at home always	11 (4.6)	3 (5.4)	8 (4.4)	
Left home to essentials only	160 (67.5)	43 (76.8)	117 (64.6)	
Left home all days	66 (27.8)	10 (17.9)	56 (30.9)	
Chronic conditions, yes (%)	141 (59.5)	29 (51.8)	112 (61.9)	0.179[a]
Reduced income during pandemic, yes (%)	100 (42.2)	20 (35.7)	80 (44.2)	0.261[a]
COVID-19 vaccine				0.866[b]
Two doses	19 (8.0)	4 (7.1)	15 (8.3)	
Three doses	131 (55.3)	33 (58.9)	98 (54.1)	
Four doses	87 (36.7)	19 (33.9)	68 (37.6)	
Physical activity before pandemic				0.035[a]
No	118 (49.8)	21 (37.5)	97 (53.6)	
Yes	119 (50.2)	35 (62.5)	84 (46.4)	
Physical activity during pandemic				0.015[a]
No	170 (71.7)	33 (58.9)	137 (75.7)	
Yes	67 (28.3)	23 (41.1)	44 (24.3)	
Change in physical activity status				0.017[b]
Sustained inactive	95 (41.5)	17 (31.5)	78 (44.6)	
Become inactive	67 (29.3)	14 (25.9)	53 (30.3)	
Become active	15 (6.6)	2 (3.7)	13 (7.4)	
Sustained active	52 (22.7)	21 (38.9)	31 (17.7)	

Physical activity before the pandemic was assessed retrospectively during wave 1 (June 2020).
Physical activity during the pandemic was assessed during wave 1 (June 2020).
[a] Pearson's Chi-squared.
[b] Fisher exact.

Table 2
Association of physical activity before and during the pandemic with the presence of general and symptoms specific long COVID in adults (N = 237).

Outcome	Before pandemic		During pandemic	
	PR (95% CI)	*P*-value	PR (95% CI)	*P*-value
Long COVID	0.88 (0.76, 1.02)	0.090	0.83 (0.69, 0.99)	0.041
Symptom-specific long COVID				
Fatigue	0.67 (0.52, 0.86)	0.002	0.66 (0.48, 0.92)	0.015
Neurological complications	0.71 (0.51, 0.97)	0.032	0.48 (0.30, 0.77)	0.002
Cough	0.73 (0.53, 1.01)	0.056	0.58 (0.38, 0.89)	0.013
Loss of sense of smell or taste	0.72 (0.47, 1.10)	0.131	0.63 (0.37, 1.09)	0.097
Headache	0.57 (0.40, 0.82)	0.003	0.75 (0.49, 1.16)	0.197

CI, confidence intervals; PR, prevalence ratio.
General long COVID was defined as any post-COVID-19 symptoms that persisted for at least 3 months.
Symptom-specific long COVID were based on individual symptoms.
Physical activity before the pandemic was assessed retrospectively during wave 1 (June 2020).
Physical activity during the pandemic was assessed during wave 1 (June 2020).
PR was estimated using robust Poisson regression models adjusted for age, sex, education, skin color, income, presence of comorbidities, and vaccination status.

complications after COVID-19 infection. Physical activity before the pandemic was associated with a lower probability of fatigue as symptom-specific long COVID, even in participants who became inactive during the pandemic.

Finally, physical activity was associated with a shorter duration of symptoms (Table 4). Physical activity before the pandemic was associated with briefer fatigue, neurological complications, and headache as symptom-specific long COVID. Participants who became physically inactive from before to during the pandemic were less likely to report persistent fatigue and headache, whereas neurological complications were less likely in those who became active in the same period (Table 5). Persistent fatigue, neurological complications, and cough after COVID-19 infection were briefer in participants who were physically active during the pandemic than in inactive participants in the same period (Table 4). General and symptom-specific long COVID was less likely in participants who remained physically active during the pandemic (Table 5).

The association between physical activity and long COVID remained significant after inverse probability weighting for successful follow-up (Supplementary Table 1). In this sensitivity analysis, cough and headache were associated with physical activity before the pandemic. In contrast, loss of sense of smell or taste was associated with physical activity during the pandemic. Remaining physically active from before to during the pandemic was consistently associated with long COVID, although becoming physically inactive was no longer related to long COVID (Supplementary Table 2).

Discussion

Our findings demonstrate the protective association between physical activity and long COVID. Adults who persisted physically active during the COVID-19 pandemic showed a lower likelihood of long COVID, including long-lasting fatigue, neurological complications, cough, loss of sense of smell or taste, and headache. Up to 80% of COVID-19 survivors live with persistent symptoms after SARS-CoV-2 infection.[4,10,18] Considering the 640 million cases of COVID-19 since the pandemic's beginning, physical activity has been shown as a potential non-pharmacological strategy to reduce the forecasted burden of long COVID-19 worldwide. Consequently, public policies focused on reducing the risk of long COVID, especially in those at higher risk, are urgently needed.

We demonstrated that people who survived COVID-19 and were physically active before and during the pandemic showed a lower likelihood of respiratory sequelae after SARS-CoV-2 infection.

Table 3
Association between change in physical activity status and the presence of general and symptoms specific long COVID in adults (N = 237).

Outcome	Persisted inactive	Became inactive	Became active	Persisted active
		PR (95% CI)	PR (95% CI)	PR (95% CI)
Long COVID	Ref	0.98 (0.83, 1.15)	1.06 (0.85, 1.33)	0.74 (0.58, 0.95)
P-value		*0.811*	*0.581*	*0.016*
Symptom-specific long COVID				
Fatigue	Ref	0.74 (0.56, 0.99)	0.87 (0.56, 1.33)	0.49 (0.32, 0.76)
P-value		*0.035*	*0.519*	*0.001*
Neurological complications	Ref	0.75 (0.53, 1.07)	0.34 (0.13, 0.88)	0.47 (0.27, 0.80)
P-value		*0.112*	*0.025*	*0.006*
Cough	Ref	0.99 (0.69, 1.41)	1.17 (0.69, 1.97)	0.40 (0.22, 0.71)
P-value		*0.956*	*0.566*	*0.002*
Loss of sense of smell or taste	Ref	0.85 (0.53, 1.36)	1.00 (0.47, 2.11)	0.43 (0.21, 0.87)
P-value		*0.452*	*0.988*	*0.018*
Headache	Ref	0.65 (0.43, 0.99)	1.14 (0.68, 1.92)	0.48 (0.27, 0.86)
P-value		*0.049*	*0.579*	*0.015*

CI, confidence interval; PR, prevalence ratio.
General long COVID was defined as any post-COVID-19 symptoms that persisted for at least 3 months.
Symptom-specific long COVID were based on individual symptoms.
Physical activity before the pandemic was assessed retrospectively during wave 1 (June 2020).
Physical activity during the pandemic was assessed during wave 1 (June 2020).
PR was estimated using robust Poisson regression models adjusted for age, sex, education, skin color, income, presence of comorbidities, and vaccination status.

Table 4
Association of physical activity before and during the pandemic and duration of general and symptoms specific long COVID in adults (N = 237).

Outcome	Before pandemic		During pandemic	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Long COVID	0.62 (0.38, 1.00)	0.051	0.44 (0.26, 0.75)	0.003
Symptom-specific long COVID				
Fatigue	0.35 (0.21, 0.59)	<0.001	0.41 (0.23, 0.74)	0.003
Neurological complications	0.53 (0.31, 0.90)	0.018	0.30 (0.15, 0.59)	0.001
Cough	0.60 (0.35, 1.03)	0.064	0.39 (0.21, 0.74)	0.004
Loss of sense of smell or taste	0.60 (0.33, 1.08)	0.087	0.54 (0.27, 1.08)	0.081
Headache	0.39 (0.22, 0.68)	0.001	0.61 (0.32, 1.15)	0.124

CI: confidence interval; OR: odds ratio.
OR >1 indicates higher odds for persistent symptoms lasting longer.
General long COVID was defined as any post-COVID-19 symptoms that persisted for at least 3 months.
Symptom-specific long COVID were based on individual symptoms.
Physical activity before the pandemic was assessed retrospectively during wave 1 (June 2020).
Physical activity during the pandemic was assessed during wave 1 (June 2020).
OR were estimated using proportional ordinal logistical regression models adjusted for age, sex, education, skin color, income, presence of comorbidities, and vaccination status.

Fatigue was the most common long COVID symptomatology, with previous corroborating studies on COVID-19, SARS-CoV-1, and MERS-COV.[4,18–20] Most patients with decreased respiratory function after SARS-CoV-1 infection also presented muscle wasting and fatigue.[27] In addition, Ahmed et al.[19] estimated a reduction of 461 m in a six-minute walking test, an indicator of exercise capacity, in patients who survived SARS-CoV-1 and MERS-COV. Decreased exercise tolerance may also be associated with modifications in peripheric oxygen uptake. After COVID-19 infection, patients showed preserved oxygen availability with reduced peripheral oxygen extraction rate and increased venous saturation, which may explain the lower cardiorespiratory fitness in these patients compared with healthy controls.[21] On the other hand, physical activity can improve mitochondrial activity and oxygen uptake, preserving energy production during cellular respiration.[22,23] For example, a previous study revealed that eight weeks of endurance and resistance training was safe and more effective than self-care recommendations and inspiratory muscle training alone to regain cardiovascular and muscular fitness and improve symptom severity and health status in adults with long COVID.[24] Thus, physical activity maintenance before and during the COVID-19 pandemic may have promoted cellular and systemic protective mechanisms, preserving pulmonary function in COVID-19 survivors.

Our findings suggest that physical activity was associated with a lower likelihood of neurological complications after COVID-19. Neurological complications were among the most common symptomatology of long COVID, known as brain 'fog'.[4,18] Different mechanisms have been suggested for the beneficial effects of physical activity on brain function. For example, regular physical activity seems to preserve brain health through the upregulation of neurotrophic factors and anti-inflammatory cytokines,[25,26] resulting in the generation of new astrocytes and promotion of neurogenesis and synaptic plasticity. These physical activity–induced modifications can improve cognitive function and reduce the risk of neurological complications and degenerative processes. Also, previous evidence suggests the critical role of astrocytes in this complication.[27–29] Astrocytes are the most abundant cells in the central nervous system and perform various functions, such as regulating the concentration of neurotransmitters and other substances with the potential to interfere with neuronal functioning, the integrity of the blood–brain barrier, and helping to maintain cerebral homeostasis.

Table 5
Association between change in physical activity status and duration of general and symptoms specific long COVID in adults (N = 237).

Outcome	Persisted inactive	Became inactive	Became active	Persisted active
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Long COVID	Ref	0.76 (0.42, 1.37)	0.58 (0.23, 1.49)	0.33 (0.17,0.64)
P-value		*0.364*	*0.227*	*0.001*
Symptom-specific long COVID				
Fatigue	Ref	0.42 (0.23, 0.78)	0.68 (0.24, 1.88)	0.20 (0.09, 0.41)
P-value		*0.025*	*0.494*	<0.001
Neurological complications	Ref	0.60 (0.32, 1.12)	0.21 (0.05, 0.79)	0.26 (0.12, 0.58)
P-value		*0.110*	*0.016*	*0.002*
Cough	Ref	1.01 (0.53, 1.92)	1.18 (0.41, 3.43)	0.23 (0.10, 0.53)
P-value		*0.953*	*0.799*	*0.001*
Loss of sense of smell or taste	Ref	0.72 (0.36, 1.43)	0.98 (0.31, 3.09)	0.30 (0.13, 0.75)
P-value		*0.313*	*0.882*	*0.009*
Headache	Ref	0.45 (0.23, 0.88)	1.14 (0.39, 3.30)	0.28 (0.12, 0.64)
P-value		*0.022*	*0.836*	*0.003*

CI: confidence interval; OR, odds ratio.
OR >1 indicates higher odds for persistent symptoms lasting longer.
General long COVID was defined as any post-COVID-19 symptoms that persisted for at least 3 months.
Symptom-specific long COVID were based on individual symptoms.
Physical activity before the pandemic was assessed retrospectively during wave 1 (June 2020).
Physical activity during the pandemic was assessed during wave 1 (June 2020).
OR were estimated using proportional ordinal logistical regression models adjusted for age, sex, education, skin color, income, presence of comorbidities, and vaccination status.

Physical activity before and during the pandemic was associated with shorter lengths of long COVID symptoms. A previous cross-sectional, population-based analysis suggested an inverse association between physical activity and the duration of symptoms.[30] However, to our knowledge, this is the first study to assess the longitudinal association of physical activity with the presence and duration of long COVID. Exposure to physical activity across the life course results in long-term benefits in different body systems. For example, physical activity during adolescence showed a lower risk of depression[31] and improved cognitive function[32] in adulthood. However, during the more restricted phases of the COVID-19 pandemic, physical activity practice in sports clubs, gyms, and public spaces were limited to control virus spreading. Alternative methods, such as online platforms, surged as options to preserve physical activity levels. Unfortunately, inequity in opportunities to continue physical activity practice during these stages may lead to an increased burden of long COVID in some population groups. Based on the available scientific literature and our findings, physical activity surges as a potential strategy to reduce the likelihood of long COVID in adult populations.

Despite this being the first study to assess the longitudinal association between physical activity and long COVID in Brazil, an epicenter of the COVID-19 pandemic, our study presents some limitations. First, physical activity, persistent symptoms, and COVID-19 infection were self-reported. However, the local ethics committee did not allow in-person research activities during baseline assessments. Also, we acknowledged the low response rate from baseline to wave 4. Data collection for wave 4 occurred between June and August 2022, simultaneously with political campaigns for the Brazilian Presidential Election. The anti-science movement that arose in Brazil during the pandemic resulted in offenses of some eligible participants against the research.[33] In addition, the results may be biased by the limited number of non-long COVID people, explained as a result of loss of follow-up. However, the results were robust after sensitivity analysis with inverse probability weighting to account for losses to follow-up.

Conclusions

In conclusion, physical activity was associated with a lower likelihood of long COVID in adults. Although experimental studies are needed to confirm our findings, public policies focused on reducing the risk of long COVID, especially in those at higher risk, are urgently needed.

Author statements

Acknowledgments

A.J.R. and F.M.D. was supported by the National Council for Scientific and Technological Development (CNPq). T.A.B. was supported by Research Initiation Scholarship Program - Affirmative Actions (PBIP-AF/UFPEL). J.S.L., I.A.P., L.S.S., J.Q.S.R., and Y.P.V. were financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

Ethical approval

The ethics board approved the study from the Physical Education Faculty (Universidade Federal de Pelotas, Brazil; CAAE: 31906920.7.0000.5313).

Funding

This study was financed in part by the Fundação de Amparo à Pesquisa do estado do Rio Grande do Sul (FAPERGS) (21/2551-0002071-7) and the National Council for Scientific and Technological Development – CNPq (405496/2021-4).

Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.05.011.

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Public Health 220 (2023) 135–141

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Review Paper

Predictors of COVID-19 vaccination hesitancy in China: a meta-analysis

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ARTICLE INFO

Article history:
Received 14 February 2023
Received in revised form
9 May 2023
Accepted 10 May 2023
Available online 16 May 2023

Keywords:
Vaccine hesitancy
COVID-19
Meta-analysis
Chinese cultural contexts

ABSTRACT

Objectives: This study aimed to examine predictors and moderators of COVID-19 vaccine hesitancy in Chinese cultural contexts.
Study design: A meta-analysis and meta-regression analyses were conducted to examine the associations between predictors and vaccine hesitancy as well as moderators that may impact these associations.
Methods: We searched relevant articles from January 1, 2020, to May 12, 2022, in the databases of Web of Science, PubMed, ProQuest, ProQuest Dissertations & Theses Global and CNKI. Weighted average effect sizes (e.g., odds ratio) and 95% confidence intervals were computed in Comprehensive Meta-Analysis 3.0 using random-effects models. Heterogeneity tests were conducted prior to moderation analyses.
Results: Results from 161 studies in 73 published articles ($N = 705{,}957$) were meta-analyzed. Perceived risk of COVID-19 infection, health status, medical workers' recommendation, recommendations from family and friends, and vaccine coverage among relatives and friends were significantly associated with COVID-19 vaccine hesitancy in Chinese cultural contexts. Participant age, operationalization of vaccine hesitancy, and the time of each study exerted significant moderation effects.
Conclusions: Both individual and relational factors influence vaccine hesitancy in Chinese cultural contexts Future vaccine promotion initiatives should focus on risk perceptions as well as influence from medical professionals, family and friends.

Introduction

Since 2020, the coronavirus disease 2019 (COVID-19) has threatened the physical and psychological well-being of people around the world. Vaccination is essential to reducing serious illness, hospitalization, and death related to COVID-19[1] and preventing the spread of infection. However, there is still resistance to vaccination.[2] Public acceptance is a critical factor that influences vaccine uptake.[3] Many countries are facing vaccine hesitancy problems, especially in low- and lower-middle-income countries,[4] such as Jordan[5] and Saudi Arabia.[6]

As is the case with the rest of the world, the pandemic is one of the most severe and complex public health emergencies in China, with fast and widespread infection and major challenges in prevention and control. In late 2022, the Chinese government abandoned its 'dynamic zero-COVID' policy, and the number of COVID-19 infections in China reached its peak. In comparison to the rapid increase in positive cases, as of February 2023, there were still more than 132 million Chinese people who had not been fully vaccinated,[7] despite nationwide efforts to provide access to and promote the benefits of vaccination.

Vaccine hesitancy refers to the refusal to vaccinate or delay in the acceptance of vaccination despite its availability.[8] Previous systematic reviews and meta-analyses examined predictors of COVID-19 vaccine hesitancy in different countries.[9] In Chinese cultural contexts, factors that influence COVID-19 vaccination hesitancy of specific populations, such as healthcare workers[10] and parents,[11] have been examined, yet no existing meta-analysis has synthesized predictors among the general Chinese public. Understanding predictors of COVID-19 vaccine hesitancy in China could extend theoretical understanding of vaccine hesitancy in specific cultural contexts and facilitate the development of effective communication strategies to address vaccine hesitancy.

Hypotheses

Predictors

The World Health Organization's (WHO's) SAGE Working Group proposed the determinants of vaccine hesitancy model,[12] which identified three sets of factors that may predict vaccine

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https://doi.org/10.1016/j.puhe.2023.05.009
0033-3506/

hesitancy: (1) contextual influences, (2) individual and group influences, and (3) vaccine- and vaccination-related factors. Researchers empirically tested factors associated with COVID-19 vaccine hesitancy among diverse populations (e.g. different age groups, occupations, health conditions, regions). Since the process through which individual, social, and cultural factors influence vaccine hesitancy may be context-dependent[13] and can vary depending on value and belief orientations across populations,[8] we focus on individual- and group-level influences for Chinese individuals' vaccine hesitancy.

First, perceived risk of COVID-19 infection may influence vaccine hesitancy. Perceived risk of disease infection refers to subjective perceived probability of contracting a disease.[14] Risk perception is a key factor in influencing individuals' health-related behaviors.[15] In the context of COVID-19, when people consider themselves more easily infected by the contagious virus, they may be more willing to get vaccinated and protect themselves against the virus.[16] Therefore, we propose:

H1. Perceived risk of COVID-19 infection will be negatively associated with COVID-19 vaccine hesitancy in China.

Health status is another individual-level factor that may affect vaccine hesitancy. Health status refers to the perceived health state[17] and experience of chronic illness.[18] Previous studies showed that people with chronic disease or poor health status were more likely to suffer from severe COVID-19 complications and death.[19] Therefore, individuals with poor health may be less hesitant to get vaccinated:

H2. Health status will be positively associated with COVID-19 vaccine hesitancy in China.

Third, medical workers' recommendation may influence individuals' vaccination hesitancy. Medical workers are typically considered professional and knowledgeable over topics such as vaccine safety and effectiveness. Therefore, medical workers' recommendations may reduce potential vaccine hesitancy.[20] Poon's study[21] showed that frontline family doctors' COVID-19 vaccine recommendations effectively motivated patients to get vaccinated in Hong Kong. Therefore, we propose:

H3. Medical workers' recommendation will be negatively associated with COVID-19 vaccine hesitancy in China.

Additionally, family's and friends' recommendations may also affect individuals' vaccine hesitancy. Family and friends tend to serve as a source of support and can provide help in health contexts.[22] With the recommendations from family and friends, people may obtain information and confidence about COVID-19 vaccination, which may subsequently reduce vaccine hesitancy.[23] For example, Hallgren found that friends were 'key facilitators for some hesitant adopters,'[24] as friends helped overcome barriers to vaccination and provided key information that facilitated the scheduling of vaccination. Therefore, we propose:

H4. (a) Family's and (b) friends' recommendations will be negatively associated with COVID-19 vaccine hesitancy in China.

Vaccination rates in individuals' social environment may also play a role in their COVID-19 vaccine hesitancy. Peer influence is a key factor associated with individual behavior.[25] For example, Ren[26] examined attitudes of psychiatric patients towards COVID-19 vaccination in China and found that vaccine coverage amongst relatives and friends had a positive influence on COVID-19 vaccine acceptance. Therefore, we propose:

H5. Vaccine coverage amongst relatives or friends will be negatively associated with COVID-19 vaccine hesitancy in China.

Potential moderators

The effects of the individual- and group-level factors on vaccine hesitancy may be moderated. In this study, we investigated three potential moderators: participants' age, the operationalization of vaccine hesitancy, and time. First, a recent meta-analysis on vaccine hesitancy and perceived behavioral control suggested that participant age could be a potential moderator.[27] For example, previous research suggested social responsibility (i.e. individuals' beliefs or sense of responsibility regarding the maintenance and safety of their community) had greater negative effects on COVID-19 vaccine hesitancy among older participants compared to younger participants.[28] Therefore, we propose:

H6. The effects of predictors on COVID-19 vaccine hesitancy will be moderated by participants' age, such that for individuals who are older, the associations between predictors and vaccine hesitancy will be stronger compared to the effects for those who are younger.

The operationalization of vaccine hesitancy may also moderate the associations between predictors and vaccine hesitancy. Vaccine intention has been operationalized as either binary (i.e. vaccine acceptance vs. hesitancy[29]) or multigroup (i.e. vaccine acceptance vs. delay vs. rejection[30]). In other words, in the former case, vaccine hesitancy includes both delay and rejection, whereas in the latter case, the effects of predictors on vaccine delay and rejection are separately examined. The associations between predictors and vaccine hesitancy in studies that adopted a binary operationalization (i.e. hesitancy operationalized as delay plus rejection) should be weaker compared to the associations between predictors and vaccine rejection in studies that adopted a multigroup operationalization of vaccine intention (i.e. hesitancy operationalized as delay), as rejection indicates as a stronger sense of refusal toward getting vaccinated compared to delay. Therefore, we propose that:

H7. The effects of predictors on vaccine hesitancy will be influenced by the operationalization of vaccine hesitancy, such that the effects will be stronger when vaccine hesitancy is operationalized as rejection than they are when vaccine hesitancy is measured with delay and rejection combined together.

Since 2020, the COVID-19 pandemic has gone through several phases, with COVID-19 variants such as Delta and Omicron emerging continuously. Wang J. found that people had higher levels of intention to get COVID-19 vaccination in 2021 than in 2020,[31] indicating that COVID-19 vaccine hesitancy changed over time. In addition, people around the world have gained more knowledge about the virus and vaccination since the outbreak of the pandemic. Therefore, the associations between predictors and vaccine hesitancy may vary depending on the time of the study. Specifically, the associations may become weaker as time goes on and information about both COVID-19 and the vaccine grows. Therefore, we propose:

H8. The effects of predictors on vaccine hesitancy will be moderated by time, such that the associations will be weaker for studies conducted later in the COVID-19 pandemic compared to those conducted earlier.

Method

Search and screen process

Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses,[32] we searched articles from January 1, 2020, to May 12, 2022, in the four English databases (Web of Science,

PubMed, ProQuest, ProQuest Dissertations & Theses Global) and one Chinese database (CNKI) using following keywords: 'China' OR 'Hong Kong' OR 'Macao' OR 'Taiwan' AND 'vaccine' AND 'hesitancy' OR 'acceptance' AND 'COVID-19.' The search resulted in 2586 studies in total.

Studies were included in the meta-analysis if they met the following inclusion criteria: the study needed to have (1) tested at least one of the six predictors of interest that influenced COVID-19 vaccine hesitancy, (2) focused on the Chinese cultural contexts (regions where Chinese is the predominant language and traditional Chinese values are prevalent, including Chinese mainland, Taiwan, Hong Kong and Macao), (3) used quantitative methods (including survey, experimental design or mixed methods), (4) been written in English or Chinese and (5) reported effect sizes (e.g. odds ratios [ORs]) among study variables. After removing duplicate records and evaluating search results, a total of 161 studies from 73 articles met the inclusion criteria and were included (see Fig. 1 for the search and screen process).

Statistical analyses

The effect sizes used in the 161 studies included adjusted OR and OR. Weighted average effect sizes (OR) and 95% confidence intervals were computed in Comprehensive Meta-Analysis (CMA) 3.0[33] using random-effects models. Heterogeneity tests were conducted prior to moderation analyses to examine the extent to which heterogeneity in effect sizes was accounted for by sampling error or potential moderators.[34]

Coding of moderators

Average age of participants was recorded from each article. The researchers coded the operationalization of vaccine hesitancy and time of the study. Specifically, studies were coded as one when vaccine hesitancy was operationalized as rejection and coded as two when vaccine hesitancy was measured as both delay and rejection. The time of each study was coded using the number of months since the beginning of the COVID-19 pandemic (i.e. January 2020). For example, studies conducted in January 2020 were coded as zero; every month thereafter, the code for time increased by one.

Results

Publication bias

In total, 161 studies from 73 articles ($N = 705{,}957$) met the inclusion criteria. Table S2 of the supplemental materials shows the characteristics of included studies. To address possible issues of publication bias, we tested the classic fail-safe *N* for the statistics of each association separately in CMA 3.0 program.[33] The results showed that a range of 144 to 4526 non-significant, unpublished studies would have to exist to bring the *P*-value of these associations above .05 (see Table 1).

Substantive analyses

To test H1, the weighted average size of the association between perceived infection risk and vaccine hesitancy was calculated. Results suggested a negative association between perceived infection risk and vaccine hesitancy (OR = .719, $P < .001$). H1 was supported. The Q statistic was significant ($P < .001$). I^2 indicated that 92.05% of the variance was explained by true dispersion among the included effect sizes rather than just sampling error. Moderators may exist.

H2 proposed that the health status of individuals would be positively associated with vaccine hesitancy. Results indicated that the effect size among the included studies was negative and significant (OR = .833, $P < .001$). Individuals with better health status were less likely to be vaccine hesitant. H2 was not supported. The *Q* statistic ($P < .001$) and I^2 (= 81.34%) indicated that the association was heterogeneous across different studies.

H3 predicted a negative association between medical workers' recommendation and vaccine hesitancy. Results indicated that medical workers' recommendation was negatively associated with vaccine hesitancy (OR = .499, $P < .001$). H3 was supported. Both the *Q* statistic ($P < .001$) and I^2 (= 95.31%) indicated that the moderators may be present.

Similarly, the weighted average association between family's recommendation and vaccine hesitancy showed a negative association (OR = .466, $P = .009$). H4a was supported. The *Q* statistic ($P < .001$) was significant and I^2 (= 95.43%) indicated heterogeneity. Results also showed a negative association between friends' recommendations and vaccine hesitancy (OR = .552, $P = .009$). H4b was supported. Both *Q* statistic ($P < .001$) and I^2 (= 95.13%) suggested heterogeneity due to true dispersion among the included effect sizes.

Finally, H5 predicted vaccine coverage among relatives or friends would be negatively associated with COVID-19 vaccine hesitancy in China. Results showed a negative association between vaccine coverage and vaccine hesitancy (OR = .566, $P = .046$). Therefore, H5 was supported. The *Q* statistic ($P < .001$) and I^2 (= 98.46%) indicated that the moderators may be present.

Moderation effects

To test moderation effects, meta-regression analyses were conducted in CMA 3.0. Among the 161 included studies, 32 studies reported the mean age of participants, 157 studies reported the beginning time of each survey, 125 studies measured vaccine hesitancy as delay plus rejection, 21 studies measured vaccine hesitancy as delay of vaccination, and 15 studies measured vaccine hesitancy as rejection in getting vaccinated.

