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Urban environment and children's health

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Association between exposure to earthquake in early life and diabetes mellitus incidence in adulthood with the modification of lifestyles: Results from the Kailuan study

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Background: Exposure to disasters in early life may induce lifetime health risk, but investigation on earthquake exposure and DM in later life is still limited. The aim of the current study is to evaluate the association between exposure to the Tangshan Earthquake in early life and diabetes mellitus (DM) incidence in adulthood, and explore the modification of lifestyles on DM development.
Methods: Participants who were free of DM at baseline from the Kailuan Study were included in this study. All participants were divided into fetal-exposed, infant-exposed, early childhood-exposed and nonexposed group. The effect of earthquake exposure on DM and modification of lifestyles were examined by multivariable-adjusted Cox proportional hazard model.
Results: The exposed group had a higher risk of DM than nonexposed group, especially in infant-exposed and early childhood-exposed group, with hazard ratio (HR) of 1.62 [95% confidence intervals (CI), 1.21–2.17] and 1.46 (95% CI, 1.06–1.99), respectively. After stratifying by lifestyles, a significant modification was observed in alcohol consumption.
Conclusion: Exposing to earthquake in early life could increase DM incidence in later life, and alcohol consumption might modify the effect of earthquake exposure on DM development. More attention should be paid on the preventions of DM among adults who exposed to earthquake in their early life.

KEYWORDS
earthquake exposure, early life, diabetes mellitus, lifestyles, the Kailuan study

Introduction

Diabetes mellitus (DM) is a common kind of metabolic disease globally with an estimation of 425 million afflicted individuals in 2017. The global prevalence of DM is increasing and expected to reach to 522 million by 2030 (1). As a metabolic disease, the origin of DM is complicated, including human genetic and lifestyle factors act to promote DM in adulthood (2). Previous studies have identified over 100 genetic loci variant associated with DM (3), and evidence suggested that the risk of DM incidence decreased by 57% among participants with healthy lifestyles, including no smoking, moderate alcohol intakes, physical activities and healthy diets, compared with participants with unhealthy lifestyles (2, 4).

Emerging evidence suggests that exposure to environmental factors may have an impact on human health, including short-term and long-term impact. For example, a study of 497 DM patients were found that the control of blood glucose had worsened in 3 months after the Great East Japan Earthquake, which indicated that the secretion of endogenous insulin induced by hyperactivity of sympathetic nerve in a relatively short term (5). Similarly, adverse experiences in childhood have also been identified as a critical risk factor of psychiatric disorders, such as depression and post-traumatic stress disorder (PTSD) in a short-term (6). It has been reported that a dose-response relationship exists between exposure to Ukraine famine (1932–1933) in prenatal development and the incidence of DM in adults, revealing the long-term impact of disaster events (7). Likewise, the "Developmental Origins of Health and Disease" (DOHaD) hypothesis provide a potential link through biological reactions to early life exposure that are posited to predispose individuals to metabolic diseases (8). However, the pathways from exposure factors affecting early life to outcomes in adult life are far from clear due to the lack of longitudinal cohort studies.

Earthquake is a kind of severe natural catastrophic event that can cause adverse physiological and mental responses by fractures, crush injuries, and the severe damages of their properties and loss of their relatives (9). Studies on earthquake experience confirmed that earthquake trauma could increase the risk of DM. A study of Kumamoto Earthquake revealed that the glycemic deterioration after earthquake could be explained by increased production of cortisol and/or catecholamine (10). In addition, along with the rapid development of China, the lifestyles of Chinese people have changed significantly. A previous study has pointed out that less ideal cardiovascular health metrics might increase the risk of CVD in the population, who have been exposed to famine during the fetal period (11). However, little longitudinal cohort studies have examined the DM risk in adults who have exposed to earthquake during early life, and the interaction of earthquake exposure and healthy lifestyles on DM development are also few investigated.

Thus, we use the Tangshan Earthquake as a natural exposure, which happened in Hebei province, China, with an epicenter at Tangshan city on July 28 in 1976, a magnitude level of 7.8 on the Richter scale. The survey data were collected from the Kailuan Study, a community-based cohort in Tangshan. We aimed to examine the association between exposure to the Tangshan Earthquake during early life and the incidence of DM, and explore the potential modification of lifestyles on DM development.