Age. Results suggested that participant average age significantly moderated the association between perceived risk of COVID-19 infection and vaccine hesitancy ($z = -2.42$, $P = .015$). Fig. 2 shows age's moderating effect on the association between perceived risk and vaccine hesitancy. Consistent with H6, the negative association between risk perception and vaccine hesitancy became stronger for studies with higher mean age of participants compared to studies with lower average age of participants.

In addition, results indicated that participant mean age significantly moderated the association between health status and vaccine hesitancy ($z = 2.13$, $P = .033$), such that the negative association between health status on vaccine hesitancy were weaker in studies with older participants compared to those in studies with younger participants. This was contrary to H6's prediction. Therefore, H6 was partially supported.

Operationalization of vaccine hesitancy. Results suggested that the negative association between health status and vaccine hesitancy was weaker ($z = 2.26$, $P = .024$; see Fig. 3) when vaccine hesitancy was measured with vaccine rejection than when vaccine hesitancy was measured with vaccine delay and rejection. H7 was not supported.

Time significantly moderated the association between health status and vaccine hesitancy ($z = -3.2$, $P = .001$; see Fig. 4), such that the negative association between health status and vaccine hesitancy became stronger as the pandemic went on. Time also

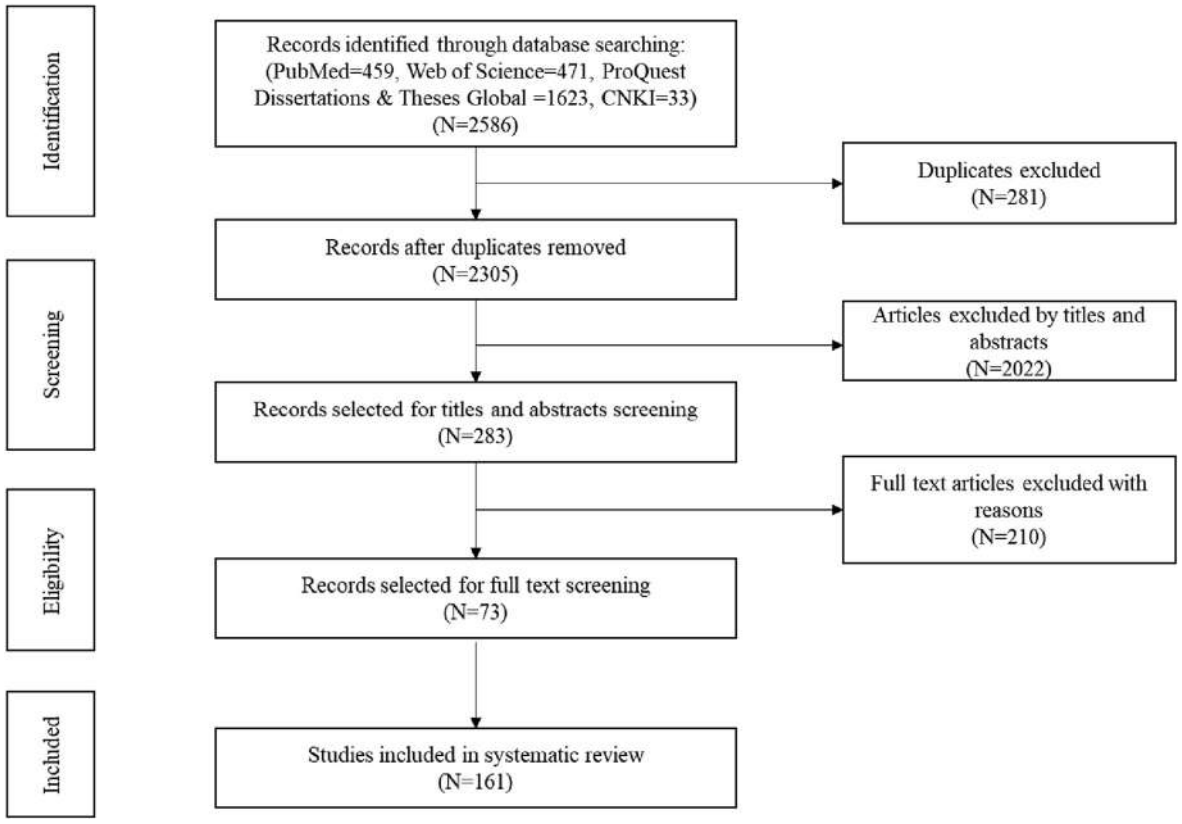

Fig. 1. Flow diagram of search and screening process.

Table 1
Publication bias of included studies and meta-analysis of predictors of COVID-19 vaccine hesitancy in Chinese cultural context.

	k	*N*	OR/aOR	CI_{95}	*Q*	I^2	Classic fail-safe *N*
Perceived risk (Reference: Low risk)	108	576,187	.719***	.669, .773	1345.687***	92.049	4526
Health status (Reference: Low)	74	305,633	.833***	.798, .868	391.159***	81.338	1666
Medical workers' recommendation (Reference: No)	18	43,116	.499***	.359, .695	362.569***	95.311	1003
Family's recommendation (Reference: No)	9	13,658	.466**	.262, .829	175.175***	95.433	273
Friends' recommendation (Reference: No)	7	12,500	.552**	.354, .861	123.088***	95.125	144
Vaccine coverage among relatives or friends (Reference: Low)	7	53,836	.566*	.323, .991	389.266***	98.459	328

Note. CI_{95} = 95% confidence intervals; *k* = number of studies; *N* = sample size; OR = odds ratio; aOR = adjusted odds ratio.
*$P < .05$, **$P < .01$, ***$P < .001$.

moderated the association between vaccine coverage among relatives or friends and vaccine hesitancy ($z = -2.72$, $P = .007$), such that this negative association became stronger over time. H8 was not supported.

Discussion

The purpose of this meta-analysis was to quantify the effects of six predictors on COVID-19 vaccine hesitancy in Chinese cultural contexts. Specifically, we drew from SAGE's vaccine hesitancy model and examined individual- (i.e. risk perception and health status) and group-level predictors (i.e. recommendations from medical workers, family, and friends; vaccination status of family and friends) among Chinese populations. Age, time of the study, and operationalization of vaccine hesitancy moderated the associations between predictors and vaccine hesitancy. We discuss theoretical and practical implications of the findings in the following sections. Table S1 of the supplemental materials presents the summary of key findings and suggestions for future studies.

Theoretical contributions

First, findings suggest that COVID-19 vaccine hesitancy in China was affected by medical workers' recommendations, family's and friends' recommendations, as well as vaccine coverage amongst relatives or friends. Chinese society is a typical 'human relationship society' ('*Renqing shehui*' in Chinese), indicating that Chinese people often care much about others' attitudes and opinions.[35] In vaccination contexts, findings of this study suggest the need to address relational factors in motivating Chinese individuals' vaccination behaviors.

As for the individual-level influence, contrary to what was predicted, results showed that health status was negatively associated with participants' COVID-19 vaccine hesitancy. This may be associated with perceived side-effects and concerns about vaccine safety. Specifically, individuals who are healthy may consider themselves less vulnerable of and more resistant to side-effects compared to those with poorer health. Future research should investigate how to explain possible side-effects clearly to the

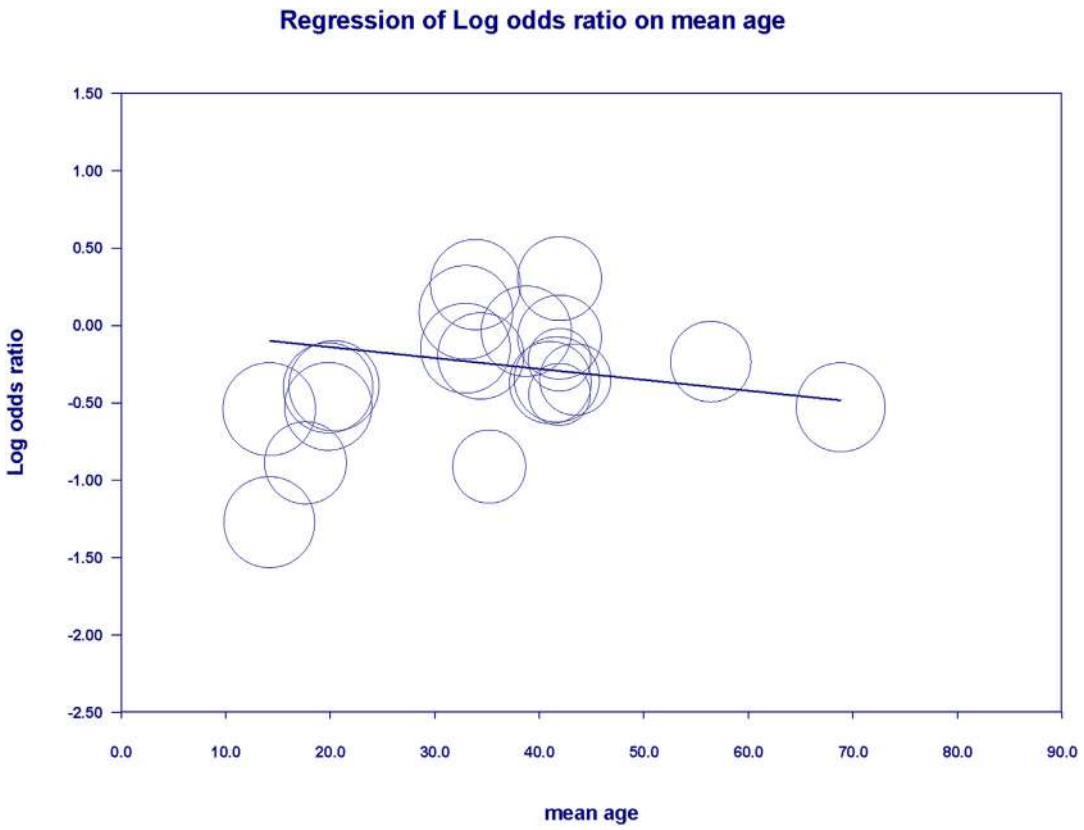

Fig. 2. Scatterplot of age's moderating effect on the association between perceived risk of COVID-19 infection and vaccine hesitancy.

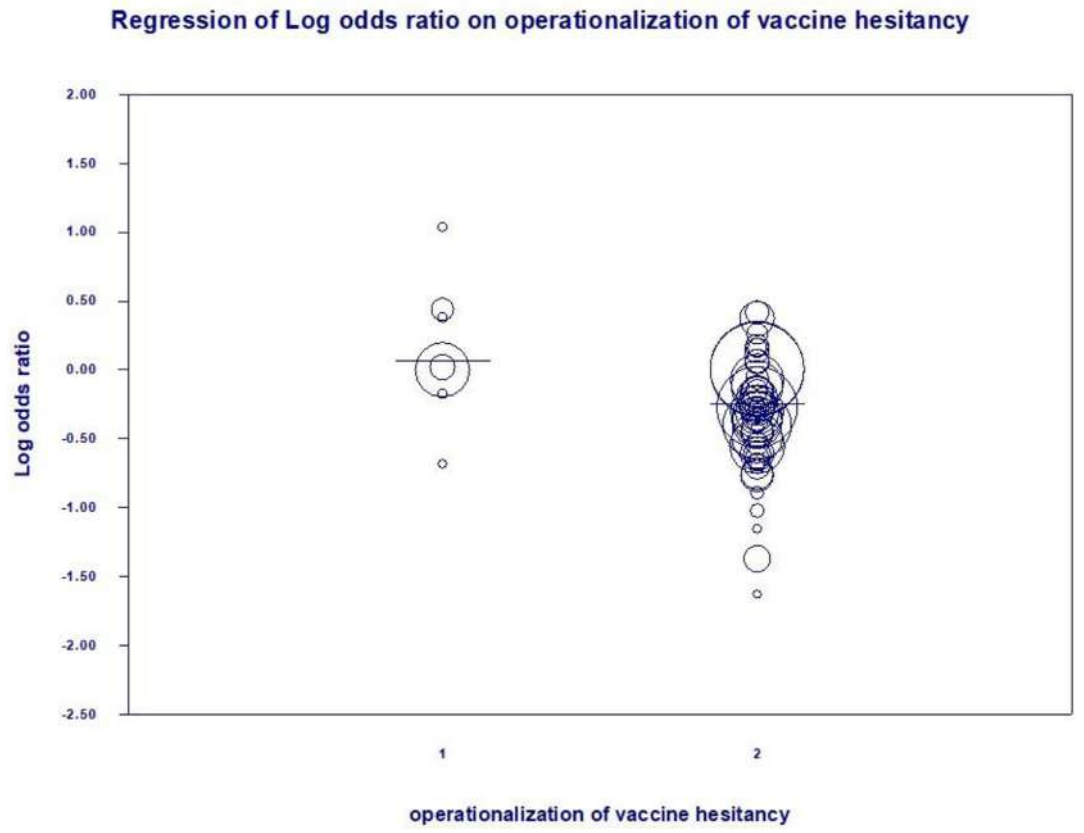

Fig. 3. Scatterplot of operationalization of vaccine hesitancy's moderating effect on the association between health status and vaccine hesitancy.

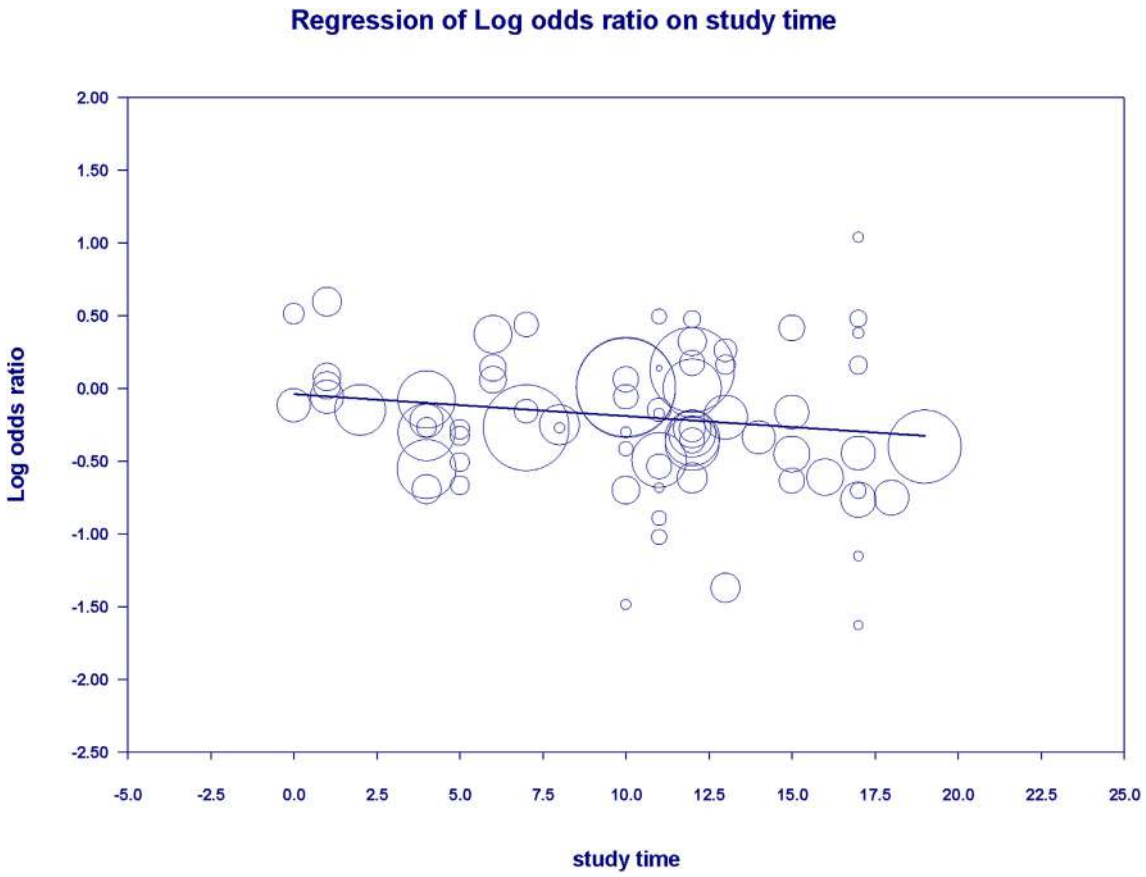

Fig. 4. Scatterplot of time's moderating effect on the association between health status and vaccine hesitancy.

public, especially to people who have pre-existing conditions, as this group needs the protection of the vaccine the most.

In addition, the operationalization of vaccine hesitancy significantly moderated associations between health status and vaccine hesitancy. This indicates that inconsistent operationalization of vaccine hesitancy can influence effect sizes. For example, Wu[36] tested parents' intention to get their children vaccinated for COVID-19. When vaccine hesitancy was operationalized as rejection, the OR between vaccine hesitancy and health status was 1.463, and when vaccine hesitancy was operationalized as delay, the OR between vaccine hesitancy and health status was 1.172. Future research should pay close attention to the conceptualization and operationalization of vaccine hesitancy.

Practical implications

Practically, findings suggest that health professionals should target both individual- and group-level factors to reduce vaccine hesitancy. First, raising awareness about the susceptibility and severity of COVID-19 infection risks may encourage vaccination. Family and friends can engage in communication efforts to influence vaccination decisions of individuals who are vaccine hesitant. Communication campaigns for vaccination can also involve more experts and doctors who are perceived credible to persuade the public.

Last but not least, the moderating effect of age suggests the need to target different age groups and address age-specific concerns related to vaccine hesitancy, as aging typically is juxtaposed with declining health status. Negative associations between health status as well as vaccine coverage of relatives/friends and vaccine hesitancy were amplified over the course of the pandemic, indicating possible 'self-reinforcing' mechanisms of these two factors' influence on vaccine hesitancy. Future research should continue to adopt longitudinal designs to unpack how vaccine hesitancy may change over time.

Limitations

Findings of this study should be considered in light of several limitations. First, WHO'S SAGE Working Group[12] tested vaccine hesitancy from three aspects, including contextual influences, individual and group influences, as well as vaccine and vaccination influences. In this study, we only focused on individual- and group-level influences. Future researchers should test how contextual influences as well as vaccine- and vaccination-related influences affect COVID-19 vaccine hesitancy. Other factors that may moderate associations between predictors and COVID-19 vaccine hesitancy, such as gender, income, and educational level, were not examined in this study.

Author statements

Acknowledgments

This research was supported by the Research Support Program for Computational Communication and Intelligent Media Laboratory at the School of Journalism and Communication, Tsinghua University.

Ethics approval

None sought.

Funding

None declared.

Competing interests

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.05.009.

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* References marked with an asterisk indicate studies included in the meta-analysis

Public Health 220 (2023) 50–56

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Prevalence and influencing factors of anaemia among pregnant women in rural areas of Northwestern China

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ARTICLE INFO

Article history:
Received 7 June 2022
Received in revised form
22 March 2023
Accepted 26 April 2023

Keywords:
Iron deficiency anaemia
Pregnant women
Rural areas
Northwestern China

ABSTRACT

Objectives: Anaemia during pregnancy is a significant public health problem that adversely impacts both the mother and foetus. However, the factors influencing maternal anaemia in deprived areas of Northwestern China have not yet been thoroughly investigated. This study aimed to describe the prevalence and potential influencing factors of anaemia among expectant mothers in rural areas of Northwestern China.

Study design: This was a cross-sectional survey.

Methods: A cross-sectional survey of 586 expectant mothers was conducted to investigate the prevalence of anaemia, prenatal healthcare coverage, dietary diversity and nutrient supplementation intake. The study population was selected from the sample areas using a random sampling method. Data were collected through a questionnaire, and haemoglobin concentrations were measured by a capillary blood test.

Results: The results show that 34.8% of the study population were anaemic, with 13% having moderate-to-severe anaemia. The results of the regression analysis showed that diet was not significantly associated with haemoglobin concentrations or the prevalence of anaemia. However, regular prenatal healthcare attendance was found to be an important influencing factor for both haemoglobin concentration ($\beta = 3.67$, $P = 0.002$) and the prevalence of anaemia (odds ratio = 0.59, $P = 0.011$).

Conclusions: Pregnant women receiving regular prenatal care were less likely to be anaemic; thus, it is essential to implement strategies to improve attendance at maternal public health services to reduce the prevalence of maternal anaemia.

Introduction

Anaemia is a ubiquitous and serious problem in developing countries.[1,2] Research suggests that anaemia in young children is associated with impaired cognition, decreased physical capacity, reduced immunity, as well as impaired psychomotor and cognitive development.[3–5] During pregnancy, women are at a greater risk for anaemia because of the increased need for red blood cells to supply the foetus and placenta. Anaemia during pregnancy is a contributing factor to intrauterine foetal death, increased risks of preterm delivery and low birth weight,[6] as well as a greater risk of the infant having anaemia at 6 months of age.

Although anaemia is influenced by various factors, such as nutrition, infectious disease and genetics, iron deficiency is the major cause, and it accounts for half of the global incidence of anaemia.[7] Unlike aplastic anaemia or thalassemia, nutritional iron deficiency anaemia can be effectively improved by increasing the daily amount of iron ingested. Pasricha et al. suggest that taking iron supplements can reduce anaemia by 50%.[8] Government officials in many developing countries have announced intentions to implement programmes to provide iron supplements to reduce the prevalence of anaemia. For instance, Galloway et al.[9] cited that a government initiative to provide iron supplements helped reduce the prevalence of anaemia among pregnant women and women of reproductive age to rates of 40% and 27.9%, respectively.

However, in China, despite the overall improvement in health and nutritional status of the population, the prevalence of maternal

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https://doi.org/10.1016/j.puhe.2023.04.024
0033-3506/

anaemia remains high. According to recent research findings, 9.7–31.7% (an average of 18.5%) of expectant mothers experienced anaemia in urban areas,[10] whereas the prevalence of maternal anaemia in western China was as high as 20–40%.[11] Other studies conducted in rural areas have suggested a maternal anaemia rate as high as 70%.[12–14] All these research findings suggest that maternal anaemia in China is already a moderate public health problem according to the World Health Organization's (WHO's) level of public health significance.[15]

The high prevalence of maternal anaemia and the wide disparity between urban and rural expectant mothers prompted researchers and policymakers to investigate the factors contributing to maternal anaemia, especially in deprived areas of western China. Studies have identified multiple high-risk factors that are associated with maternal anaemia,[16–19] including high parity and short intervals between pregnancies, early or late childbearing age (<18 years or >35 years)[16,17] and poor dietary intake. Moreover, in deprived areas, the most disadvantaged populations are the least likely to access care when needed, and this population group often has a higher usage of emergency health care than preventive health care.[20]

The Chinese government has taken several measures to promote maternal health and mitigate anaemia during pregnancy. For example, the government provides free folic acid and iron supplements to women of reproductive age and five free prenatal care visits, which include screening tests for anaemia. The government also recommends all expectant mothers have at least 13 prenatal care visits before delivery so that their anaemic status can be diagnosed and treated in a timely manner. However, the use of these preventative healthcare services in rural areas of Northwestern China has not yet been investigated, and the association between prenatal care and maternal anaemia remains unknown. While anaemia during pregnancy represents the main topic of anaemia studies in developing countries, most of the existing literature focused on demographic characteristics and dietary practices,[2,21–25] and few considered prenatal care as a potential contributing factor to maternal anaemia among expectant mothers in deprived areas in China.[26,27] Therefore, empirical evidence, based on large-scale data, is needed to better understand the factors influencing maternal anaemia in rural areas of Northwestern China to implement effective interventions.

The present study was based on a large-scale sample in rural areas of Northwestern China. The overall aim of this study was to describe the prevalence and distribution of maternal anaemia during pregnancy and to identify potential factors influencing maternal anaemia in rural areas of Northwestern China.

Methods

Sampling

In 2021, this study investigated maternal and child health outcomes in Shaanxi, a relatively poor province in western China that ranks 26 out of 31 provinces in terms of per capita disposable income indicators in rural areas.[28] China's administrative regions are divided into provinces, prefectures, counties, townships and villages. Multilevel cluster random sampling methods were used to identify potential study participants. To achieve 80% power, a sample calculation was conducted before sampling. Based on existing research data, it was assumed that there were 12 expectant mothers in each township, with the significance level of 0.05, the intragroup correlation was 0.06 and all other variables accounted for 0.35 variation. Haemoglobin level was used as the main outcome index, with a minimum effect of 0.25 standard deviation. The total sample required in each township was 60, yielding a sample size of approximately 600 participants.

The sampling process was as follows: first, 10 counties in five prefectures in Shaanxi were randomly selected. Then, 10 townships in counties with more than 10 townships were randomly selected. For counties with ≤10 townships, all townships were included. Townships that housed the county seat and townships that did not have any villages with ≥800 people were excluded. These exclusion criteria were used to ensure a rural sample and increased the likelihood of the sampled townships having enough expectant mothers. In total, the sample included 79 townships in 10 sample counties.

Within each township, a list of expectant mothers was obtained from local family planning officials. Then, 10 expectant mothers from each township were randomly selected to participate in the study. For townships with ≤10 expectant mothers, all expectant mothers were included. Overall, the survey included 602 expectant mothers. After excluding 16 invalid questionnaires, the final data included results from 586 valid questionnaires, presenting a valid recovery rate of 97.3%.

Data collection

Data were collected from March to April 2021. A consent form, with information about the programme objectives, procedure, potential risks and benefits for participants, as well as privacy protection, was distributed to each eligible participant before the face-to-face interview. To ensure accuracy and consistency during data collection, the enumerators were intensively trained, including a simulation exercise with 20 participants before data collection. All interview questions were shown on a tablet and asked, one by one, by the enumerator, whereas answers were recorded at the same time. Each interview was conducted in isolation to avoid interruptions from other family members.

The haemoglobin concentration of each participant was measured with the assistance of a local healthcare provider in each county. To measure haemoglobin concentrations, a single drop of capillary blood was obtained with pressure-activated safety lancets and analysed using a HemoCue Hb 201+ system (Hemocue, Inc, Ängelholm, Sweden). The second drop of capillary blood was used to avoid any possible contamination in the first drop of blood. The HemoCue Hb 201+ system was selected for the study because it was fast, accurate, convenient and suitable for use in outpatient units.[29] Local healthcare providers also measured the height and weight of the women to a precision of 1 cm and 0.1 kg, respectively.

Measurements

Demographic and socio-economic data were collected by trained enumerators. Each expectant mother was asked about their age, pregnancy order, gestational age, education, use of prenatal health care and the average annual household income. Gestational age was classified into three trimesters: first trimester (1–14th week), second trimester (14–27th week), and third trimester (27–40th week).

Regular prenatal care was indicated if all recommended prenatal care visits, according to their specific stage of gestation, had been attended. This variable was defined as 0 (missed at least one prenatal care visit) and 1 (attended all recommended prenatal care visits).

Previous studies have reported some correlation between anaemia and dietary intake; thus, the present study also included a modified and detailed module on dietary habits based on the 'minimum dietary diversity' (MDD), a population-level indicator

designed by the WHO.[30,31] Specifically, participants were asked whether their diet during the previous day included items from each of the seven food categories: grains, roots and tubers; legumes and nuts; dairy products; flesh foods; eggs; vitamin A–rich fruits and vegetables; as well as other fruits and vegetables. MDD was defined as a diet including items from ≥4 categories based on MDD standard.[30,31] In addition, enumerators also asked if micronutrient supplements, including iron and folic acid, had been taken during this pregnancy.

The dependent variables of the present study were haemoglobin concentration and anaemia status. Anaemia status was determined by the capillary blood analysis of haemoglobin concentrations. Following internationally accepted standards, anaemia was defined as haemoglobin <110 g/L. Anaemia was subsequently categorized as follows: mild anaemia, 100 g/L ≤ haemoglobin <110 g/L; moderate anaemia, 70 g/L ≤ haemoglobin <100 g/L; and severe anaemia, haemoglobin <70 g/L.[32] The present study sample areas were located at 303–1800 m above sea level; thus, haemoglobin levels were adjusted for altitude (>1000 m, haemoglobin-2; >1500 m, haemoglobin-5).[32]

Statistical analyses

Statistical analyses were performed using STATA 15.0 (StataCorp, College Station, TX, USA). Descriptive analyses were presented as mean (standard deviation) for haemoglobin concentrations and number (percentage) for anaemia status. Analysis of variance tests were performed on the differences in the haemoglobin concentrations of pregnant women with different demographic characteristics and dietary practices, and Chi-squared tests were used on the differences in anaemia. Bonferroni's *post hoc* comparison test was used to identify group differences. The multivariate linear regression model was used to examine factors affecting maternal haemoglobin concentrations, whereas multivariate logistic regression models were used to identify factors associated with anaemia status. All multivariable regressions were controlled for county fix effect. A *P*-value <0.05 was considered to be statistically significant.

Results

Haemoglobin concentrations and prevalence of anaemia

Table 1 summarises the mean haemoglobin concentrations and prevalence of anaemia of participants. The mean haemoglobin concentration in the study population was 115.17 ± 14.21 g/L. In total, 204 of the 586 pregnant women had haemoglobin concentrations <110 g/L, resulting in an overall anaemia prevalence of 34.8%. The rate of mild anaemia (100 g/L ≤ haemoglobin <110 g/L) was 21.7%; the rate of moderate anaemia (70 g/L ≤ haemoglobin <100 g/L) was 13.0%; and only one participant (0.2%) was severely anaemic (Hb < 70 g/L).

Table 1
Haemoglobin concentration and anaemia prevalence of study participants (n = 586).

Characteristics	Frequency (%)[a]
Overall Hb concentration, g/L (mean ± SD)	115.17 ± 14.21
Non-anaemic	382 (65.2%)
Anaemic (Hb < 110 g/L)	204 (34.8%)
Severe anaemia (Hb < 70 g/L)	1 (0.2%)
Moderate anaemia (70 g/L ≤ Hb < 100 g/L)	76 (13.0%)
Mild anaemia (100 g/L ≤ Hb < 110 g/L)	127 (21.7%)

Hb, haemoglobin; SD, standard deviation.
[a] Unless stated otherwise.

Characteristics of the study participants by haemoglobin concentrations and anaemia status

Socio-economic and demographic characteristics of the study participants are shown in Table 2. Of the 586 expectant mothers in this study, 57.3% were aged 27–34 years. More than half of the participants (60.7%) completed ≤9 years of schooling; 36.0% were first-time pregnancies, approximately one-third (32.1%) had not completed all suggested prenatal care visits and slightly less than one-quarter (22.4%) reported a family annual income of <35,000 RMB (US$ 5068). More than one-quarter (25.8%) of study participants were informed of their anaemic status.

Table 2 also presents the difference in haemoglobin concentrations and the prevalence of anaemia by sociodemographic characteristics. Haemoglobin concentrations and anaemia prevalence were significantly different by gestational age ($P < 0.001$). *Post hoc* tests indicated that haemoglobin concentrations were significantly higher in the first trimester than in the second and third trimesters, and haemoglobin concentration in the second trimester was significantly higher than in the third trimester. Women in the third trimester had significantly lower haemoglobin concentrations and higher risks of anaemia. The results also show that women who attended regular prenatal care visits had significantly higher haemoglobin concentrations and were less likely to be anaemic ($P < 0.001$). Meanwhile, among expectant mothers who were informed of their anaemic status, their haemoglobin concentrations were significantly lower, and anaemia rates were higher ($P < 0.001$). The results showed that there was no difference in haemoglobin concentrations or anaemia prevalence by age, years of education, birth order or annual household income.

Unsurprisingly, haemoglobin concentration was found to gradually decrease with the increase of gestational age (in calendar months) as illustrated in Fig. 1. In the present study, the mean haemoglobin concentrations peaked during the second month of pregnancy (145 g/L), followed by a significant onward decline. The prevalence of anaemia was highest during the eighth month of pregnancy, with an anaemia rate of 62%. The rates of anaemia remained high for each month in the third trimester.

Table 3 presents the univariate associations between haemoglobin concentrations, anaemia prevalence and dietary practices. In total, 512 (87.4%) participants achieved MDD. Participants who achieved MDD had higher haemoglobin levels and lower rates of anaemia than those who did not reach MDD; however, there were no significant correlations between haemoglobin concentrations or anaemia prevalence and MDD.

Dietary habits were also evaluated with a more detailed dietary record. Most participants reported that they had eaten cereals, vegetables and fruits during the previous day. Participants who consumed fruits and vegetables had higher haemoglobin levels; however, this study did not identify significant correlations between haemoglobin concentrations or anaemia prevalence and any of the seven food categories ($P > 0.05$).

Participants who took multiple micronutrient supplements, including iron, had significantly lower haemoglobin levels and higher rates of anaemia than their non-taking counterparts ($P < 0.05$). The results also show that multiple micronutrient supplementation, including iron, during pregnancy had a stronger correlation with moderate-to-severe anaemia ($P = 0.012$), but this significant positive correlation may be attributed to reverse causality.

Multivariate analyses

The association between factors including prenatal health care, dietary practices and other sociodemographic characteristics and

Table 2
Mean haemoglobin (Hb) concentrations and prevalence of anaemia based on sociodemographic characteristics (n = 586).

Characteristics	All (n = 586)	Hb concentrations (g/L)		Anaemia	
		Mean ± SD	P value[a]	N (%)	P value[b]
Age in years					
18–26	200 (34.1%)	116.69 ± 14.06	0.110	58 (29.0%)	0.098
27–34	336 (57.3%)	114.12 ± 13.76		126 (37.5%)	
35–46	50 (8.5%)	116.22 ± 17.23		20 (40.0%)	
Years of education					
≤9 years	356 (60.7%)	115.55 ± 14.60	0.426	118 (33.2%)	0.292
>9 years	230 (39.3%)	114.59 ± 13.60		86 (37.4%)	
Pregnancy order					
First	211 (36.0%)	116.24 ± 13.51	0.175	69 (32.7%)	0.422
Second or higher	375 (64.0%)	114.58 ± 14.58		135 (36.0%)	
Stage of gestation[c]					
First trimester	52 (8.9%)	129.60 ± 13.37[a]	<0.001 ***	7 (13.5%)	<0.001 ***
Second trimester	387 (66.0%)	116.03 ± 12.80[b]		119 (30.8%)	
Third trimester	147 (25.1%)	107.83 ± 13.55[c]		78 (53.1%)	
Regular prenatal care[d]					
0	188 (32.1%)	111.15 ± 14.20	<0.001 ***	85 (45.2%)	<0.001 ***
1	398 (67.9%)	117.08 ± 13.83		119 (29.9%)	
Annual household income[e]					
≤35,000 RMB	131 (22.4%)	115.18 ± 14.66	0.993	48 (36.6%)	0.618
>35,000 RMB	455 (77.6%)	115.17 ± 14.10		156 (34.3%)	
Expectant mothers who were informed of their anaemia status					
Yes	151 (25.8%)	106.44 ± 14.44	<0.001 ***	90 (59.6%)	<0.001 ***
No	435 (74.2%)	118.21 ± 12.83		114 (26.1%)	

[a] P-values obtained from ANOVA tests.
[b] P-values obtained from Chi-squared tests.
[c] The Bonferroni's *post hoc* test with the ANOVA showed significant differences in subgroups of stage of gestation, first > second; first > third; second > third; $P < 0.001$.ANOVA, analysis of variance; RMB, Renminbi; SD, standard deviation.
Statistical significance determined as ***$P < 0.001$.
[d] 0 = no; 1 = yes.
[e] 35,000 RMB is equivalent to US$ 5068.

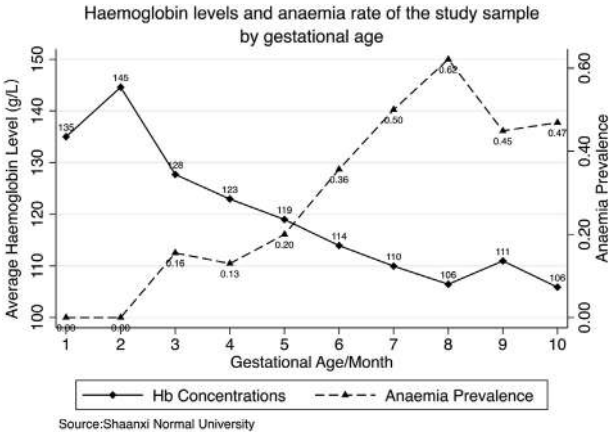

Fig. 1. Haemoglobin levels and anaemia rate of the study sample by gestational age, 2021.

anaemia status was further examined using multivariate analysis after controlling county fixed effect. As presented in Table 4, regular prenatal care might be an influencing factor of maternal anaemia. Participants who attended regular prenatal care were more likely to have higher haemoglobin concentrations (β = 3.67, P = 0.002, 95% confidence interval [CI] = 1.35–6.00) and were less likely to be anaemic (odds ratio = 0.59, P = 0.011, 95% CI = 0.39–0.88). This finding is in line with the results from the univariable analysis (Table 2).

The results indicate that for participants with moderate-to-severe anaemia, pregnancy order was also an important influencing factor (P = 0.027). First-time expectant mothers had significantly higher haemoglobin concentrations and were less likely to have moderate-to-severe anaemia. In addition, the current results suggest that dietary practice was not related to haemoglobin concentrations or anaemia prevalence.

Furthermore, when examining the reverse causality of multiple micronutrient supplementation, including iron, to anaemic status, this study controlled for whether expectant mothers were informed of their anaemic status in the multivariate analysis. According to Table 4, multiple micronutrient supplementation, including iron, was no longer associated with haemoglobin concentrations or anaemic status. Instead, expectant mothers who were informed of their anaemic status had significantly lower haemoglobin concentrations ($P < 0.001$).

Discussion

This study attempted to describe the prevalence of maternal anaemia in rural areas of Northwestern China and to identify potential associations between prenatal healthcare coverage and maternal anaemia. As predicted, anaemia remains a severe threat to maternal health in rural areas of Northwestern China. Regular prenatal care was identified as an important influencing factor of maternal anaemia.

The current findings suggest that anaemia remains one of the most serious health problems in rural areas of Shaanxi despite the high priority of maternal and child health programmes and policies. More than one-third (34.81%) of the present study participants had anaemia, and approximately 13% had moderate-to-severe anaemia. The prevalence of anaemia identified in this study is classified as a 'moderate public health problem' according to the WHO.[15] The prevalence of anaemia in this study is much higher than the average rate of maternal anaemia (18.5%) in China nationwide[10] but is consistent with some other research findings conducted in western China.[11] This suggests that the urban-rural

Table 3
Haemoglobin (Hb) concentrations and anaemia prevalence in participants by dietary practices (n = 586).

Dietary practice	All (n = 586)	Hb concentrations (g/L)		Anaemia		Moderate-to-severe anaemia	
		Mean ± SD	*P* value[a]	*n* (%)	*P* value[b]	*n* (%)	*P* value[b]
Achieved minimum dietary diversity (four groups)							
Yes	512 (87.4%)	115.16 ± 14.34	0.950	180 (35.1%)	0.646	69 (13.5%)	0.527
No	74 (12.6%)	115.27 ± 13.40		24 (32.4%)		8 (10.8%)	
Grains, roots and tubers							
Yes	583 (99.5%)	115.19 ± 14.23	0.760	203 (34.8%)	0.957	77 (13.2%)	0.500
No	3 (0.5%)	112.67 ±13.01		1 (33.3%)		0 (0.0%)	
Legumes and nuts							
Yes	312 (53.2%)	114.64 ± 14.10	0.333	111 (35.6%)	0.679	41 (13.1%)	0.999
No	274 (46.8%)	115.78 ± 14.35		93 (33.9%)		36 (13.1%)	
Dairy products							
Yes	289 (49.3%)	115.57 ± 14.15	0.505	99 (34.3%)	0.781	37 (12.8%)	0.812
No	297 (50.7%)	114.79 ± 14.29		105 (35.4%)		40 (13.5%)	
Flesh foods							
Yes	339 (57.9%)	115.15 ± 14.39	0.958	119 (35.1%)	0.863	46 (13.6%)	0.719
No	247 (42.1%)	115.21 ± 14.00		85 (34.4%)		31 (12.6%)	
Eggs							
Yes	379 (64.7%)	114.77 ± 14.48	0.350	139 (36.7%)	0.201	55 (14.5%)	0.184
No	207 (35.3%)	115.92 ± 13.71		65 (31.4%)		22 (10.6%)	
Vitamin A–rich fruits and vegetables							
Yes	558 (95.2%)	115.27 ± 14.09	0.489	193 (34.6%)	0.611	73 (13.1%)	0.854
No	28 (4.8%)	113.36 ± 16.70		11 (39.3%)		4 (14.6%)	
Other fruits and vegetables							
Yes	479 (81.7%)	115.37 ± 14.43	0.477	165 (34.5%)	0.695	62 (12.9%)	0.767
No	107 (18.3%)	114.29 ± 13.21		39 (36.5%)		15 (14.0%)	
Multiple micronutrient supplementation, including iron							
Yes	214 (36.5%)	113.53 ± 14.59	0.034 *	81 (37.9%)	0.242	38 (17.8%)	0.012 *
No	372 (63.5%)	116.12 ± 13.93		123 (33.1%)		39 (10.5%)	
Folic acid supplements							
Yes	570 (97.3%)	115.17 ± 14.27	0.983	199 (34.9%)	0.762	75 (13.2%)	0.939
No	16 (2.7%)	115.25 ± 12.24		5 (31.3%)		2 (12.5%)	

[a] *P* values obtained from ANOVA tests.
[b] *P* values obtained from Chi-squared tests.ANOVA, analysis of variance; SD, standard deviation.
Statistical significance determined as $*P < 0.05$.

Table 4
Adjusted association between different characteristics and haemoglobin (Hb) concentrations and anaemia status ($n = 586$)[a].

Characteristics	Hb concentrations (g/L)		Anaemia		Moderate-to-severe anaemia	
	β (95% CI)[b]	*P* value	OR (95% CI)[c]	*P* value	OR (95% CI)[c]	*P* value
Regular prenatal care	3.67 (1.35–6.00)	0.002 **	0.59 (0.39–0.88)	0.011 *	0.68 (0.38–1.20)	0.183
Age	−0.05 (−0.34–0.25)	0.758	1.03 (0.98–1.08)	0.270	1.05 (0.97–1.12)	0.222
Years of Education	−0.58 (−2.74–1.57)	0.595	1.21 (0.80–1.82)	0.375	1.12 (0.60–2.09)	0.730
Pregnancy order of infant	−1.51 (−3.92–−0.90)	0.220	1.07 (0.67–1.70)	0.771	2.12 (1.09–4.12)	0.027 *
Annual household income	−0.40 (−3.08–2.28)	0.770	0.87 (0.54–1.40)	0.580	0.89 (0.45–1.77)	0.743
Achieved minimum dietary diversity (≥ 4 groups)	−0.52 (−3.68–2.65)	0.748	1.24 (0.67–2.30)	0.492	1.17 (0.47–2.90)	0.731
Expectant mothers informed of their anaemia status	−11.51 (−14.1–−8.92)	<0.001 ***	4.86 (3.08–7.67)	<0.001 ***	6.67 (3.68–12.10)	<0.001 ***
Multiple micronutrient supplementation, including iron	−0.26 (−2.49–1.93)	0.805	0.88 (0.58–1.32)	0.535	1.17 (0.65–2.11)	0.604

CI, confidence interval; OR, odds ratio.
Statistical significance determined as $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.
[a] All multivariable regressions are controlled county fix effect.
[b] Adjusted regression coefficient and *P* values obtained from multivariate linear regression model.
[c] Adjusted regression coefficient and *P* values obtained from logistic regression model.

disparity in maternal anaemia does exist and that rural mothers are at greater risk of poor maternal health outcomes. Furthermore, the current findings also provide an explanation for the higher risks of infant anaemia at 6 months of age in deprived areas; as suggested by Luo et al.,[33] maternal anaemia before delivery can lead to low iron storage for the newborns.

This study also examined haemoglobin levels at different gestational ages. The WHO has stated that haemoglobin concentrations decline during the first trimester, reaching their lowest point in the second trimester and begin to rise again in the third trimester in healthy populations.[32] However, this study found that haemoglobin levels continuously declined until 33 weeks' gestation (the second month in the third trimester); and when the haemoglobin concentrations started to increase, they remained significantly lower than concentrations in the second trimester. Although this result differs slightly from the WHO report for a healthy population, it is consistent with some regional studies. For example, in Japan, Jwa et al.[34] found that 91 participating pregnant women (4.5%) were anaemic during early pregnancy, and this dramatically increased to 876 (44.1%) in mid-pregnancy and 907 (45.7%) in late pregnancy. This is thought to be partly due to the fact that during the later stages of pregnancy, the frequency of antepartum haemorrhage increased. In addition, there is an increase in plasma volume and red cell mass in the third trimester.[35] Although

it is beyond the scope of this study, investigating the effects of anaemia during different gestational ages on neonatal health outcomes is also essential. Existing studies have not yet reached a consensus. For example, some studies suggest that anaemia during the first trimester leads to a greater risk of negative pregnancy outcomes,[36] and others propose that maternal anaemia in the second trimester influences postnatal infant growth.[37]

Regular prenatal healthcare attendance was found to significantly influence haemoglobin concentrations and anaemia status. Participants who experienced regular prenatal healthcare coverage had significantly higher levels of haemoglobin and lower rates of anaemia than those who did not attend regularly. This finding is consistent with a study conducted in low-income areas of Turkey that suggested women who attended <10 prenatal care visits during pregnancy had a significantly higher prevalence of anaemia than those who attended ≥10 times.[38] One possible explanation is that expectant mothers who attended regular prenatal care were informed of their anaemia status and took appropriate measures, as suggested by the healthcare team, to mitigate anaemia. In the present study questionnaire, participants were asked if they were aware of their anaemic status; 40% of the anaemic women reported that they did not know their anaemic status, so they never received any iron supplementation beyond their regular diet. Therefore, it is evident that regular prenatal care can help expectant mothers receive early diagnosis and treatment in terms of their anaemic status and thus should be promoted.

In contrast with previous studies that suggest a significant correlation between anaemia prevalence and dietary practice, this study did not identify this association. This can be explained by two possible reasons. First, expectant mothers need a large amount of haemoglobin to support the foetus and placenta during pregnancy. If the haemoglobin levels are low while iron consumption is high, this shows that iron in food alone is not sufficient. They must rely on extra iron supplementation to improve their haemoglobin levels. Second, this study was conducted in rural Shaanxi. Although small regional differences may exist, participants' dietary practices were very similar based on the results of the diet survey. In particular, it was noted that participants rarely eat iron-rich foods, such as red meat and pork liver. And, even if they did consume iron-rich food, the amount of iron ingested from meat was not sufficient; thus, the homogeneity of the sample on dietary practice influenced the significance of regression results. This finding further supports the idea that improving haemoglobin concentration in rural areas via a better dietary practice is difficult. A more effective way to prevent anaemia is to attend regular prenatal care and monitor anaemic status so that extra iron supplementation can be taken when required.

In the present study, significantly lower haemoglobin concentrations were found in women who are taking iron supplements. This phenomenon might be attributed to reverse causation (i.e. rural expectant mothers were more likely to take iron supplementation when formally diagnosed with anaemia). The result may also be because the practice of taking iron supplements inhibits iron absorption, such as in dairy products, as suggested in previous studies.[39–41] In the present study population, >70% of women who were taking iron supplements reported that they consumed dairy products during the previous day. However, the effect of dairy products on iron absorption depends on the chemical form of iron and meal composition. Because of the limitation of the current data, it was not possible to identify the size of the effects of dairy product consumption on haemoglobin concentrations.

This present study derives some new research ideas along with the limitations. As this study used cross-sectional data, only descriptive analyses were conducted. The impact of maternal anaemia on pregnancy and neonatal outcomes needs to be explored further using panel data. Another limitation of this study was the dietary tool used in the survey. Assessing dietary intake only from the previous day may generate misleading information and potentially influence the accuracy of results. Thus, the association between dietary habits and anaemia prevalence needs further verification. In addition, to provide evidence-based policy advisory, a randomized controlled trial should be conducted to explore effective interventions to promote maternal and neonatal health.

Conclusions

Iron deficiency anaemia remains a huge public health problem for women during pregnancy in rural areas of Northwestern China. Although the Chinese government offers free prenatal care visits for rural expectant mothers to improve maternal health, the use of these preventative services remains low. In this study, it was shown that regular prenatal care can significantly help improve haemoglobin concentrations and reduce the risks of anaemia. Therefore, increasing attendance at prenatal care services is of great importance to mitigate maternal anaemia in rural areas of Northwestern China.

Author statements

Acknowledgements

The authors thank the researchers from Xi'an Jiaotong University and Shaanxi Normal University for their help in developing the study protocol. The authors are also grateful to all respondents who participated in this study and the enumerators for their data collection efforts.

The authors also thank the support of the program titled 'Supporting NGOs to advance women's decision-making through healthy start in life program in Shaanxi' for experiment implementation.

Ethical approval

The principles of the Declaration of Helsinki were followed, and ethical approval was received from the Medical Ethics Committee of Shaanxi Normal University (Xi'an, China) and Xi'an Jiaotong University (Xi'an, China, No.2020-1240). Permission was received from every participant before the interview. Participants who were found to have severe anaemia were referred to local hospitals for treatment.

Funding

This research was funded by the 111 Project (Grant No. B16031), Supported by Soft Science Research Project of Xi'an Science and Technology Plan (Grant No. 23RKYJ0053), and the Fundamental Research Funds for the Central Universities (Grant No. 2021CSWY024), Social Science Foundation Project of Shaanxi Province (2022F006) and Humanities and Social Science Research Project of Ministry of Education(22YJC840023).

Competing interests

The authors declare no conflict of interest. The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the article, and in the decision to publish the results.

Author contributions

J.Y., J.N., and Z.L. contributed to concept or design. J.Y., Z.L., H.G., Z.R., and J.Y. contributed to acquisition of data. J.Y., Z.L., H.G., and J.N. analysed or interpreted the data. J.Y., Z.L., Z.R., and J.N. drafted the article. All authors contributed to critical revision for important intellectual content.

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Public Health 220 (2023) 108–111

Contents lists available at ScienceDirect

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Short Communication

Relationship between primary vaccination coverage and booster coverage against COVID-19, socio-economic indicators, and healthcare structure in Brazil

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ARTICLE INFO

Article history:
Received 3 January 2023
Accepted 4 May 2023
Available online 10 May 2023

Keywords:
COVID-19
SARS-CoV-2
COVID-19 vaccines
Poverty
Primary health care

ABSTRACT

Objective: To investigate the relationship between vaccination coverage and booster coverage against COVID-19, socio-economic indicators, and healthcare structure in Brazil.
Study design: This is a nationwide population-based ecological study.
Methods: We have obtained data on COVID-19 vaccination for each Brazilian state until December 22, 2022. Our outcomes of interest were primary and booster vaccination coverage. The independent variables included: human development index (HDI); Gini index; population density; unemployment rate; percentage of the population covered by primary health care (PHC); percentage of the population covered by community health workers; number of family health teams; and number of public health establishments. Statistics were performed by using a multivariable linear regression model.
Results: Lower rates of primary vaccination coverage were found in states with lower HDI ($P = 0.048$), population covered by PHC ($P = 0.006$), and number of public health establishments ($P = 0.004$). Lower rates of booster coverage were also found in states with lower population density (first booster: $P = 0.004$; second booster: $P = 0.022$), PHC (first booster: $P = 0.033$; second booster: $P = 0.042$), and public health establishments (first booster: $P < 0.001$; second booster: $P = 0.027$).
Conclusion: Our findings showed heterogeneity in access to vaccination against COVID-19 in Brazil, with lower vaccination coverage in localities with the worst socio-economic indicators and limited healthcare resources.

Introduction

Brazil is one of the countries with the highest COVID-19 incidence and mortality rates worldwide, with more than 17,000 cases and 330 deaths per 100,000 inhabitants, respectively. The vaccination campaign against COVID-19 in the country started in January 2021, and until December 1, 2022, immunization uptake was higher than 80%. However, we had previously found evidence that COVID-19 disproportionately affects the most vulnerable populations in Brazil.[1–4] Since the country has significant regional disparities, vaccination coverage against the disease may be influenced by socio-economic and healthcare structure factors. We therefore conducted a nationwide population-based ecological study to examine the relationship between primary vaccination coverage and booster coverage against COVID-19, socio-economic indicators, and healthcare structure in Brazil. Given the subsequent COVID-19 waves observed in the country, the findings of this study may be useful in improving public vaccination policies in the most vulnerable areas.

Methods

Brazil is a country with approximately 8.5 million km^2, an estimated population of 213 million people, and a population density of 25 inhabitants per km^2. Brazil comprises 26 states and one federal administrative district, and its human development index (HDI) is 0.754.

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https://doi.org/10.1016/j.puhe.2023.05.003
0033-3506/

Since 1990, the Brazilian health system (called *Sistema Único de Saúde – SUS*) has been based on universality, integrality, decentralization, and community participation, and is one of the largest free-of-charge public health systems in the world. The 5570 Brazilian municipalities are responsible for providing primary health care (PHC) and health surveillance and guaranteeing access to specialized and hospital care. Currently, PHC is organized into family health teams (FHT) and covers approximately 75% of the Brazilian population (https://egestorab.saude.gov.br/). In Brazil, vaccination campaigns are organized by the Ministry of Health in cooperation with states and municipalities. The application of vaccine doses is the responsibility of the municipalities, which contributes to reducing regional and social inequalities by allowing access to vaccination for all Brazilians throughout the country.[5]

In this study, our outcomes of interest were (1) primary vaccination coverage, defined as the proportion of the population that has received the regular schedule against COVID-19 with two doses of CoronaVac (Sinovac/Butantan), Covishield (Oxford-AstraZeneca/Fiocruz), or COMIRNATY (Pfizer/BioNTech) vaccines, or a single-dose of J&J/Janssen vaccine; and (2) booster vaccination coverage, defined as the proportion of the vaccinable population that has received the first and second booster doses of COVID-19 vaccines. Data on vaccination were collected until December 22, 2022. The independent variables included: (a) HDI, a composite index of life expectancy, education, and income; (b) Gini index, which measures the degree of income concentration in a population group; (c) population density; (d) unemployment rate; (e) percentage of the population covered by PHC; (f) percentage of the population covered by community health workers; (g) number of FHT; and (h) number of health establishments with outpatient care provided by the SUS.

Data were obtained from various public data sources: the number of COVID-19 vaccine doses administered to the population in each Brazilian state was extracted from the National Health Data Network (RNDS, acronym in Portuguese; https://www.gov.br/saude/pt-br/composicao/se/demas/covid19); demographic and socio-economic indicators from the Brazilian Institute of Geography and Statistics (IBGE, acronym in Portuguese; https://cidades.ibge.gov.br/brasil/); and information on healthcare structure from the E-Gestor AB (https://egestorab.saude.gov.br/). Primary vaccination coverage was calculated based on the total population of each state. The first and second booster coverage estimates were based on the vaccinable population aged 12 years and older, as well as the vaccinable population aged 40 years and older, respectively.

Statistics were performed in a state-level analysis, and the most promising candidate predictors were incorporated into a multivariable linear regression model using a backward selection process. Assumptions of normality and homoscedasticity were checked. The significance level in the final model was set at 5%. Analyses were performed by using JASP software version 0.13 (JASP Team, Amsterdam, Netherlands). Because all data were obtained from a public domain database and were deidentified, no institutional review board approval or informed consent was required.

Results

As of December 22, 2022, approximately 80% of the Brazilian population were fully immunized against COVID-19, and the primary vaccination coverage ranged from 55% in Roraima state (North region) to 90% in São Paulo (Southeast region). Nine of the 27 federated units had vaccination coverage below 70%, all located in the North and Northeast, recognized as the poorest regions in the country. In addition, 56% of the vaccinable population received a first booster dose, ranging from 22% in Amazonas (North region) to 74% in São Paulo. Ten states had a first booster coverage less than 40%, eight of which were located in the North and Northeast regions. Finally, 47% of the vaccinable population received a second booster dose, ranging from 16% in Roraima to 80% in Piaui (Northeast region). Eight states had a second booster coverage less than 25%, six of which were located in the North and Northeast regions (Fig. 1).

A significant relationship between vaccination coverage (primary scheme and booster dose), socio-economic indicators, and healthcare structure in a state-level analysis was confirmed. Lower rates of primary vaccination coverage were found in states with lower HDI ($P = 0.048$), population covered by PHC ($P = 0.006$), and number of health establishments with outpatient care provided by the SUS ($P = 0.004$). Lower rates of booster coverage were also found in states with lower population density (first booster: $P = 0.004$; second booster: $P = 0.022$), PHC (first booster: $P = 0.033$; second booster: $P = 0.042$), and health establishments (first booster: $P < 0.001$; second booster: $P = 0.027$) (Table 1).