Materials and methods

Study population

The Kailuan study is an ongoing prospective cohort (trial registration number: ChiCTR-TNC-11001489) study in Tangshan, China (12, 13). In 2006 to 2007, a total of 169,548 participants (≥18 years, including retired individuals) from Kailuan Group received questionnaires and the first health examination at Kailuan General Hospital and 10 affiliated hospitals. Following surveys were provided every 2 years since 2006 (the median of follow-up years was 6.07 years).

In this study, we included participants who participated in at least one survey from 2006 to 2017 and were born in the destructive zone of the Tangshan earthquake between July 28th, 1974 and May 4th, 1979. And the birth location of participants was collected based on the information of identification card. Inclusion criteria for birth dates was based on the Tangshan earthquake date (July 28th, 1976) and gestation period of 280 days. According to the date of the Tangshan earthquake and birth date of each participant, participants born between May 4th, 1977 and May 4th, 1979 were not exposed to the earthquake, who were defined as nonexposed group, and participants born between July 28th, 1974 and May 4th, 1977 were exposed to earthquake in gestation or early life, who were defined as exposed group. Meanwhile, exposed group were further divided into fetal-exposed group with participants born between July 28th, 1976 and May 4th, 1977, infant-exposed group with participants born between July 28th, 1975 and July 28th, 1976, and early childhood-exposed group with participants born between July 28th, 1974 and July 28th, 1975. The criteria for excluded were as follow: (1) participants who were not born in the destructive zone of the Tangshan earthquake; (2) participants without location of birth; (3) participants with DM at the baseline survey. Ultimately, a total of 7,568 eligible participants were included in this study. More details of the included and excluded individuals are shown in **Figure 1**. The study followed the Declaration of Helsinki and was approved by the Ethics Committee of the Kailuan Medical Group. All participants gave their written informed consent.

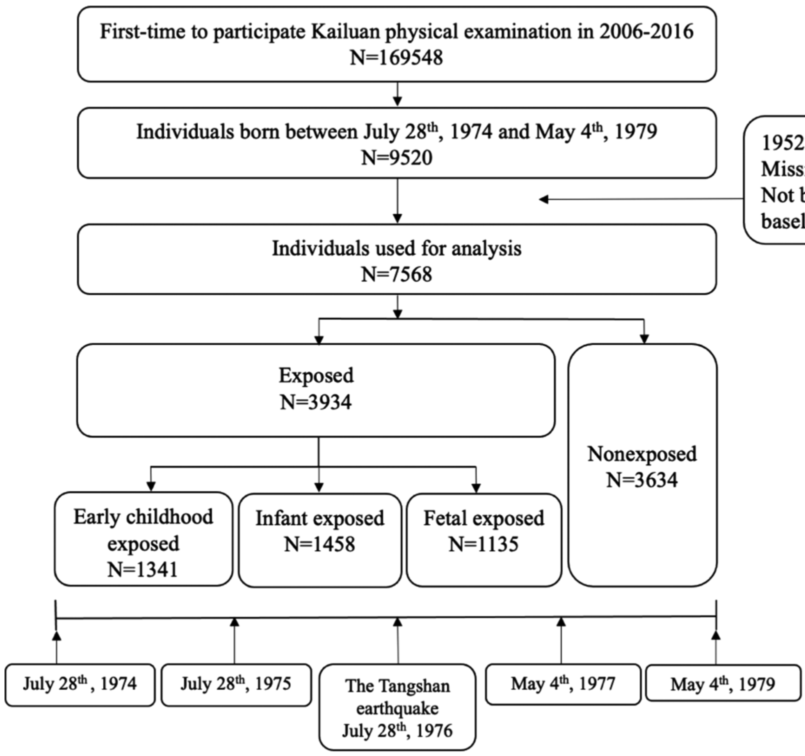

FIGURE 1
Flowchart of samples collection.

Earthquake exposure

The Tangshan earthquake was a natural disaster resulting from a magnitude 7.6 earthquake that hit the region around Tangshan, Hebei, China on July 28th, 1976. It is a kind of severe natural catastrophic event that can cause adverse physiological and mental responses. In this study, earthquake exposure was defined based on the date of the Tangshan earthquake and birth date of each participant. Earthquake severity was measured by seismic intensity according to the New Chinese Seismic Intensity Scale in 1957, which varied from I (not felt) to XI (disastrous), and the destructive zone was comprised of area where the intensity was between destructive and disastrous (V–XI) (9, 14). All participants who had similar characteristics of socio-economic status and living habits were selected from the destructive zones of the Tangshan earthquake.