Discussion

Vaccination has proven to be an essential component of a public health strategy to protect the population against COVID-19. Despite the efficacy and safety of different vaccine platforms reported in clinical trials, poorer regions may have lower access to immunizers[6]

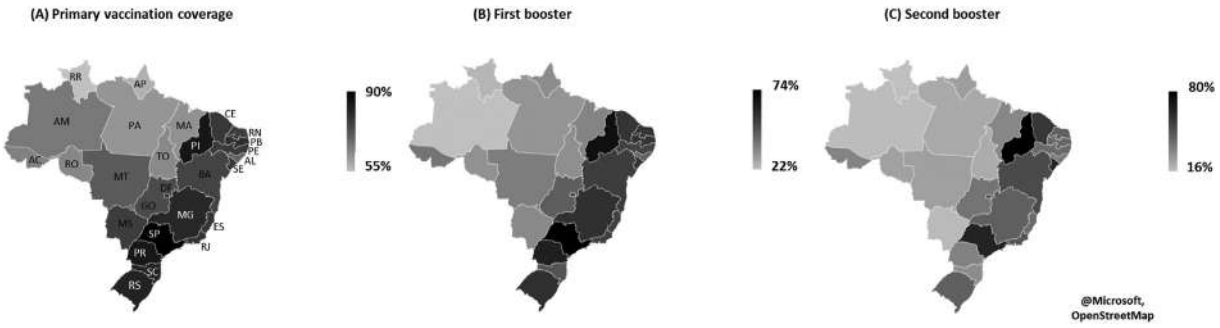

Fig. 1. Primary vaccination coverage (A), first booster coverage (B), and second booster coverage (C) of COVID-19 vaccine in Brazil. North: AM, Amazonas; AC, Acre; RR, Roraima; AP, Amapá; RO, Rondônia; PA, Pará; TO, Tocantins. Northeast: MA, Maranhão; PI, Piauí; CE, Ceará; RN, Rio Grande do Norte; PB, Paraíba; PE, Pernambuco; AL, Alagoas; SE, Sergipe; BA, Bahia. Central-West: GO, Goiás; DF, Distrito Federal; MT, Mato Grosso; MS, Mato Grosso do Sul. Southeast: MG, Minas Gerais; ES, Espírito Santo; SP, São Paulo; RJ, Rio de Janeiro. South: PR, Paraná; SC, Santa Catarina; RS, Rio Grande do Sul.

Table 1
Results of linear regression analysis on the relationship between vaccination coverage and booster coverage against COVID-19, socio-economic indicators, and healthcare structure in Brazil.

Variables	Vaccination coverage (regular schedule)				First booster				Second booster			
	Univariate model		Multivariate (final) model		Univariate model		Multivariate (final) model		Univariate model		Multivariate (final) model	
	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value	β	*P*-value
HDI	141.186	<0.001	72.286	0.048	158.082	0.013			82.065	0.299		
Gini index	−34.574	0.390			9.633	0.875			79.843	0.265		
Population density	0.026	0.062	0.021	0.074	0.040	0.061	0.050	0.004	0.048	0.057	0.054	0.022
Unemployment rate	−0.311	0.487			0.269	0.692			1.248	0.112	1.117	0.097
Primary healthcare	0.200	0.161	0.281	0.006	0.212	0.330	0.357	0.033	0.248	0.336	0.464	0.042
Community health workers	−0.135	0.133			−0.160	0.245			−0.089	0.590		
Family health teams	0.003	0.002			0.005	<0.001			0.004	0.019		
Health establishments	0.002	0.001	0.001	0.004	0.003	0.001	0.003	<0.001	0.002	0.045	0.002	0.027

Vaccination coverage: $R^2 = 0.683$. Durbin–Watson test = 1.810 ($P = 0.626$).
First booster: $R^2 = 0.573$. Durbin–Watson test = 1.897 ($P = 0.800$).
Second booster: $R^2 = 0.458$. Durbin–Watson test = 2.230 ($P = 0.534$).

and higher adversities in vaccinating their population,[7] which can lead to difficulties in controlling disease transmission, exposure of susceptible individuals to worse clinical outcomes associated with COVID-19, and overload of health systems. Areas with lower population density may also have a lower number of primary health units and less coverage of PHC teams. In Northern Brazil, for example, there are municipalities with large territories and low population density where many communities live far from the health services of urban centres. These communities must either travel long distances by river and/or road transport to access health services or wait for an itinerant PHC team that provides scheduled visits for health care, including vaccination. Furthermore, these regions are less likely to have the infrastructure and staffing required to maintain accurate health registry data and ensure timely delivery of vaccine supplies.

Although Brazil has a long history of successful immunization programs associated with the decentralized health system and a strong capillarity throughout the territory ensuring the principle of universality, vaccine hesitancy[8] and the reduction of financial resources in primary care[9] have been striking in the country in recent years. Therefore, our results suggest that the poorest states need higher investments in PHC and a better structure of basic health services to achieve more acceptable levels of vaccination coverage against COVID-19. Previously, it was found that Brazilian cities with the highest PHC coverage were less affected by COVID-19,[10] which reinforces the importance of the primary network strategy in health education and promotion, as well as disease prevention.

This study has some limitations that are inherent to ecological studies. The data were obtained from information systems, and there is a potential chance that missing data may have influenced vaccination coverage rates. Despite these limitations, our study is relevant because it provides analysis on the impact of socio-economic vulnerability indicators on vaccination coverage against COVID-19, a disease that has become the most important public health problem of the 21st century and that requires the capacity and agility of health systems to provide vaccine doses to eligible populations in a short period of time.

Our findings showed heterogeneity in access to vaccination against COVID-19 in Brazil, with lower vaccination coverage in localities with the worst socio-economic indicators and limited healthcare resources. Identifying localities with the resource limitations that may contribute to difficulty in ensuring access to COVID-19 vaccination can assist decision-makers in allocating the resources needed to improve the reach, equity, and effectiveness of the immunization campaign and expand vaccination coverage.

Author statements

Ethical approval

Since the study was a secondary data analysis, based on publicly available survey data, ethical approval and participant consent were not necessary.

Funding

None declared.

Competing interests

The authors have no conflict of interest to declare.

Author's contributions

All authors contributed equally to the manuscript.

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Public Health 220 (2023) 18–26

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Spatial variations and determinants of optimal antenatal care service utilisation in Ethiopia: spatial and survey regression analysis

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ARTICLE INFO

Article history:
Received 9 December 2022
Received in revised form
16 February 2023
Accepted 18 April 2023

Keywords:
Antenatal care
Determinant
Optimal
Spatial variation
Ethiopia

ABSTRACT

Objectives: Optimal antenatal care (ANC) services are the main strategy to reduce maternal and newborn mortality. Understanding the geographic variation of ANC service utilisation is essential for regional- and local-level interventions. However, data on spatial variation of optimal ANC service utilisation are limited. Hence, this study aimed to investigate the spatial variations and determinants of optimal ANC service utilisation in Ethiopia.

Study design: This was a spatial and survey regression analysis.

Methods: The secondary analysis of the Ethiopian Demographic and Health Survey 2019 was performed to investigate the spatial variation and determinants of optimal ANC service utilisation among women who were pregnant in the 5 years preceding the survey. Spatial dependency, clustering and prediction were conducted using Global Moran's I statistics, Getis-Ord Gi* and Kriging interpolation, respectively, using ArcGIS version 10.8. A survey binary logistic regression model was fitted to identify determinants of optimal ANC service utilisation.

Results: Of 3979 pregnant women, 1656 (41.62%) had optimal ANC visits in Ethiopia. Optimal ANC utilisation was shown more prevalent in Northern, Eastern, Central and Northwestern regions of Ethiopia. The results also identified low levels of optimum ANC utilisation in Northeastern, Southeastern, Southern and Western regions of Ethiopia. Wealth index, timing of initial ANC visit and region were significantly associated with optimal ANC service utilisation in Ethiopia.

Conclusions: Optimal ANC service utilisation showed significant spatial dependency in Ethiopia, with spatial clustering in the Northern and Northwestern regions of the country. In addition, the results from this study suggest that financial support should be considered for women living in households in the poorest wealth index and ANC initiation should begin within the first trimester. It is recommended that targeted policies and strategies are introduced to regions with low levels of optimal ANC service utilisation.

Introduction

The utilisation of optimal antenatal care (ANC) throughout pregnancy has been shown to reduce maternal and newborn mortalities and morbidities and promote safe motherhood with improved maternal health outcomes.[1] However, utilisation of ANC services is very low, particularly in sub-Saharan Africa, including Ethiopia. Optimal ANC is defined as at least four antenatal visits for women with normal pregnancies and additional visits for women with complications; otherwise, ANC is deemed as inadequate.[2]

The latest Sustainable Development Goals aim to reduce the 70 maternal deaths per 100,000 live births globally by 2030.[3] A high rate of maternal mortality (412/100,000 live births) was reported in the 2016 Ethiopian Demographic and Health Survey (EDHS), despite numerous government efforts to reduce maternal mortality.[4] Optimal ANC services could contribute to reducing maternal morbidities, mortalities, complications at birth, and the risk of low birth weight and preterm births. The World Health Organisation (WHO) stated that 'to achieve the Every Woman Every Child vision and the Global Strategy for Women's, Children's and Adolescents' Health, we need innovative, evidence-based approaches to antenatal care'.[5] Although many African nations, including Ethiopia, are

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https://doi.org/10.1016/j.puhe.2023.04.010
0033-3506/

Table 1
Definitions and categorisation of variables used in survey regression of determinants of optimal ANC service utilisation in Ethiopia, EMDHS 2019.

Variable	Definition/categorisation
Age	The age of women at interview was coded as 15–19 years = 0; 20–24 years = 1; 25–29 years = 2; 30–34 years = 3; 35–39 years = 4; 40–44 years = 5; 45–49 years = 6
Educational level	The educational status of women was coded as unable to read and write = 1; primary = 2; secondary = 3; higher = 4
Marital status	The marital status of women was coded as single = 1; married = 2; widowed = 3; divorced = 4
Wealth index	Wealth index was categorised and coded as 0 = poorest; poorer = 1; middle = 2; richer = 3; richest = 4
Place of residence	Place of residence was categorised and coded as urban = 1; rural = 2
Sex of household head	The sex of household head was coded as male = 1; female = 2
Birth order	The rank order of position of child was coded as first = 1; two to four = 2; more than 4 = 3
Timing of first ANC visit	The timing of the first ANC visit was coded as ≤12 weeks = 1; >12 weeks = 2
Region	The regions of Ethiopia were coded as Tigray = 1, Afar = 2, Amhara = 3, Oromia = 4, Somali = 5, Benishangul = 6, SNNPR = 7, Gambela = 8, Harari = 9, Addis Ababa = 10 and Dire Dawa = 11

ANC, antenatal care; EMDHS, Ethiopia Mini Demographic and Health Survey; SNNPR, Southern Nations Nationalities and Peoples Region.

still working to achieve a high percentage rate of women meeting the four ANC visits goal, the WHO recommends at least eight ANC visits for a positive pregnancy experience.[5] Evidence also indicates that compared with the recommended number of visits, perinatal mortality is higher in low- and middle-income countries when women attended three or fewer ANC visits during pregnancy.[4,6]

Studies in low- and middle-income countries have examined various factors associated with ANC visits. Socio-economic, demographic and accessibility factors, in addition to variables related to perceived quality of maternal health services, were shown to impact ANC service utilisation.[4,7] Several studies have shown that maternal educational status, place of residence, household wealth status, parity and gravidity, as well as the availability, accessibility and quality of care, are all factors influencing the optimal use of ANC services.[1,8,9]

Although there is much literature on maternal healthcare utilisation and pregnancy outcomes, more recent and current data specifically on ANC service utilisation and its determinants in Ethiopia are limited. It is important to have a thorough understanding of the current prevalence, spatial distributions and associated factors of optimal ANC service utilisation to enable policymakers to design strategies to strengthen ANC services and improve maternal and child health. This study aimed to determine the prevalence, show spatial patterns and identify factors associated with the recommended utilisation of ANC services in Ethiopia using a nationally representative data set.

Methods

Data

This study used data from the Ethiopia Mini Demographic and Health Survey (EMDHS) 2019, which was accessed via MEASURE DHS (http://www.dhsprogram.com) through formal registration and request. The data were extracted from the Individual Recode, which is individual women's data in the data sets of the EDHS 2019. This data set has one record for every eligible woman as defined by the household schedule. After cleaning and recoding the variables, weighting was performed using the weighing variables for women. Descriptive statistics were carried out and summarised using text, charts and tables. STATA version 14 and Microsoft Excel 2019 were used for data management. ArcGIS version 10.8 was used to map optimal ANC service utilisation in Ethiopia. All methods were carried out following relevant guidelines and regulations.

A secondary analysis of the EMDHS 2019 was performed to investigate the spatial regional and local variations of optimal ANC service utilisation and to identify associated factors. The study was conducted in Ethiopia, which is the second most populous country in Africa, with an average population density of 115 per km^2. Administratively, Ethiopia is divided into 11 regions (Afar, Amhara, Benishangul, Gambela, Harari, Oromia, Somali, Southern Nations Nationalities and People's Region [SNNPR], Southwestern people's region [recently added], Sidama [recently added] and Tigray) and two city administrations (Addis Ababa and Dire Dawa). Ethiopia uses a three-tier health system, as follows: (1) primary care, which

Table 2
Sociodemographic characteristics of study participants.

Characteristics		Frequency (*n*)	Percent
Age in years	15–19	296	5.15
	20–24	1143	19.87
	25–29	1858	32.30
	30–34	1239	21.54
	35–39	765	13.30
	40–44	339	5.89
	45–49	113	1.96
Education level	Unable to read and write	3149	54.74
	Primary	1823	31.69
	Secondary	480	8.34
	Higher	301	5.23
Household head sex	Male	4598	79.92
	Female	1155	20.08
Wealth index	Poorest	1964	34.14
	Poorer	994	17.28
	Middle	805	13.99
	Richer	738	12.83
	Richest	1252	21.76
Marital status	Single	31	0.54
	Married	5480	95.25
	Widowed	61	1.06
	Divorced	181	3.15
Birth order	1	1261	21.92
	2–4	2598	45.16
	>4	1894	32.92
Residence	Urban	1328	23.08
	Rural	4425	76.92
Timing of first ANC	≤12 weeks	1255	42.76
	>12 weeks	1680	57.24
Region	Tigray	454	7.89
	Afar	652	11.33
	Amhara	511	8.88
	Oromia	719	12.50
	Somali	637	11.07
	Benishangul	530	9.21
	SNNPR	660	11.47
	Gambela	450	7.82
	Harari	447	7.77
	Addis Ababa	291	5.06
	Dire Dawa	402	6.99

ANC, antenatal care; SNNPR, Southern Nations Nationalities and Peoples Region.

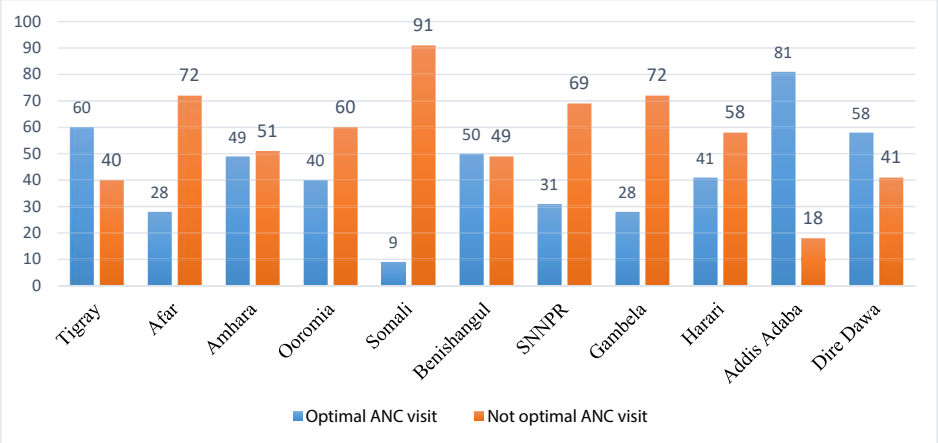

Fig. 1. Regional prevalence of optimal antenatal care (ANC) service utilisation in Ethiopia, Ethiopia Mini Demographic and Health Survey (EMDHS) 2019.

consists of health posts, health centres and primary hospitals; (2) secondary care, which includes district hospitals; and (3) tertiary care, which consists of comprehensive specialised hospitals, where ANC services are delivered.

The source population of the study was all women who were pregnant in the five years preceding the survey in Ethiopia, and the study population was all women who were pregnant in the five years preceding the survey in selected enumeration areas (sampled clusters) in Ethiopia. The EDHS 2019 uses a two-stage cluster sampling technique. In the first stage, 305 clusters/enumeration areas were randomly selected, with a probability sampling stratified with urban and rural regions. In the second stage, a fixed number of 30 households per cluster were selected using probability sampling. All reproductive-aged women in each selected household answered questions regarding pregnancies in the 5 years preceding the survey, number of ANC follow-up visits and the services provided at each ANC visit, such as iron folate supplementation and tetanus vaccinations.

Variables

The outcome variable for this study was optimal ANC service utilisation, dichotomised into 'yes' for pregnant women who had four or more ANC visits for the most recent live birth in the 5 years

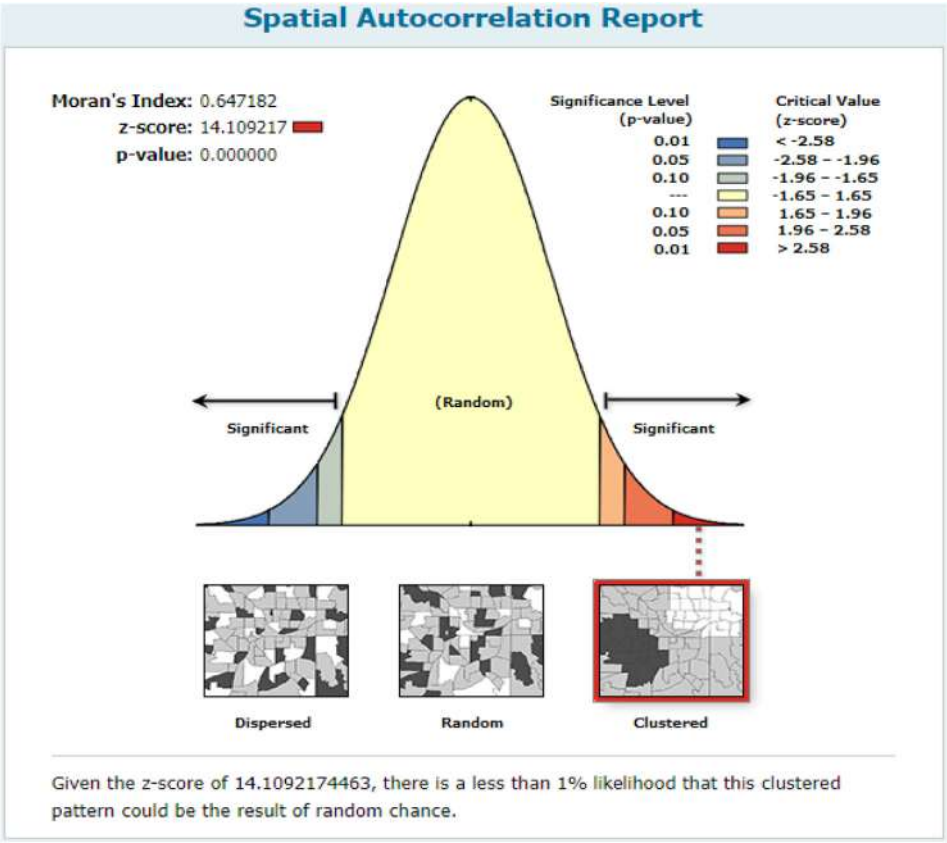

Fig. 2. Spatial autocorrelation of optimal ANC visits in Ethiopia, EMDHS 2019. ANC, antenatal care; EMDHS, Ethiopia Mini Demographic and Health Survey.

preceding the survey and 'no' for women who had less than four ANC visits.

Sociodemographic and socio-economic variables (sex, religion, educational status, age and wealth index), in addition to community factors (region and residence), were included in the study. Variables were coded based on the analytical framework used by EMDHS 2019 (Table 1).

Spatial analysis

Spatial autocorrelations of optimal ANC service utilisation

The spatial autocorrelation (Global Moran's I) was used to test for the spatial dependency of optimal ANC service utilisation in Ethiopia. The value of Moran's I statistics is between −1 and 1. A Moran's I value close to −1 indicates that the distribution is dispersed, and a value close to 1 indicates the distribution is clustered, whereas a Moran's I value of 0 means that the data are randomly distributed. A statistically significant Moran's I ($P < 0.05$) indicates the presence of spatial dependence.

Hotspot analysis of optimal ANC service utilisation

Hotspot analysis (Getis-Ord Gi*) was used to determine the spatial clustering of optimal ANC service utilisation in Ethiopia.

The spatial scan statistical analysis (Satscan) was fitted using the Bernoulli model to investigate spatial clustering of optimal ANC service utilisation. The spatial scan statistics use a circular scanning window that moves across the study area. Cases, controls and geographic coordinate data were fitted to the Bernoulli model. For each potential cluster, log-likelihood ratio, relative risk and *P*-values were used to determine whether the number of observed cases within the potential cluster was significantly higher than expected or not.

Spatial interpolation

Spatial prediction of optimal ANC service utilisation was conducted in an unsampled area using the observed data by an ordinary Kriging interpolation.

Survey regression analysis

A binary outcome survey regression model was fitted to identify factors associated with optimal ANC service utilisation in Ethiopia. This analysis was selected for its quality in considering complex survey designs, such as weighting, clustering and strata.

Results

Sociodemographic characteristics of study participants

A total of 3979 pregnant women were included in the analysis, with a mean age of 28 years (32.3% were in the age group of 25–29 years). In terms of household wealth status, 51.42% of participants had poor (poorer and poorest) wealth status, and more than half (54.74%) could not read and write. Most (76.9%) participants were rural residents (Table 2).

Prevalence of optimal ANC service utilisation in Ethiopia

Of 3979 pregnant women, 1656 (41.62%; 95% confidence interval [CI] of 40.09, 43.16) had optimal ANC visits in Ethiopia for the most recent live birth in the 5 years preceding the 2019 EMDHS. The regional prevalence of optimal ANC service utilisation in Ethiopia was observed to be highest in Addis Abba (81%) and lowest in Somali (9%; Fig. 1).

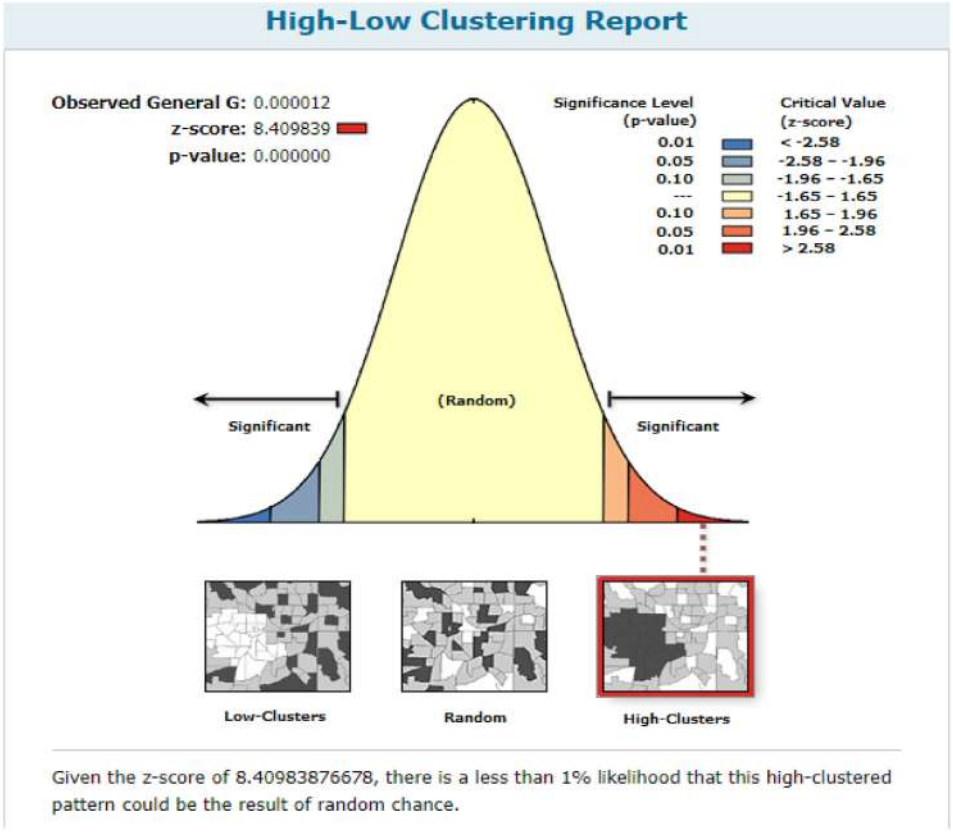

Fig. 3. Spatial clustering of optimal ANC service utilisation in Ethiopia, EMDHS 2019. ANC, antenatal care; EMDHS, Ethiopia Mini Demographic and Health Survey.

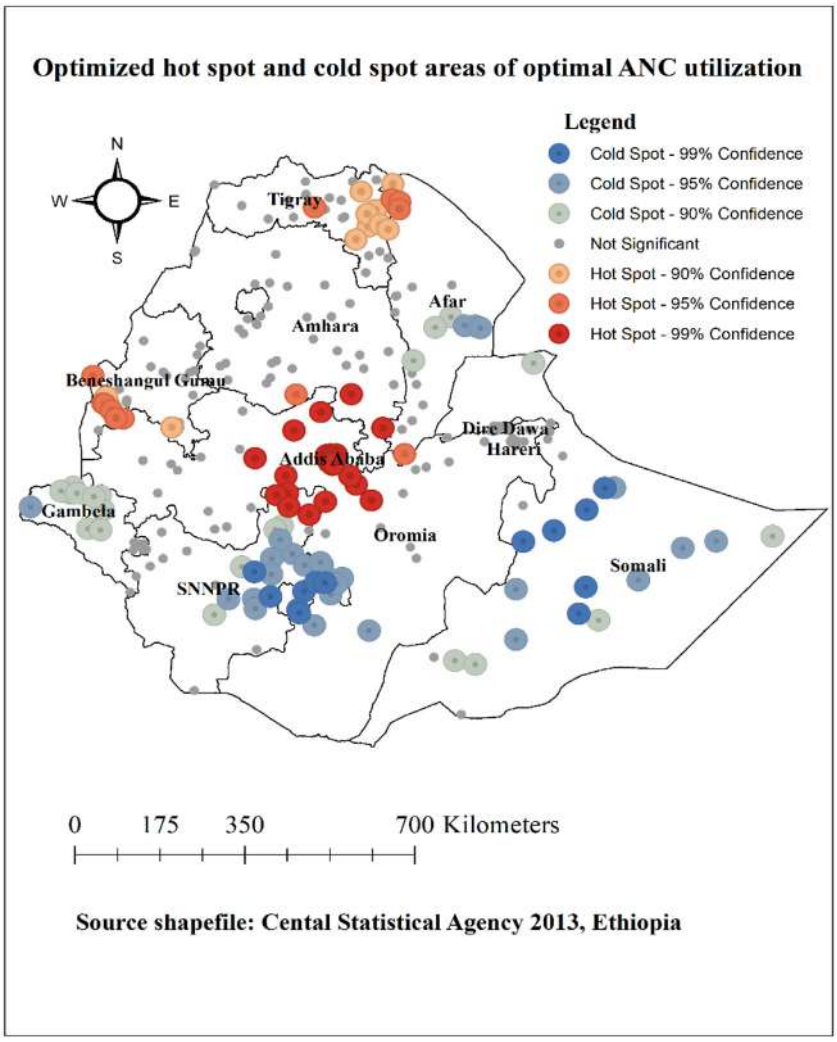

Fig. 4. Optimised hotspot analysis of optimal ANC service utilisation in Ethiopia, EMDHS 2019. ANC, antenatal care; EMDHS, Ethiopia Mini Demographic and Health Survey; SNNPR, Southern Nations Nationalities and Peoples Region.

Spatial analysis

Spatial autocorrelation and clustering

According to the spatial autocorrelation results, optimal ANC visits showed a clustering effect in Ethiopia, meaning that in some locations, the number of ANC visits was high, and in other regions, the number of ANC visits was low. In Figs. 2 and 3, on the right and left sides of each panel, the outputs show automatically generated keys. The clustered pattern has a z-score of 14.109, meaning that there was <1% probability that it was a random coincidence. The

Table 3
Satscan analysis of optimal ANC service utilisation in Ethiopia, EMDHS 2019.