Definitions of lifestyles status at baseline

The demographic characteristics (including gender, age, date of birth, education level and earthquake bereavement), lifestyles (including smoking status, alcohol intake, physical activity, sedentary behaviors and salt intake) and medical history of participants were collected face-to-face by trained staff using a standard questionnaire, which had been described in previous research (15), the earthquake bereavement was also collected through a structured questionnaire, with the following question, "Did you lose any relatives in the earthquake?". Healthy lifestyle score was assigned for each component of the five predefined lifestyles, with 0, 1, and 2 representing poor, intermediate, and ideal levels, respectively. The combined lifestyle score was the sum of the 5 lifestyle factors with a range from 0 to 10. Participants with a score of 0 was considered the worst possible scenario and those with 10 was considered the optimal scenario, and total score were divided into three quartiles, poor, intermediate and ideal (15). More details were presented in **Supplementary Table S1**.

Current smokers were defined as individuals who have smoked at least one cigarette per day over the last 6 months. Past smokers were defined as individuals who have quit smoking before or during the baseline survey. Meanwhile, current drinkers were defined as individuals who have drunk at least once a month over the past year, and past drinkers were defined as individuals who have quit drinking before or during the baseline survey. The sedentary behavior was defined as poor, intermediate or ideal with a relative sedentary time of ≥8, 4–7 and <4 h/day, respectively. For individuals who had physical activity 1–2 times per week and lasted for more than 20 min per time were defined as intermediate physical activity. The diet status of individuals was defined as poor, intermediate and ideal based on salt intake of ≥10, 6–9 and <6 g/day, respectively (15).

Covariates at baseline

DM was defined as either a self-reported physician diagnosis, or taking antidiabetic medication, or fasting blood glucose (FBG) ≥7.0 mmol/L in physical examination (16). Self-report of a physician diagnosis and an antidiabetic medication were collected by questionnaires provided by the survey among Kailuan General Hospital and 10 affiliated hospitals participants. Fasting blood glucose was measured using the hexokinase/glucose-6-phosphate dehydrogenase method (Mind Bioengineering Co Ltd., Shanghai, China) (17). Blood pressure was measured in the morning using physical examination, coffee, tea or physical exercise and other behaviors may affected the blood pressure were prohibited within 30 min before measurement. The measurement of blood pressure was repeated for 3 times, with 1–2 min interval for each measurement, and the mean value of blood pressure was taken. The height and weight of participants were measured by trained nurses, and body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Biochemical evaluation used the same fasting blood sample taken in the morning. Concentrations of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were measured at Kailuan General Hospital and 10 affiliated hospitals using an autoanalyzer (Hitachi 747; Hitachi, Tokyo, Japan).

Statistical analyses

For baseline characteristics of the study participants, mean ± standard deviation ($\bar{\chi} \pm s$) or median values with interquartile range (IQR) were used for continuous variables. Number and percentage (%) were used to describe categorical variables. Kolmogorov–Smirnov tests were performed for checking data normality. Pearson χ^2 test for categorical variables and Student t test or Mann-Whitney U test for continuous variables were used to compare the characteristics of the participants across baseline groups. The follow-up period was defined from the baseline survey to the onset of DM or the last visit on December 31th, 2017.

The comparison of the DM incidence with earthquake exposure was calculated by multivariate cox regression model, and hazard ratios (HR) with 95% CI were also calculated, with nonexposed individuals as the reference category. Except for all exposure and outcome variables, the missing covariates were imputed by multiple imputation methods (15). Model 1 adjusted for gender (male or female). Model 2 additionally adjusted for body mass index (≥24 or <24 kg/m^2), high education level (below high school or high school or above), income level (more than 5,000¥), earthquake bereavement (no, yes) and healthy lifestyle score (poor, intermediate, ideal). Model 3 included Model 2 and additionally adjusted for systolic blood pressure (SBP) (continuous variables), diastolic blood pressure (DBP) (continuous variables), TG (continuous variables), HDL (continuous variables), and LDL (continuous variables).

To demonstrate the possible modification of lifestyles in the development of DM, we generated interaction terms using the cross products of earthquake exposure with healthy lifestyle score, smoking status, alcohol consumption, physical exercise, sedentary time, and salt intake into multivariate cox regression model, respectively. The interactions between the lifestyles and DM development were examined by likelihood ratio testing. The P for interaction was calculated based on the number of exposure groups (nonexposed and exposed) and the number of subgroups for each modificator in subgroup analysis. The sensitivity analysis was performed to examine the effect of earthquake bereavement. We analyzed the 2014 and 2016 bereavement questionnaires ($n = 6{,}373$), and further compared the risk of DM with stratification of non-bereaved and bereaved earthquake survivors, with the nonexposed group as the reference. Furthermore, we compared the risk of incident DM with stratification of earthquake exposure (fetal-exposed, infant-exposed, and early childhood-exposed group) with the nonexposed group as the reference category. As the incidence of DM and other factors is not linearly increase with age, and the age difference between born during the earthquake and post-earthquake may introduce substantial bias in analysis. Many previous studies have employed the age-balance method to minimize the bias between earthquake (exposed group) and post-earthquake births (nonexposed group) (18–20), which was conducted by combining the pre-earthquake births and post-earthquake births as a new control group.

All analyses were conducted using SAS (Version 9.4; SAS Institute, Cary, NC), and a two-tailed $P < 0.05$ was considered as statistically significant.

Results

Among 169,548 individuals who participated Kailuan physical examinations between 2006 and 2017, 9,520 participants were born between July 28th, 1974 and May 4th, 1979. After excluding participants who had missing information of birth places ($n = 1{,}449$), were not born in earthquake destructive zone ($n = 309$) and had DM at the baseline ($n = 194$), 7,568 participants were included in this

TABLE 1 Baseline characteristics by different earthquake exposure groups.

	Earthquake nonexposed	Earthquake exposed	F/χ^2	*P*
Date of birth	May 4th, 1977-May 4th, 1979	July 28th, 1974-May 4th, 1977		
Participates, *n* (%)	3,634 (48.02)	3,934 (51.98)		
Age at survey ($\chi \pm s$, year)*	32.3 ± 3.9	34.7 ± 4.0	−27.17	<0.01
Male, *n* (%)	2,957 (81.37)	3,154 (80.17)	1.67	0.2
Smoking (%)	1,641 (45.16)	1,707 (43.39)	2.32	0.13
Drinking (%)	1,673 (46.04)	1,787 (45.42)	0.26	0.61
Salt preference (%)	630 (17.34)	678 (17.23)	0.05	0.98
Sedentary (%)	302 (8.31)	347 (8.82)	1.23	0.54
Regular physical exercise, *n* (%)	334 (9.19)	329 (8.36)	2.72	0.26
High education level, *n* (%)	1,914 (52.67)	1,895 (48.17)	15.12	<0.01
High income, *n* (%)	136 (3.74)	157 (3.99)	0.89	0.64
Earthquake bereavement, *n* (%)	147 (6.43)	251 (9.16)	12.36	<0.01
Body mass index ($\chi \pm s$, kg/m^2)*	24.6 ± 3.8	24.7 ± 3.6	−0.92	0.36
Systolic blood pressure ($\chi \pm$ s, mmHg)*	121.1 ± 15.4	122.1 ± 15.5	−3.01	<0.01
Diastolic blood pressure ($\chi \pm$ s, mmHg)*	79.1 ± 10.0	80.1 ± 10.2	−4.36	<0.01
Total cholesterol ($\chi \pm s$, mmol/L)*	4.7 ± 1.1	4.7 ± 1.1	−1.33	0.18
Triglycerides (IQR, mmol/L)[†]	1.2 (0.8,1.9)	1.2 (0.8,1.9)	−0.41	0.68
Low-density lipoprotein ($\chi \pm s$, mmol/L)*	2.5 ± 0.8	2.5 ± 0.8	−0.91	0.36
High-density lipoprotein ($\chi \pm s$, mmol/L)*	1.5 ± 0.4	1.5 ± 0.4	−1.57	0.11

*Data are presented as mean ± SD or percentage.
[†]IQR denotes interquartile range.

TABLE 2 Association between earthquake exposure and risk of DM in adulthood.

Model	Nonexposed	Exposed
Case subjects/total number	140/3,634	225/3,934
Incidence	6.59	9.91
Crude Model	1.000	1.50 (1.22–1.85)
Adjusted Model 1	1.000	1.53 (1.24–1.89)
Adjusted Model 2	1.000	1.46 (1.15–1.85)
Adjusted Model 3	1.000	1.47 (1.14–1.84)

Adjusted model 1 was adjusted for gender (male or female). Adjusted model 2 included adjusted model 1 plus body mass index (≥24 or <24 kg/m^2), high education level (less than high school or high school or above), income level (more than 5,000¥), earthquake bereavement (no, yes), healthy lifestyle (poor, intermediate, ideal). Adjusted model 3 included adjusted model 2 plus systolic blood pressure (continuous variables), diastolic blood pressure (continuous variables), triglycerides (continuous variables), high-density lipoprotein (continuous variables), low-density lipoprotein (continuous variables).