Cluster	Enumeration areas (cluster) detected	Coordinates/radius	Population (*n*)	Cases (*n*)	RR	LLR	*P*-value
1	74, 54, 81, 59, 75, 53, 57, 84, 82, 79, 83, 76, 70, 165, 80, 58, 162, 72, 77, 60, 71, 52, 56, 163, 148, 61, 78, 85, 55, 166, 73, 65, 164, 119, 161, 158, 62, 159, 22, 160, 51, 9, 63, 21, 100, 99, 66, 18, 167, 67, 8, 168, 7, 23, 20, 169, 98, 13, 2, 1, 64, 14, 4, 44, 150, 149, 87, 46, 24, 156, 29, 12, 19, 93, 5, 11, 6, 68, 17, 157, 86, 151, 262, 25, 257, 153, 146, 256, 258, 259, 154, 45, 265, 266, 261, 263, 260, 155, 152, 48, 267, 36, 269, 147, 264, 276, 268, 275, 273, 271, 112, 47, 270, 272, 3, 92, 277, 274, 279, 49, 120, 16, 280, 278, 69, 10, 50, 118, 33, 174, 171, 38, 170, 27, 35, 42, 15, 37, 101	(11.691682 N, 37.219547 E)/396.55 km	1782	953	1.67	93.79	< 0.00001
2	286, 288, 287, 296, 294, 292, 291, 285, 284, 283, 293, 295, 297, 290	(9.585229N, 41.849281E)/3.72 km	115	92	1.98	36.52	< 0.0001
3	237, 246, 243, 233, 235, 236, 242, 234, 240, 232, 241, 231, 239, 244, 238	(9.312125N, 42.112335 E)/3.34 km	150	95	1.55	14.88	< 0.001

ANC, antenatal care, EMDHS, Ethiopia Mini Demographic and Health Survey; LLR, log-likelihood ratio; RR, relative risk.

table demonstrates that the observed value was higher than the anticipated value, and the *P*-value was <0.05, indicating statistical significance. This shows that there was spatial variation in the use of optimal ANC service utilisation in Ethiopia (Fig. 2). The high clustering of optimal ANC service utilisation was reflected in the Getis-Ord General G statistic (z-score = 8.40983876678, *P*-value <0.0001; Fig. 3).

Hotspot analysis of optimal ANC service utilisation in Ethiopia

Optimised hotspot analysis was used to determine significant hot and cold spots for optimal ANC service utilisation. Due to the randomly displaced nature of clusters, a buffer of 10 km was used for significant clusters. The average distance at which a cluster has at least one neighbour was 35 km. The maximum calculated band distance from the neighbour for clustering of optimal ANC service utilisation was 187 km. In the optimised hotspot analysis (with false discovery rate correction), a total of 125 statistically significant spots (64 hotspots and 61 cold spots) were revealed. The red- and orange-coloured dots on the map indicate hotspots (higher values) of optimal ANC service utilisation, which was found in Addis Ababa, Tigray region, Southern border of Amhara, Western Benishangul and Northern border of Southern Nations Nationalities and Peoples Region (SNNPR), whereas, the blue colour indicates cold spots (lower values) of optimal ANC service utilisation, which was observed in the Somali, Amhara, Afar, Oromia, SNNPR and Gambela regions of Ethiopia (Fig. 4).

Satscan analysis

The Satscan analysis results identified 168 significant clusters (139 primary, 14 secondary and 15 tertiary clusters). The primary clusters were located at 11.691682 N and 37.219547 E, with a 396.55 km radius. Pregnant women living in the primary cluster were 67% more likely to have optimal ANC visits than women outside the cluster (relative risk = 1.67 and log-likelihood ratio = 93.79, *P*-value <0.0001; Table 3). The most likely clusters for optimal ANC service utilisation were identified in Tigray, Amhara, Addis Ababa, Benishangul and part of the Afar regions of Ethiopia (Fig. 5).

Interpolation of optimal ANC service utilisation

According to the Kriging interpolation analysis, red to yellow colours on the map of Ethiopia (Fig. 6) show areas of optimal ANC service utilisation, whereas green colours show areas of low ANC service utilisation. Optimal ANC service utilisation was shown in the Northern, Eastern, Central and Northwestern regions of Ethiopia. However, the results predict low levels of ANC service utilisation in Northeastern, Southeastern, Southern and Western regions of Ethiopia.

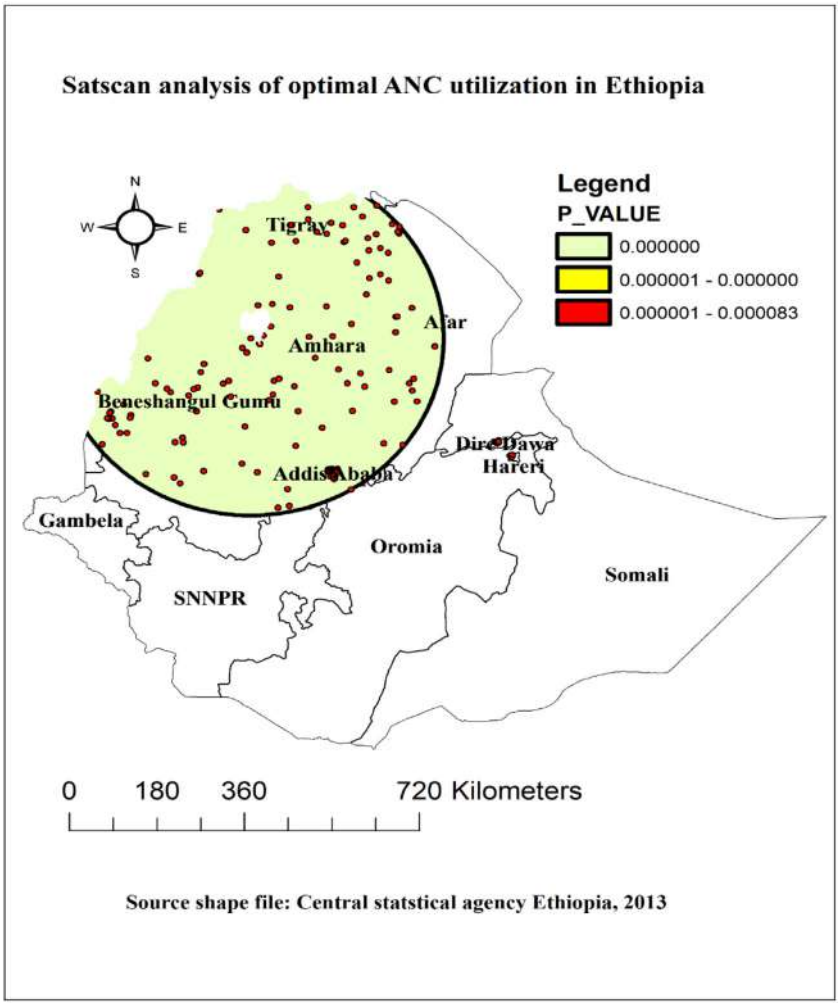

Fig. 5. Satscan analysis of optimal ANC utilisation in Ethiopia, EMDHS 2019. ANC, antenatal care, EMDHS, Ethiopia Mini Demographic and Health Survey; SNNPR, Southern Nations Nationalities and Peoples Region.

Determinants of optimal ANC service utilisation in Ethiopia

This study used survey binary logistic regression analysis to determine factors associated with optimal ANC visits in Ethiopia. Multivariable binary logistic regression analysis showed that the following factors were significantly associated with optimal ANC visits in Ethiopia: household wealth status (wealth index), the timing of the first ANC visit and region of residence. The likelihood of optimal ANC visits was reduced by 54% among women living in a household in the poorest wealth status (adjusted odds ratio [AOR] = 0.46, 95% CI: 0.25, 0.85) compared with women living in a household of the richest wealth status. The likelihood of having at least four ANC visits was 3.22 times greater for women who had their first ANC visit at ≤12 weeks' gestation (AOR = 3.22, 95% CI: 2.48, 4.15) than for women who had their first ANC visit >12 weeks' gestation. Compared with women living in Addis Ababa, the odds of optimal ANC service utilisation were reduced by 52% (AOR = 0.48, 95% CI: 0.24, 0.93), 41% (AOR = 0.59, 95% CI: 0.35, 0.99), 70% (AOR = 0.30, 95% CI: 0.14, 0.64), 62% (AOR = 0.38, 95% CI: 0.22, 0.68), 80% (AOR = 0.20, 95% CI: 0.11, 0.37) and 81% (AOR = 0.19, 95% CI: 0.12, 0.31) for women living in Afar, Oromia, Somali, SNNPR, Gambela and Harari, respectively (Table 4).

Discussion

This study revealed the prevalence, spatial patterns and determinants of optimal ANC service utilisation in Ethiopia using data from the EMDHS 2019.

The national prevalence of optimal ANC service utilisation in Ethiopia for the most recent live birth in the 5 years preceding EMDHS 2019 was found to be 41.62% (95% CI: 40.09, 43.16). This finding was lower than a study conducted in Bangladesh, where optimal ANC service utilisation was found to be 47%.[10] This discrepancy in optimal ANC service utilisation could be explained by the nature of the survey; the prevalence in the present study was calculated using the number of ANC visits in the 5 years preceding the survey, whereas the prevalence in the study from Bangladesh was calculated using the number of ANC visits in the 3 years preceding the survey. The difference in prevalence may also be because of the fact that the health system in Bangladesh has undergone several reforms, with a robust infrastructure for health services in both the public and private sectors, and significant progress has been made in improving population health metrics, such as maternal mortality and immunisation coverage.[11]

The prevalence of optimal ANC service utilisation in this study was higher in urban areas than in rural areas of Ethiopia. This

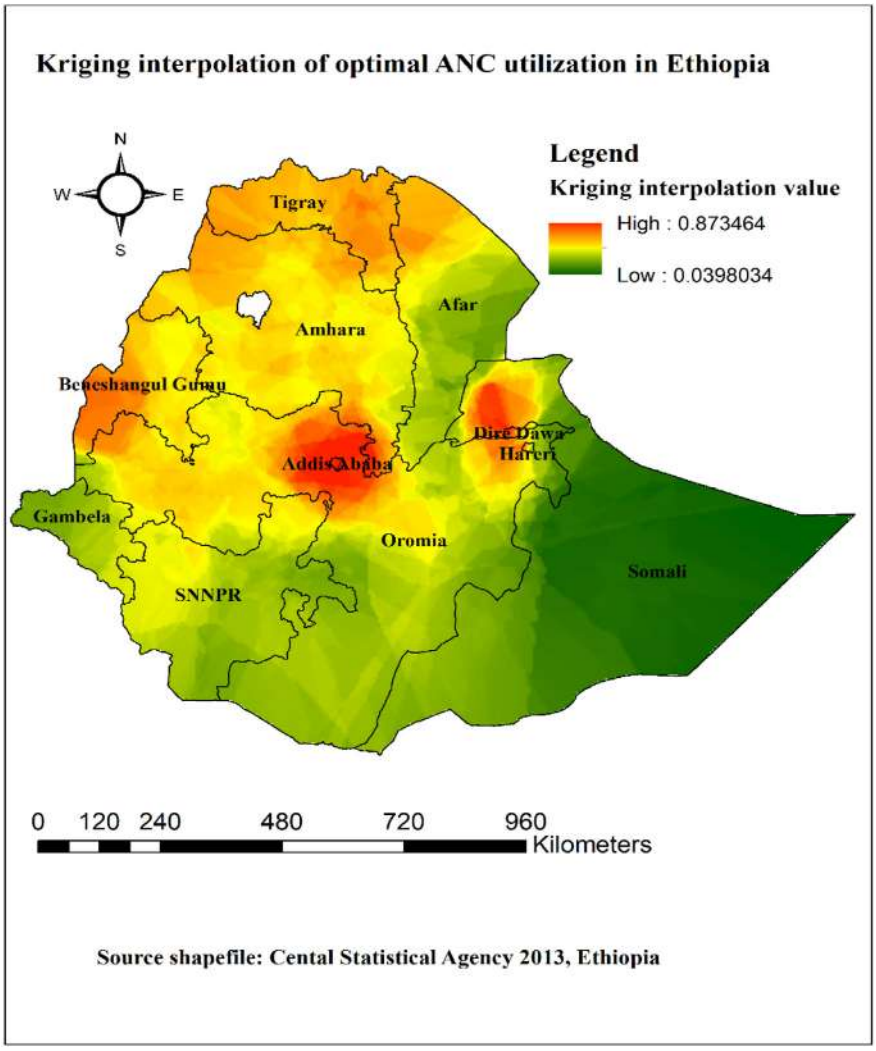

Fig. 6. Interpolation of optimal ANC utilisation in Ethiopia, EMDHS 2019. ANC, antenatal care, EMDHS, Ethiopia Mini Demographic and Health Survey; SNNPR, Southern Nations Nationalities and Peoples Region.

Table 4
Survey analysis of determinants of optimal ANC visits in Ethiopia.

Variables		Optimal ANC visits (*n*)		AOR (95% CI)
		Yes	No	
Age in years	15–19	73	173	0.62 (0.29, 1.32)
	20–24	344	464	0.74 (0.51, 1.06)
	25–29	551	674	1
	30–34	349	460	1.22 (0.88, 1.68)
	35–39	227	331	1.11 (0.78, 1.60)
	40–44	86	161	1.28 (0.79, 2.07)
	45–49	26	60	1.84 (0.64, 5.24)
Education level	Unable to read and write	615	1450	0.53 (0.25, 1.12)
	Primary	614	692	0.69 (0.32, 1.51)
	Secondary	247	129	1.39 (0.55, 3.52)
	Higher	180	52	1
Marital status	Single	6	23	0.21 (0.04, 1.16)
	Married	1570	2188	1.40 (0.42, 4.61)
	Widowed	15	29	1
	Divorced	65	83	0.89 (0.23, 3.47)
Sex of household head	Male	1315	1849	1
	Female	341	474	0.86 (0.53, 1.40)
Birth order	1	431	420	1.10 (0.62, 1.94)
	2–4	793	997	0.91 (0.66, 1.26)
	>4	432	906	1
Wealth index	Poorest	246	943	0.46 (0.25, 0.85) *
	Poorer	253	430	0.71 (0.41, 1.23)
	Middle	235	351	0.56 (0.31, 0.98) *
	Richer	259	284	0.76 (0.45, 1.294)
	Richest	663	315	1
Timing of first ANC visit	≤12 weeks	910	345	3.22 (2.5, 4.15)*
	>12 weeks	746	934	1
Residence	Urban	645	359	1
	Rural	1011	1964	0.99 (0.71, 1.40)
Region	Tigray	208	138	0.76 (0.43, 1.32)
	Afar	108	281	0.48 (0.24, 0.93) *
	Amhara	201	207	0.59 (0.33, 1.03)
	Oromia	196	295	0.59 (0.35, 0.99)*
	Somali	30	312	0.30 (0.14, 0.64)*
	Benishangul	188	183	0.97 (0.50, 1.88)
	SNNPR	146	323	0.38 (0.22, 0.68) *
	Gambela	94	244	0.20 (0.11, 0.37) *
	Harari	127	180	0.19 (0.12, 0.31)*
	Addis Ababa	43	193	1
	Dire Dawa	165	117	0.62 (0.35, 1.09)

ANC, antenatal care, AOR, adjusted odds ratio; CI, confidence interval; SNNPR: Southern Nations Nationalities and Peoples Region.
*$P < 0.05$ (significantly associated).

difference is supported by previous evidence[12,13] and may be a result of socio-economic disparities and unequal access to health care between rural and urban regions in Ethiopia. This indicates a need for designing and implementing policies and strategies focusing on the utilisation of recommended ANC services in rural areas of Ethiopia.

The results from the spatial analysis showed random variation of optimal ANC service utilisation in Ethiopia and predicted areas achieving high levels of ANC service utilisation. Optimal ANC service utilisation was predicted to be present in the Northern, Eastern, Central and Northwestern regions of Ethiopia. On the contrary, the study predicted low levels of optimal ANC service utilisation in Northeastern, Southeastern, Southern and Western regions of Ethiopia. This random variation of optimal ANC service utilisation across the country is supported by a previous study in Ethiopia.[4]

In the present study, wealth index, timing of first ANC visit and region of residence were significantly associated with optimal ANC service utilisation in Ethiopia.

Pregnant women living in a household in the poorest, poorer and middle wealth status were less likely to use a recommended ANC service compared with women living in a household of richer and richest wealth index. Previous studies support this conclusion.[14–16] Women with low socio-economic status may experience difficulties affording indirect health costs, although ANC service is free of charge. In the majority of low- and middle-income nations, the cost of travel and services have been reported as the major obstacles to receiving ANC.[17]

The likelihood of optimal ANC service utilisation was higher for women who had their first ANC visit at ≤12 weeks' gestation compared with women who had their first ANC visit at >12 weeks' gestation. This result is supported by previous studies.[18–20] To receive optimal ANC, the WHO recommends women commence ANC service utilisation early in the first trimester.[5] Pregnant women who begin ANC visits early in pregnancy receive sufficient consultations and services to identify potential pregnancy concerns and initiate appropriate treatment.[21] The timing of the first ANC visit is important for maintaining ANC services throughout pregnancy.[22]

Residents in the Afar, Oromia, Somali, SNNPR, Gambela and Harari regions were less likely to have optimal ANC service utilisation compared with residents in Addis Ababa. This result is supported by another study.[23] This may be because women living in Addis Ababa have improved access to information regarding benefits and recommendations for ANC service utilisation, which leads to frequent ANC visits.

This study used a survey regression model to identify the determinants of optimal ANC service utilisation in Ethiopia. The most

recent demographic and health survey data were used, which is a strength of this study.

The main limitation of this study was using data from a mini demographic and health survey that interviewed only half of the eligible women and clusters usually surveyed in the full demographic survey in Ethiopia. Therefore, the results in this study may not represent accurate clustering. This can also be observed by comparing the hotspot analysis of the present study with that of the study conducted by Tessema and Animut.[4]

Conclusion

Optimal ANC service utilisation showed significant spatial dependency in Ethiopia, with spatial clustering in the Northern and Northwestern regions of the country. In addition, the results from this study suggest that financial support should be considered for women living in households in the poorest wealth index, and ANC initiation should begin within the first trimester. It is recommended that targeted policies and strategies are introduced to regions with low levels of optimal ANC service utilisation.

Author statements

Ethical approval

Data used in the present study were obtained from the Measure DHS programme Web site through formal requests after registering on the Web site. It is free to use by researchers for further analysis. The EMDHS 2019 data were gathered in compliance with national and international ethical standards. Ethical clearance was provided by the Ethiopian Public-Health Institute Review Board, the National Research Ethics Review Committee at the Ministry of Science and Technology, the Institutional Review Board of ICF International and the United States Centres for Disease Control and Prevention. At the time of data collection for the EMDHS 2019, mothers and caregivers provided written informed consent, and data were collected anonymously.

Funding

None declared.

Competing interests

The authors have no conflicts of interest to declare.

Author contributions

T.T.T. conceived and designed the study, completed the analysis and drafted the manuscript. T.T.T. and K.A.A. checked the analysis and made substantial contributions to reviewing the design of the study and the drafted manuscript. Both authors critically reviewed the manuscript for important intellectual content and contributed to the final approval of the version to be submitted.

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Public Health 220 (2023) 1–9

Contents lists available at ScienceDirect

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Review Paper

The global burden and trends of four major types of heart disease, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019

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ARTICLE INFO

Article history:
Received 15 December 2022
Received in revised form
28 March 2023
Accepted 2 April 2023

Keywords:
Heart disease
Global burden
Prevalence
Deaths
DALYs

ABSTRACT

Objectives: The global burden of heart disease is severe and increasing in the coming years. This study aims to analyze the global burden of heart disease.

Study design: Rheumatic heart disease (RHD), ischemic heart disease (IHD), hypertensive heart disease (HHD), and non-rheumatic valvular heart disease (NRVHD) were selected and analyzed from the Global Burden of Disease Study 2019.

Methods: The prevalence, deaths, disability-adjusted life years and their corresponding age-standardized rates were obtained from the Global Burden of Disease Study 2019. In addition, estimated annual percentage change was calculated to better assess epidemiological trends. In addition, we performed an age-period-cohort analysis using the Nordpred package in R program to predict death trends over the next 20 years.

Results: Globally, the prevalence of four heart diseases (RHD, IHD, HHD, and NRVHD) increased by 70.5%, 103.5%, 137.9%, and 110.0% compared with 1990, respectively. The deaths cases of RHD decreased by 15.6%, whereas IHD, HHD, and NRVHD increased by 60.4%, 76.6%, and 110.6%. Compared with absolute values, their corresponding age-standardized rates only showed a slight increase trend or even decreased in some areas with high sociodemographic index. In the next 20 years, the absolute values of deaths will continue to increase, whereas their age-standardized rates of deaths will flatten out.

Conclusions: Globally, the absolute values of heart disease have increased over the past 30 years and will continue to increase over the next 20 years. Targeted prevention and control strategies and measures need to be developed and improved to reduce this burden.

Introduction

Recent years have witnessed a spurt of progress in non-communicable diseases (NCDs), which account for more than seven-tenths of global deaths and NCDs have become one of the major global burden of disease.[1] As an important part of NCDs, heart disease has long been recognized as the leading cause of death and disability throughout the world.[2,3] Over the past 30 years, heart disease remains the leading killer of human health despite breakthroughs in the diagnosis and treatment, especially in some low- and middle-income countries.[4,5] According to Global Burden of Disease Study 2019 (GBD2019) estimates, among the 523.2 million cardiovascular disease patients, the prevalence cases of rheumatic heart disease (RHD), ischemic heart disease (IHD), hypertensive heart disease (HHD), and non-rheumatic valvular heart disease (NRVHD) were 40.5 million, 197.2 million, 18.6 million, and 32.6 million respectively.[6] In addition, with the population growth and aging, the absolute number of crowds with heart disease will continue to increase.[7]

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https://doi.org/10.1016/j.puhe.2023.04.005
0033-3506/

The GBD2019 provides assessments of the four heart diseases from the perspective of location, age, sex, cause, and risk factors.[8] In this study, the data obtained from GBD2019 were applied to comprehensive analysis of the global burden of four heart diseases at the national, regional, and global levels. The increasing number of heart disease patients and healthcare costs suggested that we need to improve and optimize current strategies for preventing heart disease to avoid unnecessary waste of medical resources. Previous studies had only explored the global burden of individual heart diseases.[9–13] But there were many commonalities between different types of heart disease, such as target organs, risk factors, and prevention methods. With this in mind, the present study attempted to explore the commonalities and differences of the epidemiological patterns of the four types of heart disease to facilitate the comprehensive prevention and treatment in each region. We hope that this article can provide a basis for future research on heart disease and help countries and regions formulate public health policies to reduce the rising financial and health burdens caused by heart disease.

Methods

Study data

The four heart diseases data, including the numbers of prevalence, deaths, disability-adjusted life years (DALYs), and age-standardized rates of prevalence (ASPR), age-standardized rates of deaths (ASDR), and age-standardized rates of DALYs (ASDALYs) were obtained from GBD2019 (http://ghdx.healthdata.org/gbd-results-tool).[14] The description of four heart diseases in this study followed the sequence of appearance in Global Burden of Disease (GBD) database, namely RHD, IHD, HHD, and NRVHD. Sociodemographic index (SDI) was a combination of Lag Distributed Income per Capita and Mean Education for Those Age 15 and Older and Total Fertility Rate Under 25, which was closely associated with the global burden of disease.[15,16] GBD2019 divided the world into 21 regions based on epidemiological and geographical factors. In addition, the Human Development Index (HDI) of 193 countries and regions was obtained in the 2019 human development report (http://hdr.undp.org/en/composite/trends), whereas the GBD database can obtain the health data of 204 countries and regions around the world. So to make sense of the analysis, we excluded 11 countries and regions where HDI data were not available. The 11 excluded countries and regions were the United States Virgin Islands, Tokelau, American Samoa, Taiwan (Province of China), Northern Mariana Islands, Puerto Rico, Guam, Niue, Greenland, Cook Islands, and Bermuda.

Statistical analysis

In this study, the prevalence, deaths, DALYs, and corresponding age-standardized rates (ASRs) of heart disease were used to analysis the burden. Suppose a_i represented the specific-age rate for the ith age group, A represented the total number of age groups, and w_i represented the weight for the ith age group, which was calculated from the GBD2019 world standard population. Then the truncated ASR calculation formula was as follows:

$$ASR = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_1} \times 100000$$

In addition, a widely accepted indicator, estimated annual percentage change (EAPC), was introduced to better demonstrate temporal trends in heart disease.[17] EAPC was used to describe and evaluate the change trend of ASR in a given period, which was calculated by fitting a regression line to the natural logarithm of the ASR.[18] EAPC was calculated as follows:

$$y = \alpha + \beta x + \varepsilon$$

$$EAPC = 100 \times (e^{\beta} - 1)$$

where y = ln (ASR), and x = calendar year.

The positive and negative values of EAPC correspond to the increase and decrease of the change trend, respectively. In addition, we conducted correlation analysis on EAPC and ASR in 1990 and ASR and HDI both in 1990 and 2019. Then we showed the global burden of heart disease through maps, percentage accumulation graph, and correlation analysis. The R indices and P values for the relationship between variables were explored by Pearson correlation analysis with the utilization of the R version of 4.2.1. Statistical significance was considered when the P value was <0.05. In addition, we performed an age-period-cohort (APC) analysis using the Bayesian age-period-cohort (BAPC) and Nordpred packages in the R program to predict the numbers and rates of deaths due to heart disease from 2020 to 2039, taking into account changes in population size and age structure, which has been proved in previous researches to be able to predict the trend of disease sufficiently.[19] To verify the stability of the prediction results, the Bayesian APC model ensemble nested Laplace Approximation (INLA) was further applied, and the sensitivity analysis was performed using the BAPC and INLA packages in R.[20]

Results

Prevalence, deaths, and DALYs of heart disease

According to GBD2019 estimates, the prevalence cases of four heart diseases in 2019 were 40.5 (95% uncertainty interval [UI]: 32.1–50.1), 197.2 (95% UI: 177.7–219.5), 18.6 (95% UI: 13.5–24.9), and 32.6 (95% UI: 30.9–34.3) million, respectively (Fig. 1, Table 1). The four heart diseases vary in age, with the highest prevalence cases of RHD occurring between 20 and 30 years old, whereas IHD, HHD, and NRVHD occur between 65 and 75 years old (Fig. 2A). Compared with the female group, the male group had a severer burden of all four heart diseases, which was particularly obvious in the DALYs (Fig. 2D–F).

In terms of regional analysis, the burden in low and middle SDI regions was higher than that in high SDI regions both in absolute values and percentage changes (Fig. 3, Figs. S4–S5). The prevalence of RHD and IHD was predominant in the low and middle SDI regions, whereas IHD and NRVHD were predominant in high SDI regions. The most prominent prevalence cases of RHD were in South Asia, East Asia, and Eastern Sub-Saharan Africa, among which India (9.7 million, 95% UI: 7.2–11.9 million), China (6.0 million, 95% UI: 4.9–7.4 million), and Brazil (2.1 million, 95% UI: 1.6–2.6 million) were the most serious (Fig. 1A, Table S5). IHD, HHD, and NRVHD all had the highest absolute values of prevalence in East Asia, whereas Oceania had the lowest (Fig. 3B). The highest prevalence cases of IHD and HHD were estimated in China, with 45.20 million (95% UI: 39.1–52.5 million) and 7.9 million (95% UI: 5.7–10.8 million), respectively. The highest estimates of NRVHD prevalence were observed in the United States of America, with a value of 7.7 million (95% UI: 7.4–8.1 million). The heart disease burden of deaths, DALYs, and ASRs was described in the supplementary materials.

Temporal trends of prevalence, deaths, and DALYs from 1990 to 2019

From 1990 to 2019, globally, there was a significant increase in the prevalence of heart disease, with HHD growing the fastest at 137.9%. In terms of deaths and DALYs, RHD was the only one that showed a decreasing trend, whereas the others all showed varying degrees of increase. The most pronounced increase in RHD

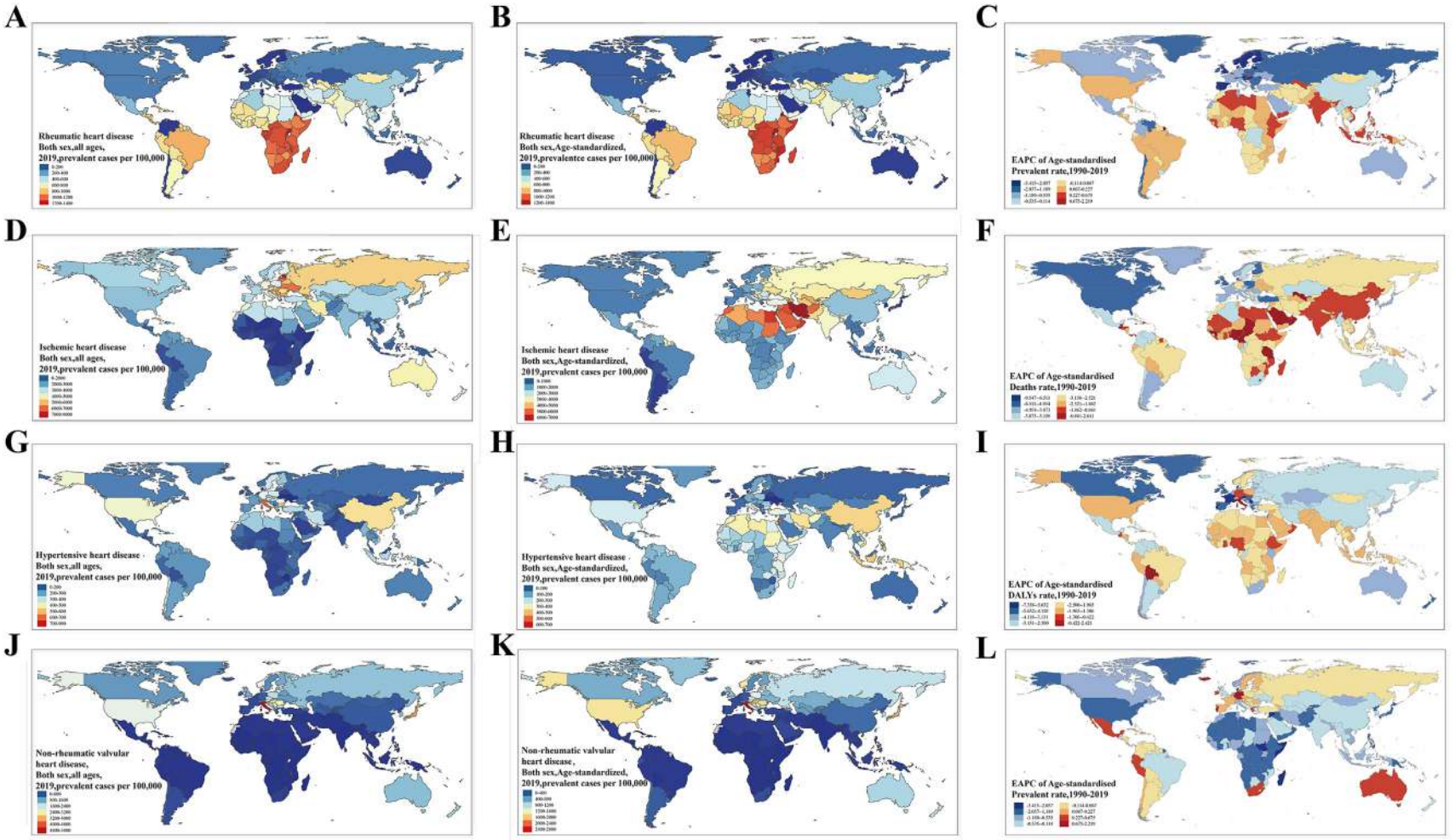

Fig. 1. The global prevalence burden of RHD, IHD, HHD, and NRVHD by countries and territories for both sexes combined. (A–C) The absolute numbers of prevalence, ASPR, and EAPC of RHD in 2019. (D–F) The absolute numbers of prevalence, ASPR, and EAPC of IHD in 2019. (G–I) The absolute numbers of prevalence, ASPR, and EAPC of HHD in 2019. (J–L) The absolute numbers of prevalence, ASPR, and EAPC of NRVHD in 2019. RHD, rheumatic heart disease; IHD, ischemic heart disease; HHD, hypertensive heart disease; NRVHD, non-rheumatic valvular heart disease; ASPR, age-standardized prevalence rate; EAPC, estimated annual percentage change.

prevalence was observed in Western Sub-Saharan Africa (162.1%), whereas the highest increase in IHD, HHD, and NRVHD occurred in Andean Latin America, with an increase of 183.5%, 253.5%, and 1392.8%, respectively (Tables S1–S4). At the national level, United Arab Emirates was observed with the largest increase in the prevalence of RHD, IHD, and HHD, with 494.6%, 907.6%, and 883.9%, respectively. The absolute number of NRVHD prevalence increased rapidly in most countries, especially in Cyprus (2747.6%), Ecuador (2249.9%), and Iceland (1672.3%). However, this rapid growth trend was not seen in ASPR, ASDR, and ASDALYs. Over the 30-year period, the situation for ASR of heart disease has improved and fell in most areas. Temporal trends of deaths, DALYs, ASPR, ASDR, and ASDALYs in heart disease were detailed in the supplement.

From 1990 to 2019, only RHD deaths and DALYs decreased, whereas the rest showed a significant increase trend (Tables S1–S3). To better observe the change trend, we calculated the EAPC values for the prevalence of four heart diseases, which were 0.57 (95% UI: 0.50–0.63), −0.20 (95% UI: −0.22 to 0.18), 0.17 (95% UI: 0.15–0.18), 0.09 (95% UI: 0.01–0.17), respectively (Tables S1–S3). It was noteworthy that the EAPC of NRVHD males was significantly higher than that of females (Table S4). Globally, Oceania (0.34, 95% UI: 0.27–0.41) and Sub-Saharan Africa (0.38, 95% UI: 0.32–0.44) had the largest EAPC value of RHD and IHD prevalence. Andean Latin America was found to have the largest EAPC value of HHD and NRVHD prevalence, with values of 0.43 (95% UI: 0.37–0.50) and 5.88 (95% UI: 5.30–6.46), respectively. In addition, EAPC values for death and DALYs were shown in the supplementary materials.

Factors correlated with the prevalence, deaths, and DALYs of heart disease

The risk factor data were obtained from the GBD2019 database, mainly including metabolic risk, behavioral risk, and environmental/occupational risk. Generally, high systolic blood of metabolic risks was the greatest distributor of DALYs of all these heart diseases (RHD, IHD, HHD, and NRVHD) globally, with the values of 29.7 (95% UI: 20.3–41.9), 1881.3 (95% UI: 1697.8–2054.7), 268.2 (95% UI: 204.6–298.1), 8.0 (95% UI: 6.1–10.2) per 100,000, respectively (Table S8). For RHD, the risk attributed to high systolic blood in low and middle SDI regions was significantly higher than that in high SDI region, with the variation as 2.2-fold. In addition to high systolic blood pressure, diet high in sodium (4.7 per 100,000 person, 95% UI: 1.2–11.2) and lead exposure (2.6 per 100,000 person, 95% UI: 1.3–4.6) also increased the DALYs of RHD. As for IHD, high low-density lipoprotein cholesterol, high fasting plasma glucose, and tobacco were also major risk factors. High systolic blood pressure was the most important risk factor for HHD and NRVHD. In addition, diet high in sodium and lead exposure were also observed as risk factors (Table S8). The association of ASR with EAPC and HDI for four types of heart diseases was described in the supplement.

Predictions of deaths and ASDR of heart disease from 2020 to 2039

Based on the GBD database and world standard population data, we further predicted the number of deaths and ASDR of heart disease over the next 20 years (Fig. 4, Fig. S10). Deaths of IHD, HHD, and NRVHD will continue to increase over the next 20 years for both males and females, whereas RHD is expected to level off (Fig. 4A, C, E, G). ASDR for all four heart diseases showed a slight decline over the next 20 years, compared with the continued increase in deaths (Fig. 4B, D, F, H). In 2039, the total number of deaths from all four heart diseases will increase to 310,258.8, 15.8 million, 1.8 million, and 265,963.1, respectively (Table S8). With the

Table 1
The prevalence, deaths, DALYs and corresponding ASR of heart disease in 2019 as well as the EAPC from 1990 to 2019 at the global level.

Disease	Prevalence (95% uncertainty interval)			Deaths (95% uncertainty interval)			DALYs (95% uncertainty interval)		
	Counts, 2019 No. × 10^6	Age-standardized estimates 2019 No. × 10^2	EAPC No.	Counts, 2019 No. × 10^4	Age-standardized estimates 2019 No.	EAPC No.	Counts, 2019 No. × 10^6	Age-standardized estimates 2019 No. × 10	EAPC No.
RHD	40.50 (32.05 to 50.06)	5.14 (4.05 to 6.36)	0.57 (0.50 to 0.63)	30.57 (25.92 to 34.05)	3.85 (3.29 to 4.29)	−2.98 (−3.03 to −2.94)	10.67 (9.21 to 12.12)	13.29 (11.50 to 15.03)	−2.7 (−2.75 to −2.65)
IHD	197.22 (177.69 to 219.50)	24.21 (21.81 to 26.93)	−0.20 (−0.22 to −0.18)	913.78 (839.57 to 974.36)	11.8 (10.78 to 12.59)	−1.36 (−1.39 to −1.32)	182.03 (170.21 to 193.5)	224.35 (209.87 to 238.50)	−1.26 (−1.30 to −1.21)
HHD	18.60 (13.54 to 24.90)	2.34 (1.71 to 3.13)	0.17 (0.15 to 0.18)	115.67 (85.98 to 127.86)	15.16 (11.20 to 16.75)	−0.74 (−0.91 to −0.57)	21.51 (16.40 to 23.90)	26.82 (20.46 to 29.81)	−1.02 (−1.18 to −0.86)
NRVHD	32.60 (30.86 to 34.34)	4.00 (3.78 to 4.21)	0.09 (0.01 to 0.17)	16.41 (14.01 to 1796)	2.25 (1.89 to 2.47)	−0.32 (−0.39 to −0.25)	2.79 (2.52 to 3.13)	3.59 (3.23 to 4.02)	−0.80 (−0.87 to −0.74)

DALYs, disability-adjusted life years; IHD, ischemic heart disease; HHD, hypertensive heart disease; NRVHD, non-rheumatic valvular heart disease.

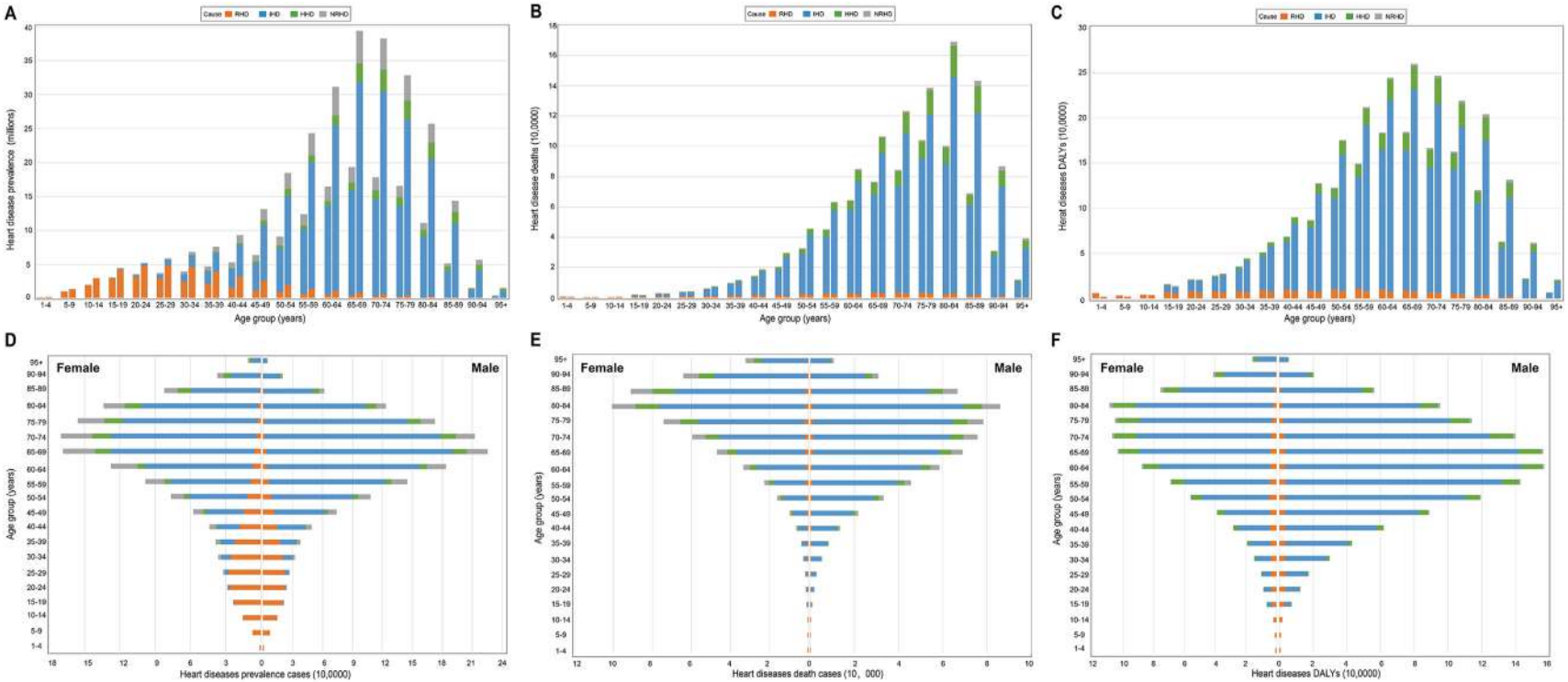

Fig. 2. Global prevalence, deaths, and DALYs cases of RHD, IHD, HHD, and NRVHD stratified by GBD age group and sex in 2019. (A–C) The prevalence, deaths, and DALYs of four heart diseases stratified by GBD age group. (D–F) The prevalence, deaths, and DALYs of four heart diseases stratified by both age and sex. RHD, rheumatic heart disease; IHD, ischemic heart disease; HHD, hypertensive heart disease; NRVHD, non-rheumatic valvular heart disease; DALYs, disability-adjusted life years; GBD, the Global Burden of Disease.

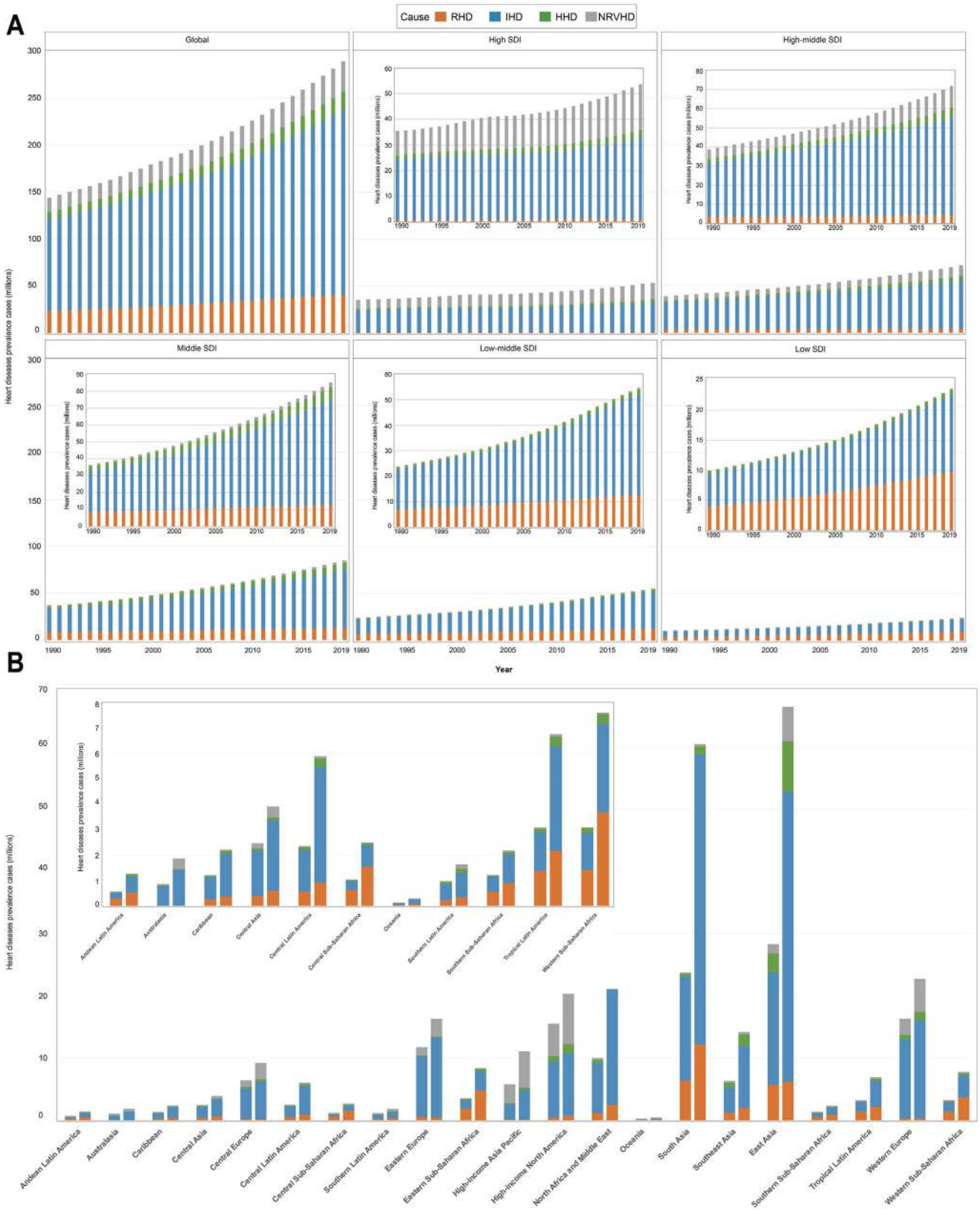

Fig. 3. Global prevalence cases of four heart diseases by SDI areas and 21 GBD regions for both sexes combined. (A) The prevalence cases of four heart diseases by five SDI regions, from 1990 to 2019. (B) Prevalence cases of four heart diseases by 21 GBD regions, in 1990 and 2019. For each group, the left column shows case data in 1990, and the right column shows data in 2019. Certain regions are magnified to the top-right of the panel. SDI, sociodemographic index; GBD, the Global Burden of Disease.

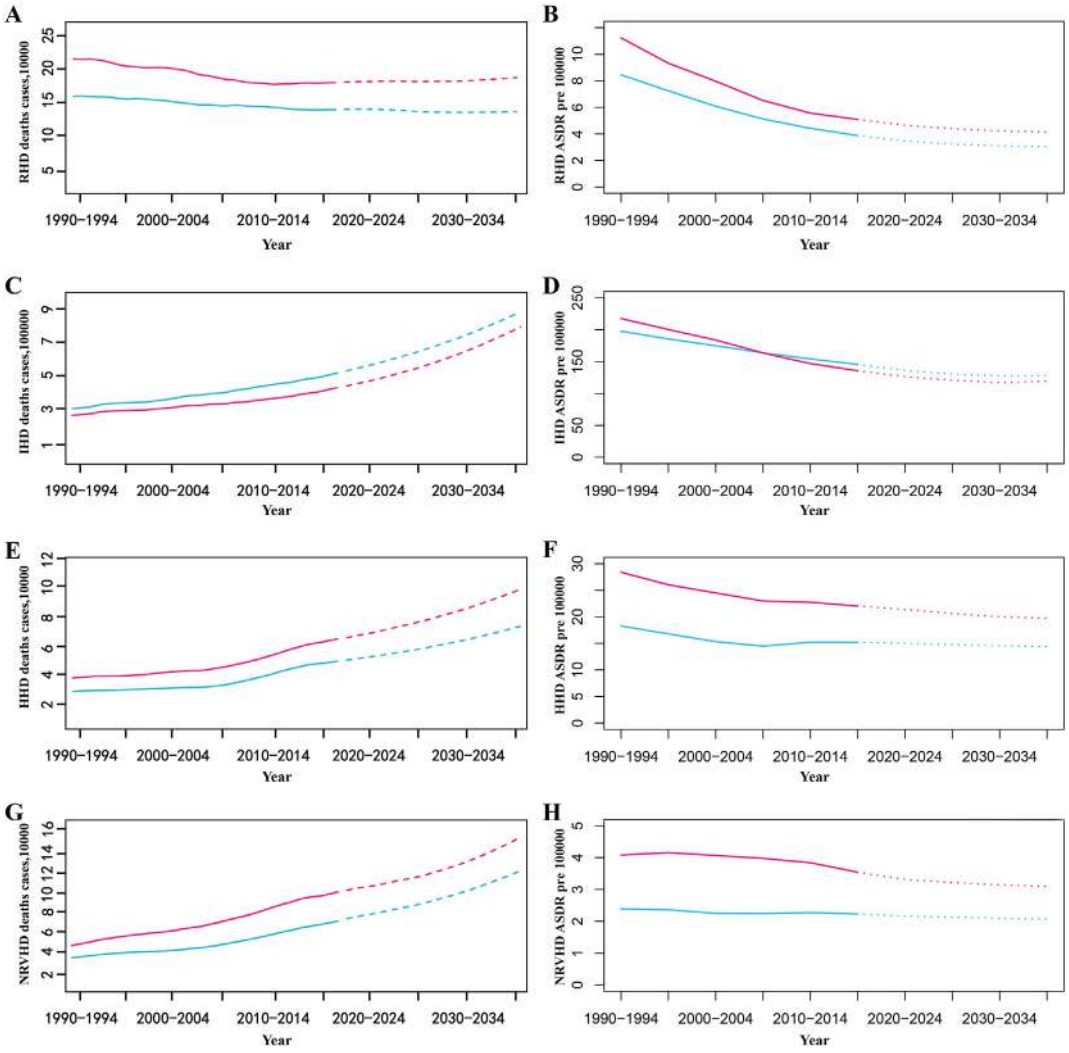

Fig. 4. Trends in heart disease death and ASDR by sex at the global level: observed (solid lines) and predicted rates (dashed lines). (A) RHD deaths. (B) RHD ASDR. (C) IHD deaths. (D) IHD ASDR. (E) HHD deaths. (F) HHD ASDR. (G) NRVHD deaths. (H) NRVHD ASDR. RHD, rheumatic heart disease; IHD, ischemic heart disease; HHD, hypertensive heart disease; NRVHD, non-rheumatic valvular heart disease; ASDR, age-standardized death rate.

exception of IHD, females continue to have a higher risk of death than males, as will ASDR. Women's ASDR fell a little faster over the next 20 years so that the difference between men and women gradually narrowed. However, for both males and females, the decline in ASDR has gradually slowed to a plateau.

Discussion

Our study provides the first comprehensive analysis of the global burden of four heart diseases and predicts the burden of death over the next 20 years. With the population growth and aging, the burden of four heart diseases has been rising, especially the absolute number.[21] From 1990 to 2019, the prevalence cases of the four heart diseases had increased significantly by 70.5%, 103.5%, 137.9%, and 110.0%, respectively. Compared with absolute values, ASRs perform relatively smoothly, even decreasing. Although the ASPR, ASDR, and ASDALYs of all four heart diseases moderated, this did not represent a reduction in the burden of heart disease. According to World Population Prospects 2019 reported by the United Nations, the world population in 2019 was 7.7 billion, an increase of 44.8% compared with 5.3 billion in 1990.[22] The substantial growth of the world population base has brought severe challenges to the economy and medical treatment, and the situation will be more and more serious.[23] In addition, there were significant regional and national differences in the global epidemiological distribution of the four heart diseases, which requires that each region should take into account the specific local conditions when developing primary and secondary prevention strategies for heart diseases.

According to WHO's 2019 Global Health Estimates, heart disease remained the leading threat to human health globally, and the DALYs caused by heart disease had also increased significantly.[24] Globally, only RHD deaths and DALYs decreased. This decreasing trend may be attributed to prevention strategies over the past few decades, such as reducing the causes of rheumatic fever, improving sanitation, and international cooperation.[25,26] The epidemiological indicators of IHD, HHD, and NRVHD showed an obvious increase trend, especially the prevalence cases increased more than twice. In contrast, their ASPR increased slowly, and ASDR and ASDALYs even showed a significant decreasing trend. This phenomenon indicates that population growth and aging may play an important role in the prevalence, deaths, and DALYs increase of heart disease.[27] In addition, our study found that males had a significantly higher risk of IHD than females, which may be related to the protective effect of estrogen on the heart.[28,29] However, this protective effect was not

seen in the other three types of heart diseases. RHD is the sequela of one or more episodes of acute rheumatic fever, which causes cumulative heart valve damage. Carapetis et al.[30] reported that although RHD can occur in children, its peak incidence occurs in adulthood, which was consistent with our findings. In recent years, the deaths and DALYs of the four heart diseases are mainly attributed to metabolic risk. Rapid economic development and urbanization have changed diets in developed countries, which have contributed significantly to the increase in metabolic diseases, especially in the regions where prevention measures are lagging behind.[27] In addition, smoking, obesity, and unhealthy diet were also important risk factors for all heart diseases. Males were more likely to be exposed to these risk factors than females, which may explain part of the gender difference in heart disease distribution.[31] Studies of ASR have found a decline in the burden of heart disease in many countries and regions. This downward trend may be attributed to the increased coverage of the health care system, the implementation of related secondary prevention measures, and the optimization of community health environment.[32] Effective anti-smoking measures and national health promotion strategies have also helped curb the prevalence of heart disease.[33,34]

As for ASRs, the decline was concentrated in some high and middle SDI regions, indicating that social economic level is closely related to the distribution of heart disease. The study found that the prevalence of heart disease continued to worsen in some poor countries. The reasons for this phenomenon may be because of the uneven distribution of medical resources, poor housing environment, and backward education level.[35,36] South Asia was observed to have the most severe burden of RHD, especially in terms of deaths and DALYs, accounting for more than half of the global total. The prevalence, deaths, and DALYs of RHD were mainly concentrated in China and India, which may be because of the huge population base.[37,38] Faced with such grim figures, it was high time that the health departments in these countries take some targeted measures, such as universal health education, controlling the tobacco epidemic, and strengthening residents' exercise.[39,40] Some developed countries have implemented effective measures to prevent and control heart disease, in contrast to some developing countries such as East and South Asia where high burdens of IHD and HHD are still observed. In these areas, some secondary prevention measures for obesity, diabetes, smoking, and other risk factors are necessary in the long run, although they do not have quick results in the short term.[41–43] The deaths of IHD increased in most regions, with declines in a few high SDI regions, such as Western Europe and Australasia. Similar to previous studies,[44] we also found an increasing burden of IHD and HHD in regions affected by population aging, such as Ethiopia. A similar pattern of growth has also been observed in sub-Saharan Africa.[42] The HHD prevalence cases in middle SDI regions such as Andean Latin America and Tropical Latin America were found a significant increase, whereas HHD deaths in high SDI regions such as Eastern Europe and high-income North America increased the fastest. Although the current burden of heart disease in these high-income areas is not severe, the high growth trend behind this has prompted local health authorities to pay attention. The burden of NRVHD was mainly concentrated in high SDI regions, such as Western Europe and high-income North America, whereas the burden of middle and low SDI regions, such as Oceania and Central Sub-Saharan Africa, was relatively low. Higher life expectancy in developed countries and underlying genetic factors may partly explain this distribution.[45] In addition, as the only effective treatment at present, the technical level and acceptance rate of aortic valve replacement also affect the prevalence of NRVHD.[46] Therefore, in addition to routine secondary prevention strategies, some high-income countries should strengthen monitoring of heart valve health.

For all that, this study has the general limitations of all studies that use GBD as a data source.[6,32] First, although GBD adopts reliable statistical methods, some systematic biases, such as the authenticity of health data acquisition and the rationality of data reprocessing, are still unavoidable. Second, although civil registration system and hospital death certificates are important sources of death data, their coverage is limited and cannot fully reflect the real death data. Moreover, this study only involves country-level analysis; however, country-level data may mask large differences between different regions within countries. Finally, because of limited data access, we are unable to analyze from the perspective of the environment, the individual, and the health care system and to take into account the interactions between co-existing diseases. In spite of this, our study is the first comprehensive analysis of the global epidemiological distribution of four major heart diseases, which can provide a basis for subsequent research and the formulation of relevant policies.

Conclusion

In summary, the study conducted a comprehensive analysis of the global burden of four heart diseases and found a significant increasing trend. Targeted measures need to be developed to reduce the negative financial and health impact. Our findings highlight the need to develop and refine secondary prevention strategies, as well as improve sanitation and explore effective treatments, in low and middle SDI regions. At the same time, some specific high-income countries should also pay more attention to the early diagnosis and prevention of NRVHD.

Author statements

Acknowledgments

The authors highly appreciate the work by the GBD2019 collaborators.

Ethical approval

No ethical approval was required for this study.

Funding

This work was supported by grants from the National Natural Science Foundation of China (81872683), the Scientific Research Promotion Plan of Anhui Medical University (2022xkjT005), and the Peak Discipline Construction Project of Anhui Medical University (2022080009).

Competing interests

The authors have declared no conflict of interests.

Data availability

All data used in this research are publicly available at http://ghdx.healthdata.org/gbd-results-tool.

Author contributions

G.-H.Y. contributed to conceptualization, data curation, formal analysis, methodology, software, visualization, and writing an original draft. X.-Y.G., Y.X., H.-Y.S., and Y.-Q.L. contributed to methodology, software, and visualization. W.-Q.H., D.-T.H., Q.-Q.Z., and C.-X.Z. contributed to conceptualization, data curation,

validation, software, and visualization. L.-L.W. and Y.-H.W. contributed to data curation and supervision. T.-Y.Z. and Z.-Y.Y. contributed to data curation and supervision. F.W. contributed to software and reviewing and editing the article. Y.-F.Z. contributed to conceptualization, methodology, and reviewing and editing the article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.04.005.

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Public Health 220 (2023) 165–171

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

The risk of incident depression when assessed with the Lifestyle and Well-Being Index

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ARTICLE INFO

Article history:
Received 7 December 2022
Received in revised form
5 April 2023
Accepted 4 May 2023

Keywords:
Lifestyle habits
Precision medicine
Unipolar depression
Depressive disorder

ABSTRACT

Objectives: Novel findings indicate links between unhealthy lifestyles and depression based on active inflammatory processes. Thus, identifying participants with poor habits could reveal differences in trends of incident depression. This study aimed to examine the association between an objective lifestyle assessment, as measured by the Lifestyle and Well-Being Index (LWB-I), and incident depression in healthy participants of a Spanish cohort.

Study design: This was a longitudinal analysis of a subsample of 10,063 participants from the *Seguimiento Universidad de Navarra* cohort study.

Methods: Group comparisons and Cox proportional hazard models were conducted using the LWB-I, which categorizes the sample into groups with healthy and unhealthy lifestyles and well-being. The main outcome was incident depression as well as secondary outcomes.

Results: Those classified to the transition category of LWB-I were associated with a hazard ratio of 0.67 (95% confidence interval: 0.52–0.87), and those in the excellent category showed a hazard ratio of 0.44 (95% confidence interval: 0.33–0.58), which in both groups reflects a significantly lower risk of incident depression compared with the group including those classified in the poor LWB-I level. Moreover, the available sensitivity analyses concerning time of depression diagnosis or antidepressant treatment further supported the role of nutrition and physical activity on incident depression. Interestingly, throughout the follow-up, incident depression was inversely related to healthier daily habits as measured by the LWB-I.

Conclusions: A global assessment of lifestyles such as the LWB-I provides valuable insight into the complex relationship between lifestyle factors and their link to depression risk.

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https://doi.org/10.1016/j.puhe.2023.05.002

Introduction

Depression is a complex disease with diverse risk factors that are only partially uncovered.[1] A recent summary of evidence highlights the links between these risk factors and proinflammatory phenomena occurring in various organs within and beyond the central nervous system.[2] Similar chronic low-grade inflammation processes are present in cardiovascular diseases (CVDs)[3] and are known to be related to nutrition and physical activity (PA) among other lifestyle habits.[4] For CVD, healthy lifestyles form the basis of its prevention, and now these risk factors could serve the same purpose for depression as an important noncommunicable disease.[5,6]

To this day, no single biological mechanism is known to completely explain the features observed in patients with depression.[7] However, within the most accepted hypothesis of disease, signs of active inflammatory processes have been found.[8] The main features in patients with depression are monoamine neurotransmitter dysfunction, alterations of the brain-derived neurotrophic factor (BDNF), and an improper response to stress.[2,7] Monoamines are primarily derived from B-complex vitamins; thus, it has been proposed that ensuring adequate levels of these nutrients could also promote adequate neurotransmitter activity.[9,10] These patients also present an inability to establish new neuronal synapses because of low BDNF levels.[11,12] In this regard, vitamin A, vitamin B12, and an active lifestyle have been related to improved BDNF release and activity and provide a basis for the role of daily habits in this disease.[11,12] Finally, chronic stress is common in patients with depression and is known to alter sleep patterns and promote the formation of inflammatory molecules in the gut.[2] These molecules are short-chain fatty acids and are produced by specific strains of bacteria in the gut that flourish in patients with sedentary habits and unhealthy diets.[13] Under these conditions, short-chain fatty acids flow into the bloodstream and have inflammatory qualities in the brain as well as the peripheral nervous system.[2,7] In summary, inflammation is highly relevant for depression and thus could signal to early pathological disturbances in patients with poor lifestyles.

Given the potential implications of lifestyles in depression, a precision medicine framework that can characterize an individual's risk behaviors could help identify those at risk of developing depression.[5,14,15] In this regard, the Lifestyle and Well-Being Index (LWB-I) was recently conceptualized to stratify individuals into three health and well-being groups based on socio-economic, anthropometric, history of diseases, and, more importantly, lifestyle habits.[16] By quantitatively pondering 12 items, which include diet, PA, smoking, and sleep, among others, the LWB-I allocates individuals to three different states of increasingly better lifestyles and well-being. Thus, an assessment of lifestyle and well-being features may be linked to depression incidence stemming from the previously mentioned inflammatory mechanisms.[16]

The aim of this investigation was to longitudinally evaluate this LWB-I in association with incident depression in a subsample of the *Seguimiento Universidad de Navarra* (SUN) study.

Methods

Study population

This was a longitudinal analysis of a subsample of the SUN cohort study, which is a prospective, multipurpose, dynamic cohort, that began recruitment in 1999 with the purpose of establishing associations between lifestyles and chronic conditions.[17] Briefly, university graduates are sent an invitation letter with a description of the cohort, a baseline questionnaire, and a prepaid return package for participants to submit their completed questionnaire. Furthermore, data collection is obtained through subsequent standardized questionnaires every 2 years. The submission of the baseline questionnaire through national post is considered informed consent. These methods and the study protocol were approved by the Ethics Committee of the University of Navarra (code 2001/30) in accordance with the Declaration of Helsinki.

Selected participants were observed starting at baseline, which was defined as the fourth year of follow-up until the occurrence of the outcome or until the participant was censored due to causes other than the outcome. From the SUN cohort participants ($n = 22{,}894$), the following selection criteria were applied to ensure complete records on the exposure and outcome. Participants were required to provide complete information on the 12 items of the LWB-I at baseline ($n = 7819$ exclusions). Prevalent cases of depression (including cases occurring before the first year after baseline), prevalent use antidepressant therapy or hypnotics ($n = 2960$), and prevalent CVD (including coronary heart disease, stroke, and thromboembolic events), diabetes, and cancer ($n = 846$) were excluded. As dietary intake represented a critical component of the LWB-I, implausible energy intakes or intakes in the top 99th and bottom first percentile for their corresponding sex were excluded ($n = 268$). Finally, participants who did not provide follow-up information 2 years and 9 months after baseline ($n = 938$) were excluded. Thus, these analyses were conducted on a total of 10,063 participants (retention rate of 91.5%).

The LWB-I

Based on 12 anthropometric, sociodemographic, and lifestyle items, the LWB-I[12] estimates the quality of individual habits to calculate a single continuous score ranging from 0 (unhealthy lifestyle and well-being) to 100 (excellent lifestyles and well-being). The items and coding are (1) sex (male, female), (2) age (years), (3) body mass index (in kg/m^2 categorized as underweight <18.5 kg/m^2, normal weight 18.5–24.9 kg/m^2, overweight 25.0–29.9 kg/m^2, and obesity >30.0 kg/m^2), (4) family history of diseases for either parent (identifying the presence of obesity, diabetes, cancer, or CVD in one or both of the participants' parents ranging from 0 to 2), (5) pre-existing medical conditions (identifying the presence of diabetes, hypertension, or hypercholesterolemia; ranging from 0 to 3), (6) smoking habits (describing never, current, and former smokers of at least 100 cigarettes), (7) presence of insomnia (identifying participants without insomnia and currently experiencing insomnia or having at some point experienced insomnia), (8) leisure-time PA (categorized as exerting <2.5 h/wk of moderate intensity activities, exerting the recommended 2.5–5 h/wk of moderate/vigorous intensity according to the World Health Organization, and those exceeding the 5 h/wk of leisure-time PA), (9) fruits and vegetable consumption (continuous variable presented as servings/day), (10) sugary products (consisting of sodas, including "low calorie," sugar, marmalade, and honey; categorized as null consumption, <1 servings/day, and those consuming one or more serving daily), finally (11) an item evaluating the presence of sadness or diminished mood in the prior 4 weeks "*Have you felt downhearted and blue?*" and (12) an item evaluating tiredness in the previous four weeks "*Did you feel tired?*" (both coded in the categories of "*All of the time*," "*Most of the time*," "*A good bit of the time*," "*Some of the time*," "*A little bit of the time*," or "*None of the time*"). Weighting of variables was done using the coefficients of the prior publication, which are added to a constant of 98.1 points. In addition, the authors described a categorization method based on two systematically defined cut-points; participants with scores <80 were categorized as having *poor* LWB, from

80 to 86 (including these integers) participants were *transitioning* LWB, and those scoring >86 points were in the *excellent* LWB group.[12]

Outcome assessment

Within the SUN cohort, validation of self-reported incident depression was conducted in a separate study relying on a psychiatric evaluation.[14] For the present study, three definitions of increasing stringency for incident depression were used: (1) a newly diagnosed report of depression, (2) initiation of antidepressant therapy even if depression was not reported by participants, and (3) a self-reported diagnosis of depression accompanied by antidepressant therapy (earliest time were criteria 1 and 2 were fulfilled).

Statistical analyses

The description measures were means and standard deviations for normally distributed data, using analysis of variance, and percentages for categorical data, analyzed using Chi-squared distributions. Cox proportional hazard models were performed with time zero defined as year 4 of follow-up, until the occurrence of the outcomes or censorship. Models were adjusted for working hours-day, cigarette packs-year, alcohol consumption (excluding wine), total daily energy intake in model 1, and model 2 was additionally adjusted for supplement intake, competitiveness, psychological tension, and dependence. Nelson–Allen curves of incident cases were obtained and adjusted for the list of confounders of model 2 using the inverse probability of the treatment weighting method. Sensitivity analyses included narrowing the diagnostic window further to include only those diagnosed between the 6th and 10th year of follow-up; previously excluded participants with non-communicable diseases were reintroduced into the sample; and participants who had prevalent consumption of antidepressant drugs were reintroduced into the analyses. The analyses were performed with the STATA statistical software package version 16 (College Station, TX, USA; Stata Corp LLC). All *P*-values presented are two tailed, and the statistical significance was set at 0.05.

Results

The final sample (n = 10,063 participants, 60% females, mean age 37.5 years [SD 11.3]) is shown in Fig. 1. When comparing categories of poor and excellent LWB-I, participants with poor LWB were prominently female (69.1%) and had a greater prevalence of obesity (6.5% compared with 3.2%) and family members who experienced non-communicable diseases more often (20.8% compared with 16.4%; Table 1). In comparison, participants in the excellent LWB had healthier habits and fewer reports of diminished well-being; more than half of the participants did not smoke (55.2% compared with 48.6%) nor experienced insomnia (52.3% compared with 26.6%) and performed higher amounts of PA overall (25.0 [5.7] METs-h/wk compared with 18.5 [3.6] METs-h/wk; Table 1).

After an average follow-up of 9 years, a total of 319 participants reported a case of incident depression, 283 cases of antidepressant initiation, and 106 cases reported incident depression in combination with the use of antidepressants. The crude Cox proportional hazards models, using as a reference the category of poor LWB, revealed crude estimations for participants with transitioning LWB experienced a hazard ratio (HR) of 0.62 (95% confidence interval [CI]: 0.48-0.80) and for those in the category of excellent LWB experienced an HR of 0.38 (95% CI:0.29-0.51). Fully adjusted models remained significant, revealing an HR of 0.67 (95% CI: 0.52-0.87) and HR of 0.44 (95% CI: 0.33-0.58) for the transitioning and excellent LWB groups, respectively. These models also revealed a significant linear trend $P < 0.001$. As for the alternative definitions of the outcome, participants incident in the group of excellent LWB compared with poor, an HR of 0.32 (95% CI: 0.24-0.45) was found for the outcome of antidepressant therapy initiation. Finally, the strict criteria of incident depression and initiation of antidepressant drugs (Table 2), those in the category of excellent LWB an HR of 0.26 (95% CI: 0.15–0.44) was found; *P* for trend <0.001.

The sensitivity analyses revealed that these estimates remained highly significant when the diagnostic window was narrowed: fully adjusted HR of 0.51 (95% CI: 0.36-0.71) with only 106 cases of incident depression (Table 3). Finally, the Nelson–Allen curves further identified distinct differences in trends of incident depression across groups (Fig. 2). While the poor LWB group observed a constant cumulative incidence of cases, the transitioning and excellent LWB groups revealed less prominent slopes during the follow-up.

Discussion

In this longitudinal study evaluating the 12 items of the LWB-I, which included anthropometric, dietary, PA, and sleep, participants classified into the groups of transitioning or excellent lifestyles and well-being were less likely to report incident depression, initiate an antidepressant therapy, or report incident depression that required treatment with antidepressants. In contrast, the group of poor lifestyles and well-being had higher cases of depression, which could be attributed to a higher prevalence of obesity, hypertension, or dyslipidemia, but also lower PA levels and experiencing insomnia. These results add to the discussion of the biological links between lifestyles and depression, which involve inflammatory mechanisms and biomarkers. With tools such as the LWB-I, it is plausible to identify subgroups of the population at higher risk of this and other non-communicable diseases.

Clinical trials intervening on diet and PA (along with standard care) are known to improve depressive symptomatology; however, there is limited evidence of these interventions on incident depression.[19,20] In practice, healthful diets have yet to demonstrate a preventive effect depression incidence.[21,22] Despite this fact, benefits to patients' well-being have been reported and novel trials have set out to determine the size of these effects of dietary interventions such as a Mediterranean diet or through intermittent fasting.[23,24] In contrast, there are concrete examples of PA interventions and their ability to reduce the risk of incident depression in a Brazilian population.[25] These benefits have also been extended to patients with anxiety.[26] Adding to this evidence, a recent review and meta-analysis also concluded that aside from PA, reducing alcohol intake, improving insomnia, and smoking cessation are also effective in controlling depressive symptoms.[27] For these reasons, the simultaneous assessment of key determinants provided by the LWB-I questionnaire[16] could facilitate the identification of subjects at higher susceptibility to depression and the prescription of tailored recommendations to improve their mental health.[8]

Assessment of the items contained in the LWB-I, but more importantly, the weighted contributions of each factor, provides (1) an integral assessment of lifestyle determinants and (2) an objective understanding of the contributions of each item to the index.[28] Although these were observational analyses, sequence of events was accounted for in our primary and sensitivity analyses and in agreement with current literature.[4,28] Previous studies, including

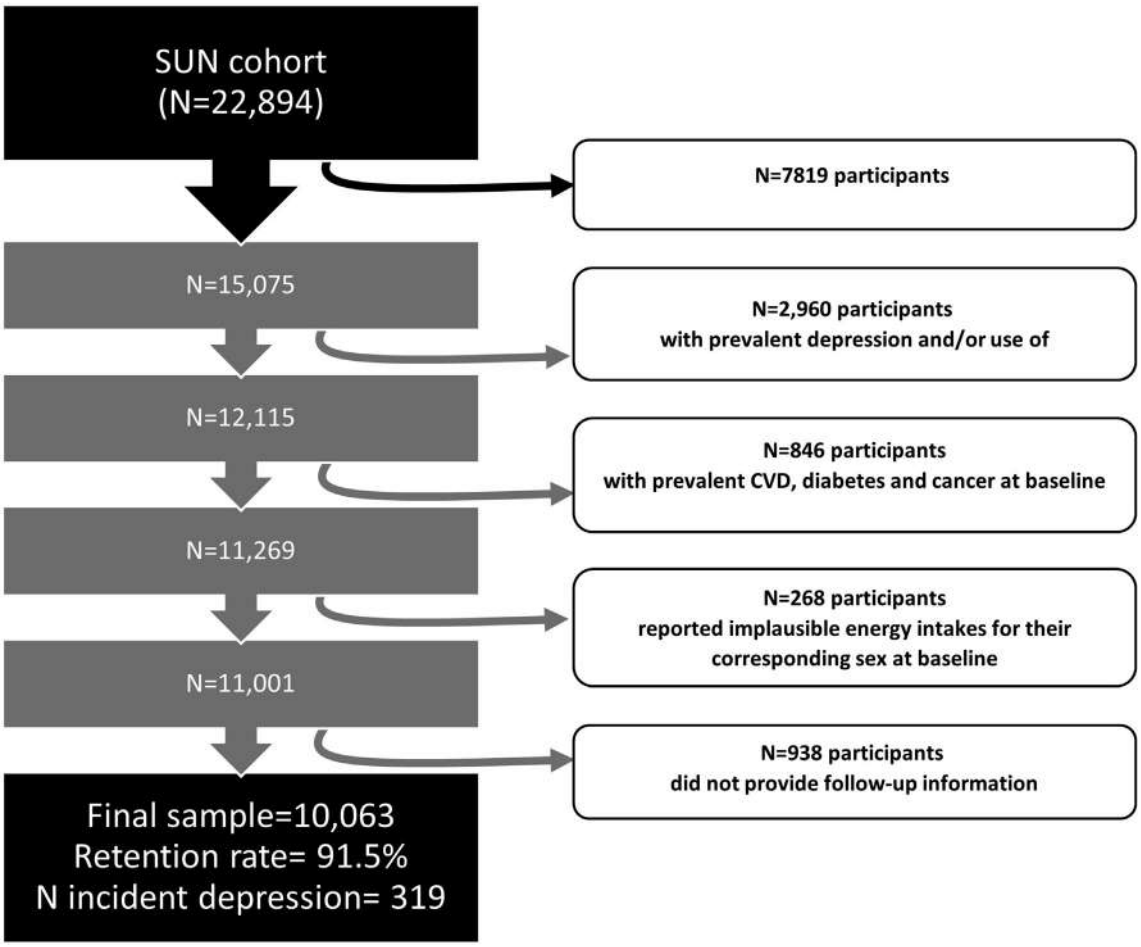

Fig. 1. Flowchart of inclusion criteria and final sample selection.

clinical trials, indicate that adherence to healthy lifestyles reduce the risk for CVD, diabetes, and premature death primarily through the reduction of inflammatory markers, and similar mechanisms are theorized to occur in depression.[4] Thus, questionnaires evaluating stress, sleep quality, comprehensive health status, dietary habits, obesity, smoking status, as well as age and gender can contribute to a personalized disease management through daily modifiable factors.[29]

The present analysis is not without some limitations. The characteristics of the sample, highly educated individuals with low prevalence of mood disorders, limit our ability to make assumptions of these associations in other economic groups and yet ensure minimal differences in well-being and life satisfaction across the sample. In addition, the cohort relies on self-reported data and outcomes prone to measurement error; however, these measures have been extensively validated.[18] The LWB-I, on the other hand, was designed as a general measure of health and not specifically for incident depression. However, the utilization of this tool is founded on the previously described biological mechanisms and thus valid under this assumption. Regarding its items, it has been suggested that weight perception and the measures of well-being lead participants to report poor life satisfaction in the absence of inflammatory markers.[30,31] This would entail a misclassification of individuals to the poor LWB group and drive our results to the null. In this regard, we cannot be certain of the degree of misclassification; however, the differences between the poor and transitioning groups would be expected to increase. Our sensitivity analyses targeted matters of inverse causality as well as long follow-up periods, ensuring a link between exposure and outcome. Replicating this study, using the LWB-I in different samples could provide external validation of this measure and give insights into the robustness of the tool; however, these require a thorough description of these described associations. The strengths of our study include the longitudinal and prospective design that reduces the risk of bias due to reverse causality. We have conducted a wide array of sensitivity analyses to test the robustness of our results and the LWB-I to shed light around alternative explanations for the association between unhealthy lifestyles and increased risk of incident depression.

Overall, multicomponent lifestyle interventions could potentially help manage depressive symptoms; for this purpose, a personalized assessment of lifestyle measures is required to potentially reduce the risk of incident depression.[14,19,23] With the LWB-I, a quantitative assessment of lifestyles, we observed a lower relative risk of incident depression in participants assigned to the transition and excellent LWB groups. Both were characterized by lower magnitudes of CVD and metabolic risk factors (two proinflammatory conditions), suggesting that habits and perceived health status measured by the LWB-I are also associated with depression risk.

Table 1
Description of the sample according to the LWB-I items and categories at baseline ($N = 10,063$).

Characteristics	Poor LWB (<80 points)	Transition LWB (80–86 points)	Excellent LWB (>86 points)	*P* value[a]
n (%)	2631 (26.2)	3173 (31.5)	4259 (42.3)	
Sex, female (%)	69.1	62.0	52.9	<0.001
Age (years)	36.9 (10.8)	38.1 (11.6)	37.4 (11.4)	<0.001
BMI (kg/m^2)	23.4 (3.6)	23.3 (3.4)	23.3 (3.1)	0.540
Underweight (<18.5; %)	3.2	3.2	3.0	<0.001
Normal weight (18.5–24.9; %)	63.6	63.9	66.8	
Overweight (25.0–29.9; %)	26.7	27.6	27.0	
Obesity (>30.0; %)	6.5	5.3	3.2	
Family history of diseases[b] (%)				<0.001
None	35.0	36.9	39.4	
1	44.2	43.1	44.2	
2	20.8	20.0	16.4	
Pre-existing diseases[b] (%)				<0.001
None	68.6	68.6	75.2	
1	24.2	25.0	21.7	
2	7.2	6.4	3.1	
Smoking status (%)				<0.001
Never	48.6	47.0	55.2	
Current	28.2	26.9	21.5	
Former	23.2	26.1	23.3	
Insomnia (%)				<0.001
Never	26.6	31.5	53.2	
Rarely	51.0	52.5	42.2	
Yes	22.4	16.0	4.6	
Physical activity (METs-h/week)	18.5 (3.6)	20.8 (21.1)	25.0 (5.7)	<0.001
Fruits + vegetables (servings/day)	4.8 (2.9)	4.7 (2.8)	5.0 (3.3)	<0.001
Added sugars[c] (total servings)	2.0 (1.9)	2.0 (1.8)	1.9 (1.7)	0.007
None	3.8	4.0	4.7	<0.001
<1/day	92.1	92.2	92.8	
>1/day	4.1	3.8	2.5	

BMI, body mass index; LWB-I, Lifestyle and Well-Being Index.
Data are presented as unadjusted means (SD) or percentages for categorical data.
Units of measurement are presented along with each variable.
Prior assessment of data distribution of continuous variables was analyzed using tests for normality and graphical means.
[a] P-values were obtained using Chi-squared distribution for categorical variables and one-way analyses of variance for continuous variables.
[b] Identifies the number of diseases present for each subject. Diseases include diabetes, hypertension, and hypercholesterolemia.
[c] Pooled analysis of standard servings of sodas including products labeled as "low calorie" (200 cc), sugar (10 g), and marmalade (10 g), and honey were included.

Table 2
Relative risk of incident depression, antidepressant therapy initiation, and incident depression accompanied by antidepressant therapy (hazard ratios and 95% CI) according to the categories of the LWB-Index among participants of the SUN cohort.

	LWB-Index categories[a]			*P* trend[b]
Outcomes	Poor LWB	Transition LWB	Excellent LWB	
Incident depression (*N*)	2631	3173	4259	
Number of cases	133	101	85	
Person-years	23,950	29,561	40,154	
Crude model	1.00 (Ref)	0.62 (0.48–0.80)	0.38 (0.29–0.51)	<0.001
Multivariate model 1[c]	1.00 (Ref)	0.64 (0.49–0.83)	0.40 (0.30–0.52)	<0.001
Multivariate model 2[d]	1.00 (Ref)	0.67 (0.52–0.87)	0.44 (0.33–0.58)	<0.001
Antidepressant therapy				
Total cases ($n = 283$)				
Crude model	1.00 (Ref)	0.53 (0.41–0.70)	0.28 (0.20–0.37)	<0.001
Multivariate model 1[c]	1.00 (Ref)	0.54 (0.42–0.71)	0.33 (0.24–0.45)	<0.001
Multivariate model 2[d]	1.00 (Ref)	0.58 (0.45–0.77)	0.32 (0.24–0.45)	<0.001
Incident depression and antidepressant therapy				
Total cases ($n = 106$)				
Crude model	1.00 (Ref)	0.56 (0.37–0.87)	0.21 (0.12–0.35)	<0.001
Multivariate model 1[c]	1.00 (Ref)	0.58 (0.38–0.90)	0.22 (0.13–0.38)	<0.001
Multivariate model 2[d]	1.00 (Ref)	0.63 (0.41–0.93)	0.26 (0.15–0.44)	2<0.001

CI, confidence interval; HR, hazard ratio; LWB-I, Lifestyle and Well-Being Index.
[a] LWB-I scores (0–100 points) categorized as poor LWB (<80 points), transition LWB (80–86 points), and excellent LWB (>86 points).
[b] Test for lineal trend calculated for the three categories of LWB-I.
[c] Adjusted for working hours-day, cigarette packs-year, alcohol consumption (excluding wine), and total daily energy intake.
[d] Same adjustments as model 1 and additionally: supplement intake, level of competitiveness, psychological tension, and dependence.

Table 3
Sensitivity analyses: relative risk of incident depression (hazard ratios and 95% CI) according to the categories of the LWB-Index among participants using alternative exclusions and follow-up times.

Sensitivity Analysis	Total cases	Person-years[a]	LWB-Index categories[b]			*P* trend[c]
			Poor LWB	Transition LWB	Excellent LWB	
N			2631	3173	4259	
1. Narrowed diagnostic window (between 6th and 10th year of FU)[d]	214	83,810	1.00 (Ref)	0.73 (0.53–1.00)	0.51 (0.36–0.71)	<0.001
2. Including participants with prevalent chronic diseases[d]	344	99,389	1.00 (Ref)	0.66 (0.51–0.84)	0.44 (0.34–0.57)	<0.001
3. Including participants with prevalent use of antidepressants[d]	331	95,756	1.00 (Ref)	0.68 (0.52–0.87)	0.46 (0.35–0.60)	<0.001

CI, confidence interval; FU, follow-up; HR, hazard ratio; LWB-I, Lifestyle and Well-Being Index.
[a] Person-years for the entire sample.
[b] LWB-I scores (0–100 points) categorized as poor LWB (<80 points), transition LWB (80–86 points), and excellent LWB (>86 points).
[c] Test for lineal trend calculated for the three categories of LWB-I.
[d] Estimates are adjusted for working hours-day, cigarette packs-year, alcohol consumption (excluding wine), total daily energy intake, supplement intake, level of competitiveness, psychological tension, and dependence.

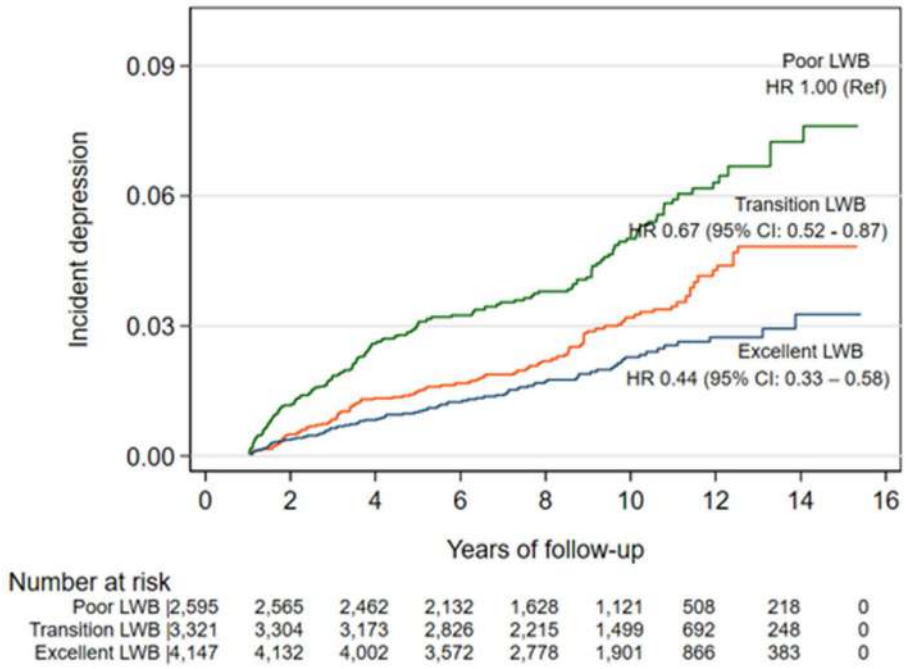

Fig. 2. Nelson–Allen curves for incident depression (percentage) and the LWB-I. Adjusted with inverse probability weighting method.

Conclusion

In a sample of Spanish university graduates, good health and well-being based on an assessment of lifestyles—according to the LWB-I—was significantly and inversely associated with the risk of subsequent depression. Using this index, individuals who were categorized into the "excellent" and "transitioning" LWB-I groups showed lower rates of incident depression and lower rates of antidepressant initiation, all compared with their unhealthy counterparts.

Author statements

Acknowledgment

A special thanks to Martínez-González, MA, Head of the Department at the University of Navarre, for his support and guidance throughout this work and to the other members of the SUN study group: Aguilera-Buenosvinos I, Alonso A, Álvarez-Álvarez I, Balaguer A, Barbería-Latasa M, Barrio-López MT, Basterra-Gortari FJ, Battezzati A, Bazal P, Benito S, Bertoli S, Beunza JJ, Buil-Cosiales P, Carlos S, de Irala J, de la Fuente-Arrillaga C, de la Rosa PA, Delgado-Rodríguez M, Díaz-Gutiérrez J, Díez Espino J, Domínguez L, Donat-Vargas C, Donazar M, Eguaras S, Fernández-Montero A, Fresán U, Galbete C, García-Arellano A, Gardeazábal I, Gea A, Gutiérrez-Bedmar M, Gomes-Domingos AL, Gómez-Donoso C, Gómez-Gracia E, Goñi E, Goñi L, Guillén F, Hernández-Hernández A, Hidalgo-Santamaría M, Hu E, Lahortiga F, Leone A, Llavero M, Llorca J, López del Burgo C, Marí A, Martí A, Martín-Calvo N, Martín-Moreno JM, Mendonça R, Menéndez C, Molendijk M, Molero P, Muñoz M, Navarro AM, Pérez de Ciriza P, Pérez-Cornago A, Pérez de Rojas J, Pimenta AM, Ramallal R, Razquin C, Rico-Campà A, Romanos-Nanclares A, Ruiz L, Ruiz-Canela M, San Julián B, Sánchez D, Sánchez-Bayona R, Sánchez-Tainta A, Santiago S, Toledo E, and Vázquez Z, Zazpe I.

Ethical approval

The study design, methods, and informed consent were approved by the Research Ethics Committee of the University of Navarra (2001/03) in line with the principles of the Declaration of Helsinki. Each participant voluntarily submitted their completed

baseline questionnaire in a prepaid package through the national post; this was considered as an informed consent to participate in the study.

Funding

Funding was received from the Spanish Government-Instituto de Salud Carlos III, the European Regional Development Fund (FEDER; RD 06/0045, CIBER-OBN, grants PI10/02658, PI10/02293, PI13/00615, PI14/01668, PI14/01798, PI14/01764, PI17/01795, PI20/00564 and G03/140), the Navarra Regional Government (27/2011, 45/2011, 122/2014), the National Plan on Drugs (2020/021), and the University of Navarra.

Competing interests

The authors declare no competing interests of any kind.

Author contributions

O.P., C.S.O., and J.A.M. contributed to the conception and design of the study. C.S.O., M.B.R., and J.A.M. were involved in the acquisition of data. O.P., M.S.H., and C.S.O. conducted the data analysis, in addition to J.A.M. and V.O. with whom data were interpreted. O.P., C.S.O., V.O., and J.A.M. drafted the first article, and all authors contributed equally to the revision of the article and intellectual content. Final approval of the version to be submitted was given by O.P., M.S.H., C.S.O., V.O., C.F.L., M.B.R., A.S.V., and J.A.M.

Research data (data sharing and collaboration)

Data are not readily available. Requests for data will be reviewed by the team.

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Public Health 220 (2023) 27–32

Contents lists available at ScienceDirect

Public Health

journal homepage: www.elsevier.com/locate/puhe

Original Research

Trends and seasonal variation of antibiotic consumption by community residents in Hefei, China, 2012–2016

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ARTICLE INFO

Article history:
Received 12 October 2022
Received in revised form
13 February 2023
Accepted 19 April 2023

Keywords:
Antibiotics
Trends
Interrupted time series
Community

ABSTRACT

Objectives: The aim of this study was to evaluate the trends and seasonal variations of antibiotic consumption by community residents in Hefei, China, over a 5-year period.
Study design: This was an ecological study.
Methods: Data on antibiotic consumption by community residents in Hefei between 2012 and 2016 were collected from the Hefei Center for Disease Control and Prevention. Statistical analysis was carried out using Microsoft Excel 2021, SPSS 26.0 and R4.1.3. An interrupted time series (ITS) analysis was modelled to assess the impact of policies on antibiotic consumption trends.
Results: Amoxicillin and cephalosporins accounted for 63.64% and 30.48%, respectively, of the total defined daily dose per 1000 inhabitant-days (DID) of antibiotics in 2016. The total consumption of antibiotics decreased from 6.92 DID in 2012 to 5.61 DID in 2016 ($P_{trend} = 0.017$). Seasonal analysis showed an average of 34.24% antibiotic consumption in the winter over the 5 years. The equation constructed by the ITS analysis was $Y = 5.530 + 0.323X1 - 7.574X2 - 0.323X3 + \varepsilon$.
Conclusion: Between 2012 and 2016, overall antibiotic consumption by community residents in Hefei decreased significantly. The impact of antibiotic policies, implemented between 2011 and 2013, started to appear in 2014 when the consumption of antibiotics decreased. This study has important policy implications for the use of antibiotics at the community level. Further studies on the trends of antibiotic consumption are required, and strategies should be designed to promote appropriate use of antibiotics.

Introduction

Antibiotics have paved the way for today's modern medicine. The mid-20th century was even named the 'antibiotic era', and it was thought that infectious diseases could be eradicated by the end of the last century.[1] However, the overuse and inappropriate use of antibiotics have been identified as a serious global public health problem because of the increase of drug-resistant bacteria, the decline of antibiotic efficacy, multiple infections and other factors.[2] Meanwhile, the increasing levels of antimicrobial resistance and lack of new effective antibiotics have been found to correlate with resistance genes in microorganisms, and the overuse of antibiotics has also increased the economic burden to health care.[3] Epidemiological surveillance networks in Europe and Asia (European Antimicrobial Resistance Surveillance Network-EARS-Net and Central Asia and Eastern European Surveillance of Antimicrobial Resistance) have shown that antibiotic-resistant bacteria have become much more prevalent during the last decade.[4] Therefore, it is important to reduce inappropriate use of antibiotics to limit the number of infections caused by resistant bacteria.[5]

Analysis of antibiotic sales data can help elucidate trends of antibiotic use in the community and provide a scientific basis for improving policies and assessing the effectiveness of interventions for antibiotic use. By monitoring antibiotic use and costs, the European Surveillance of Antimicrobial Consumption reported that surveillance can drive the actions to promote appropriate antibiotic use and contain antimicrobial resistance.[6] A population-based study in France observed a significant reduction in antibiotic prescriptions after the implementation of policies to reduce unnecessary use of antibiotics.[7] A study in the United States showed that antibiotic prescription rate decreased after implementation of a

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https://doi.org/10.1016/j.puhe.2023.04.011
0033-3506/

new policy.[8] However, Durkin observed insignificant changes in individual and overall annual antibiotic prescribing rates.[9]

China, as the largest developing country, with a population approaching 1.4 billion, had the second highest usage of antibiotics in the world.[10] A systematic review presented the high level of antibiotic consumption in China.[11] Antibiotic sales records from a hospital in Shanghai showed that the average antibiotic consumption was 20.75 defined daily dose per 1000 inhabitant-days (DID) from 2009 to 2014,[12] which is much higher than the average antibiotic consumption in other countries (18.0 DID).[13] A national survey in China also found that >30% of outpatient antibiotic consumption in primary care institutions may be inappropriate.[14] In China, the national health expenditure increased sharply from US $423 billion in 2012 (based on the value of US $1 = 6.64 yuan in 2016) to US $698 billion in 2016, with antibiotics being the highest cost among expenditure on drugs.[15] The societal economic burden attributed to antibiotic resistance was estimated to be $77 billion in 2017, which is equivalent to 0.37% of China's yearly gross domestic product, with $57 billion associated with multidrug resistance.[16]

A series of measures and policies for limiting the overuse and misuse of antibiotics was launched by the Ministry of Health of China in the recent years.[17] For example, the restrictions on antibiotic use in primary care commenced in 2009.[18] However, a few years after implementing these policies, no obvious reduction of antibiotic prescribing was seen.[19] In 2011, the Ministry of Health of China launched a 3-year national-level regulatory campaign to control the overuse of antibiotics. On this basis, on 1 August 2012, the Chinese government also issued the 'administrative rules for the clinical use of antibiotics' to have tight regulation over the prescription of antibiotics.[20] In 2015, the National Health and Family Planning Commission revised the 'guiding principles for clinical application of antibacterial drugs'. In May 2018, the National Health Commission issued the 'notice on continuously doing a good job in the management of clinical application of antibiotics'. It is important that these organisations continue to manage and control the use of antibiotics.[21]

After the implementation of a series of policies and strategies, studies have reported conflicting trends in the consumption of total antibiotics. In one study conducted in China's tertiary hospitals, an increasing trend in antibiotic consumption from an average of 7.97 DID in 2011 to 10.08 DID in 2015 was seen.[22] A recent study analysing data from the Center for Antibacterial Surveillance reported that antibiotic use in outpatients declined by approximately 7% from 2012 to 2016.[23] Antibiotic consumption and resistance were influenced by multiple environmental and social factors.[24] Antibiotic consumption also showed significant seasonal variation, which decreased over time.[25] One epidemiological study reported that the seasonal variation of antibiotic usage for outpatients was influenced by the seasonal increase in infectious diseases, such as influenza and diarrhoea.[26] Thus, it is important to identify how antibiotic use changes over time and the main patterns in consumption so that policies can be appropriately designed for regional interventions and to optimise the use of antibiotics.

The goal of the present study was to describe antibiotic consumption by community residents in Hefei, China, over a 5-year period, after policy implementation. This study also assessed the trends and seasonal variations of community antibiotic consumption. Interrupted time series (ITS) analysis was used to investigate the changes in antibiotic consumption before and after the implementation of a series of policies between 2011 and 2013. A better understanding of the trends and seasonal variations of antibiotic consumption is useful in the design of interventions to reduce inappropriate antibiotic use.

Methods

Research location

Hefei, the capital city of Anhui province, is located in the east-central region of China (31° 52N, 117° 17E), with a population of approximately 7.9 million (2016 data) across a geographical area of 11,445.1 km^2. It has a subtropical humid monsoon climate with four distinct seasons.

Data collection

Data of antibiotic prescriptions from the electronic database of the surveillance system from 1 January 2012 to 31 December 2016 were obtained from Hefei Center for Disease Control and Prevention (CDC). Data of antibiotic consumption were analysed from the largest chain of pharmacies from 2012 to 2016 in Hefei. The selected pharmacies had the highest annual sales of drugs and accounted for 25–30% of drug sales in the whole region. The annual total counts were calculated for oral and injectable systemic antibiotics, including amoxicillin, azithromycin, cephalosporin and norfloxacin, which represented most antibiotics sold in the monitored pharmacies. Antibiotic consumption data in the selected pharmacies were converted into the defined DID recommended by the World Health Organisation (WHO) Collaborating Centre for Drug Statistics Methodology.[27] The population of Hefei was obtained by mid-year estimates reported by the China Census Bureau in 2012–2016. For the analysis of seasonal variations of antibiotic consumption, December, January and February were defined as the winter months.

Data analyses

The original data on antibiotic prescriptions were managed in Microsoft Excel 2021. The analysis of variance of parametric test, Kruskal–Wallis H of non-parametric test and trend test were used to investigate differences and trends of antibiotic consumption measured as DID over the 5-year period. Seasonal variations in the sale counts of antibiotics were also assessed in this study. In all statistical analyses, the two-sided statistical significance level was set at $\alpha = 0.05$. The analysis was completed using Statistical Product and Service Solutions (SPSS), version 26.0 (SPSS Inc, Chicago, IL, USA). ITS analysis was performed using R4.1.3.

Results

Trends and patterns of antibiotic consumption

Table 1 illustrates the annual consumption of antibiotics. The total consumption of antibiotics increased from 6.92 DID in 2012 to 9.98 DID in 2013 but decreased to 5.61 DID in 2016 ($P = 0.001$; Table 1 and Fig. 1A). A decrease in the trend of total consumption of antibiotics was seen ($P_{trend} = 0.017$). In 2016, amoxicillin (3.57 DID) was the most common therapeutic group of antibiotics consumed in Hefei, followed by cephalosporins (1.71 DID). Significant decreasing trends were observed for cephalosporins (33.20% decrease) and azithromycins (57.14% decrease) between 2012 and 2016 ($P_{trend} < 0.01$).

Seasonal variation of antibiotic consumption

Consumption of total antibiotics and different types of antibiotics fluctuated with the seasons. An average of 34.24% of total antibiotics were sold in the winter months over all 5 years, reflecting seasonality of total antibiotic consumption. Significantly

Table 1
Annual antibiotic consumption in Hefei from 2012 to 2016.

Antibiotic	Antibiotic consumption (daily defined dose/1000 inhabitants/day [%])					*P*-value	*P*-value for trend
	2012	2013	2014	2015	2016		
Total antibiotics	6.92	9.98	8.62	6.89	5.61	0.001	0.017
Amoxicillin	3.74 (54.05)	3.97 (39.78)	4.25 (49.30)	4.21 (61.10)	3.57 (63.64)	0.655	0.922
Azithromycin	0.42 (6.07)	0.28 (2.81)	0.34 (3.94)	0.23 (3.34)	0.18 (3.21)	<0.001	<0.001
Norfloxacin	0.19 (2.75)	0.21 (2.10)	0.25 (2.90)	0.23 (3.34)	0.16 (2.85)	0.006	0.657
Cephalosporin	2.56 (37.00)	5.51 (55.21)	3.79 (43.97)	2.21 (32.08)	1.71 (30.48)	<0.001	0.001

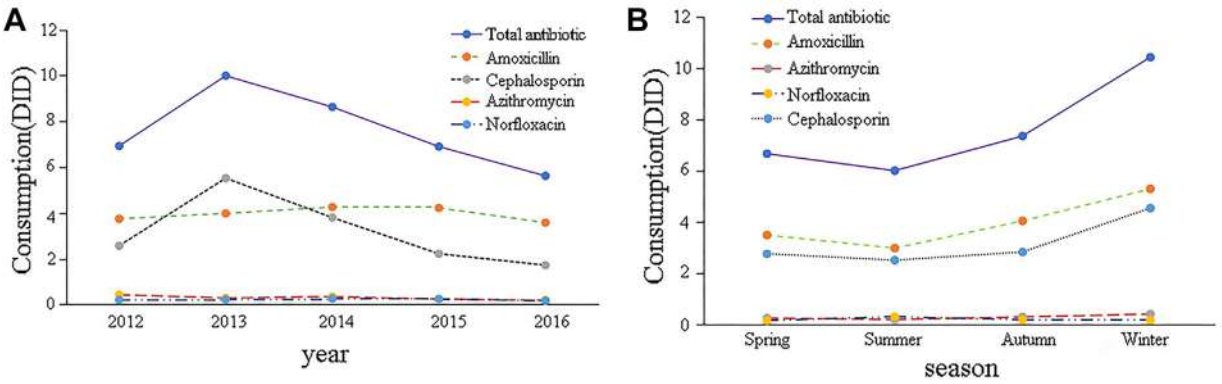

Fig. 1. (A) Yearly variation of rate of antibiotic usage by antibiotic class. (B) Seasonal antibiotic consumption in Hefei from 2012 to 2016. DID, daily defined dose/1000 inhabitants/day.

higher consumption of amoxicillin, cephalosporins and azithromycin was seen during the winter months, which corresponded with more frequent use of antibiotics for respiratory infections during the influenza season. In contrast, the consumption of norfloxacin was higher in the summer months (Table 2, Fig. 1B).

Changes in total antibiotic consumption before and after policy intervention

Table 3 and Fig. 2 show the results of the ITS analysis; the model equation is as follows: $Y = 5.530 + 0.323X1 - 7.574X2 - 0.323X3 + \varepsilon$. The results show that before the policy effect (2012–2014), total antibiotic consumption showed an upward trend, with a statistically significant difference ($\beta_1 = 0.323$, $P = 0.009$); however, after the policy effect appeared (2014–2016), total antibiotic consumption showed a downward trend, with a statistically significant difference ($\beta_3 = -0.323$, $P = 0.041$).

Table 3
Interrupted time series analysis of total antibiotic consumption.

Variables	Coefficient (β)	*t* value	*P*-value
Constant term	5.530	2.938	0.005
Time (X1)	0.323	2.725	0.009
Intervention (X2)	−7.574	−3.955	<0.001
Slope (X3)	−0.323	−2.089	0.041

X1, the time after the start of the study; X2, dummy variable of intervention; X3, change of slope before and after intervention.

Discussion

The present study evaluated the trends and seasonal variations in community antibiotic consumption by analysing data from retail pharmacies in Hefei, China, between 2012 and 2016. During the study period, there was a decreasing trend in the consumption of total antibiotics at the community level. In addition, the consumption of different types of antibiotic showed seasonal variations in the time series analysis.

The main composition of total antibiotic consumption was amoxicillin and cephalosporins (63.64% and 30.48%, respectively) in 2016. This result is consistent with an analysis based on prescriptions of 139 hospitals in 28 provincial regions, which found that most antibiotics were cephalosporins.[28] In contrast with results from Shanghai and Nepal, amoxicillin and cephalosporins are the most frequently consumed antibiotics in Hefei pharmacies.[29] Previous studies have shown that the main antibiotic consumed in hospitals and primary healthcare institutions was cephalosporins in Shanghai[21] and penicillins in Europe. Differences in results could be due to the fact that in the present study, antibiotic usage was assessed for community residents in the retail pharmacy

Table 2
Seasonal antibiotic consumption in Hefei from 2012 to 2016.

Antibiotic	Antibiotic consumption (daily defined dose/1000 inhabitants/day [%])				*P*-Value
	Spring (March to May)	Summer (June to August)	Autumn (September to November)	Winter (December to February)	
Total antibiotics	6.66 (21.89)	6.00 (19.72)	7.35 (24.15)	10.42 (34.24)	<0.001
Amoxicillin	3.49 (22.09)	2.98 (18.86)	4.04 (25.57)	5.29 (33.48)	<0.001
Azithromycin	0.25 (21.55)	0.20 (17.24)	0.30 (25.86)	0.41 (35.34)	<0.001
Norfloxacin	0.16 (19.05)	0.31 (36.90)	0.19 (22.62)	0.18 (21.43)	<0.001
Cephalosporin	2.76 (21.84)	2.51 (19.86)	2.83 (22.39)	4.54 (35.92)	0.040

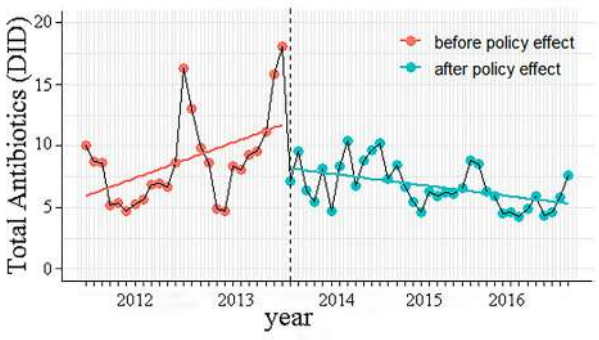

Fig. 2. Interrupted time series analysis results of total antibiotic consumption (daily defined dose/1000 inhabitants/day [DDI]). The black dotted line is the time when the policy effect appeared (February 2014). Model equation: $Y = 5.530 + 0.323X1 - 7.574X2 - 0.323X3 + \varepsilon$. Y, total antibiotic consumption; X1, the time after the start of the study; X2, dummy variable of intervention; X3, change of slope before and after intervention; ε, residual item.

setting, rather than inpatient settings in Shanghai and ambulatory care settings in high-income countries.[12] The results of the present study also show that residents prefer to buy non-restricted antibiotics at retail pharmacies, which was different from findings from Europe, where penicillins and β-lactamase inhibitors were primarily consumed.[30,31] This may be because of the fact that in China, patients are required to undergo skin testing before using penicillins in accordance with the national guidelines.

The increasing consumption of antibiotics has been identified as the main determinant of antimicrobial resistance. Antimicrobial resistance can lead to an increase in morbidity and mortality of infectious diseases and burden on public health.[32] Hence, investigating the trends and seasonal variations of antibiotic use provides useful information for the design of future policies. Most studies have documented the high level of antibiotic consumption using anatomical therapeutic chemical/DID methodology.[33,34] One study suggested that there was an increasing trend of antibiotic consumption, with an average consumption of antibiotics of 7.97 DID in 2011 and 10.08 DID in 2015.[22] In contrast, the study conducted in the Shanghai municipality including total antibiotic consumption of a minimum of 160 hospitals and 241 primary healthcare setting showed a decreasing trend from 25.9 DID in 2010 to 17.8 DID in 2012.[14] The results of the present study showed that the range of average antibiotic consumption was 5.61–9.98 DID. In addition, a significantly increasing trend was observed between 2012 and 2015. In this study, antibiotic usage alone was lower than in other countries, such as South Korea (average 23.1 in 2012) and Europe (range 15.3–42.3 in 2011),[34,35] which may be because of an underestimation of antibiotic consumption as a result of using data from retail pharmacies.

The results of antibiotic consumption trends are also inconsistent. Edelstein reported that the proportion of broad-spectrum antibiotic consumption increased under the trend of out-of-hours prescribing volume for antibiotics using the consumption data of 143 clinical commissioning group in the England from 2010 to 2014.[36] One 10-year trends study of antibiotic usage also illustrated a stepwise increase in the consumption of broad-spectrum antibiotics in Korea from 2004 to 2013.[32] According to a study conducted in South Korea, antibiotic usage averaged 23.5 DID in 2007 and 27.7 DID in 2014.[33] However, a study in the United States revealed that antibiotic prescription rate had a decreasing trend from 892/1000 population in 2006 to 867/1000 population in 2010.[26] In addition, one cohort study evaluated the trend of antibiotic usage and suggested that there was no trend in annual antibiotic prescribing of outpatients from 2013 to 2015.[9] This discrepancy could be attributed to the regional management policies for antibiotic usage and different levels of medical care.

In addition to evaluating the changes in levels and trends of antibiotics usage, it is important to examine changes in seasonal variation because this provides information on inappropriate antibiotic consumption. Several studies have reported seasonal variations in the prescribing of antibiotics in Europe, Canada, the United States and Korea. In Europe and the United States, the consumption of antibiotics in the winter months ranged from 21% to 44%.[26,37] The findings also revealed that outpatient use of antibiotics was higher in the winter in both the United States and England (December, January and February).[36,38] These results are similar to those of the present study. In the present study, the prescription of total antibiotics had a seasonal variation, with higher use in winter than in other seasons. The seasonal trends in total antibiotic usage were mainly because of the increase in the prescription of amoxicillin and cephalosporins. Seasonal trends of antibiotic prescription are likely to be related to the increasing incidence of respiratory tract infections and diarrhoea. The consumption of antibiotics associated with respiratory tract infection (e.g. amoxicillin, azithromycin and cephalosporins) were higher in winter, which is consistent with seasonal variations of influenza according to the surveillance conducted by the CDC.[39] It has been suggested a better understanding of the seasonal variations of antibiotic prescribing, if the WHO and CDC initiated the work about using antibiotics before the peak of antibiotic consumption, strategies, including publicity and guidelines, may have the most impact on reducing the inappropriate use of antibiotics.

From 2011 to 2013, a 3-year national-level regulatory campaign and administrative rules were launched by the Ministry of Health of China to control the inappropriate usage of antibiotics. The increased focus on antibiotic regulatory activities in China may be a result of the public's growing concern over antibiotic misuse globally. The present study showed that there was a sustained reduction in community antibiotic consumption across a wide area of pharmacies in Hefei after the measures were implemented from 2011 to 2013, consistent with the period of implementation of interventions to improve antibiotic use.[40] Measures of antibiotic management can control the overuse of antibiotics at many levels, such as transferring pressures top-down from presidents to directors of departments and eventually to individual prescribers.[41] From 2014 to 2016, the use of antibiotics reduced by 34.92%. This is consistent with results from a study in Ecuador. In response to the Antibiotic Management Plan (ASP) proposed by the WHO, Hugo Fernando conducted a study in Ecuador to assess the impact of ASP consisting of carbapenem restriction measures. According to the data, ASP has been successful in lowering the use of carbapenem antibiotic usage, but additional interventions are still required to provide a strategy to prevent unintended consequences.[42] It may be related to a series of intervention policies and measures in antibiotic prescription. Interestingly, this study also found that the consumption of antibiotics rebounded after the implementation of the policies. The main objective of these policies was the clinical management of antibiotics, so there may be a transition period between the implementation of these policies and the effective management of antibiotics in community pharmacies. Second, this may be because community residents began to stockpile medicine under the influence of policies. Although the present study results indicated that policy intervention has an inhibitory effect on the consumption of antibiotics, other studies suggested that policy intervention had little effect on the consumption of antibiotics.[43] Based on a 2200-bed teaching hospital in China, a study was conducted on the impact of strengthening the policy of Chinese special rectification activity (CSRA). The findings demonstrated a

connection between the implementation of CSRA policy and the reduction of antibiotic use and expenditure of hospital patients. It is also essential to keep in mind that the decrease in antibiotic consumption has slowed down as a result of the CSRA's limited ability to reverse the trend in the later stages of intervention.[44] Therefore, repeated policy implementation is conducive to further antibiotic management and control. However, to obtain the desired result (i.e. reduced antibiotic usage), it is also necessary to enhance and redesign current strategies.

Some limitations in the current study should be considered. First, the data of antibiotic consumption was mainly from the public health surveillance system in Hefei and may not be representative of the whole region. Second, this study may underestimate the individual level of antibiotic prescription because some sources of antibiotic prescription were not included in our study (such as hospitals, healthcare settings, the leftover of antibiotic consumption at home and antibiotics purchased outside the local pharmacy). Finally, the trends of antibiotic consumption may be influenced by many factors, such as geographical area, immune status or other factors. Despite these limitations, this is the first study to investigate the trends of antibiotic consumption in Hefei, and the data derived from this study are likely to be a reasonable indicator of trends in systemic antibiotic consumption for community residents.

Conclusions

In conclusion, this study used aggregated sales records data of retail pharmacies to analyse community antibiotic consumption in Hefei from 2012 to 2016. Amoxicillin and cephalosporins were the most commonly prescribed classes of antibiotics. The consumption of total antibiotics showed seasonal variations, with higher usage in winter. The implementation of policies to reduce antibiotic use has a proven effect on the control of antibiotic consumption in the community. The study results of the variations in antibiotic consumption have important policy implications for the control of inappropriate use of antibiotics at the community level. More efforts are required in the future to design an optimal intervention strategy to promote appropriate antibiotic use.

Author statements

Acknowledgements

The authors appreciate the Hefei Center for Disease Control and Prevention for providing the data set of antibiotic usage and the counts of daily infectious diseases used in this study.

Ethical approval

There was no ethical approval in the paper because the present study is based on de-identified data provided by Hefei CDC for the secondary analysis research.

Funding

The authors gratefully acknowledge financial support from the Grants for Scientific Research of BSKY (0307026201) from Anhui Medical University and Natural Science Research Project of universities in Anhui province (KJ2021A0227).

Competing interests

The author(s) declared no conflicts of interest with respect to the research, authorship and/or publication of this article.

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