study (**Figure 1**). Among them, 6,111 (81.37%) were males, and the mean age was 33.5 ± 4.0 years. As shown in **Table 1**, compared with participants in the nonexposed group, participants in the exposed group were significantly older and had higher average SBP and DBP ($P < 0.05$). The distributions of high education level and earthquake bereavement were significantly different in two groups ($P < 0.05$) In addition, the baseline characteristics were almost comparable between participants included and those excluded due to missing birth places information, except that participants without birth places information had a lower proportion of males (**Supplementary Table S2**).

As shown in **Table 2**, 365 (4.82%) DM cases were identified during a median 5.8 years of follow-up, and the incidence density of DM was 6.59/1,000 person-years and 9.91/1,000 person-years for the nonexposed and exposed groups, respectively. The proportional hazard assumption for the Cox model was tested and found valid ($P = 0.32$). Compared with the nonexposed participants, the exposed participants had increased risks of DM in adulthood with HR of 1.47 (95% CI, 1.19–1.82) after multivariable adjustment in Model 3. Furthermore, in the age-balance analysis, the group combined of pre-earthquake and post-earthquake births was set as reference group, the increased risk of DM in exposed group remained statistically significant [HR 1.24, 95% CI, (1.05–1.48)] (**Supplementary Table S3**).

The interactions of lifestyles and earthquake exposure in early life on incidence of DM were presented in **Table 3**. According to the healthy lifestyle score, all participants were further stratified to poor, intermediate and ideal. After the stratified analysis, the results showed that no interaction effect was observed in healthy lifestyle score (*P*-interaction = 0.23). However, a positive modification effect was found in an individual lifestyle factor, alcohol consumption (*P*-interaction

< 0.05), and the HR of drinkers and non-drinkers were 1.82 (95% CI, 1.31–2.52) and 1.14 (95% CI, 0.80–1.62), respectively. Sensitivity analysis showed that the incidence density of DM was 10.44/1,000 person-years and 11.35/1,000 person-year for the non-bereaved and bereaved survivors, respectively (Table 4). Compared with nonexposed participants, the non-bereaved and bereaved survivors had increased risks of DM in adulthood with HR of 1.52 (95% CI, 1.21–1.90) and 1.71 (95% CI, 1.08–2.68) after multivariable adjustment in Model 3.

To explore the sensitive window during early life, the exposed group was further stratified to fetal-exposed, infant-exposed, and early childhood-exposed group based on the birth date and earthquake date. The incidence density of DM was 8.76/1,000 person-years, 11.29/1,000 person-years and 9.37 person-years for the fetal, infant and early childhood, respectively. Compared with nonexposed participants, infant and early childhood had increased risks of DM in adulthood with HR of 1.62 (95% CI, 1.21–2.17) and 1.46 (95% CI, 1.06–1.99) after multivariable adjustment in Model 3 (Table 5).

TABLE 3 Multivariable-adjusted HRs (95% CIs) for the association between earthquake exposure in early life and DM according to subgroup analysis among participants.

Model	Case subjects/*n*	HR (95% CI)	*P*-interaction
Healthy lifestyle score			0.23
Poor	93/1,598	1.61 (0.99–2.62)	
Intermediate	209/4,923	1.68 (1.22–2.31)	
Ideal	63/1,047	0.87 (0.49–1.57)	
Smoking status			0.46
Non-smokers	187/4,220	1.56 (1.10–2.20)	
Smokers	178/3,348	1.37 (0.98–1.91)	
Alcohol consumption			<0.05
Non-drinkers	154/4,108	1.14 (0.80–1.62)	
Drinkers	211/3,460	1.82 (1.31–2.52)	
Physical exercise			0.81
No	75/1,544	1.85 (1.05–3.25)	
Occasionally	256/5,361	1.40 (1.06–1.86)	
Regular	34/663	1.41 (0.63–3.15)	
Sedentary time, h/day			0.13
<4	177/3,235	1.26 (0.90–1.78)	
4–8	166/3,684	1.87 (1.30–2.70)	
≥8	22/649	0.59 (0.21–1.68)	
Diet, based on daily salt intake (g/day)			0.06
<6	38/893	2.67 (1.16–6.18)	
6–9	268/5,367	1.26 (0.96–1.66)	
≥9	59/1,308	1.79 (0.96–3.36)	

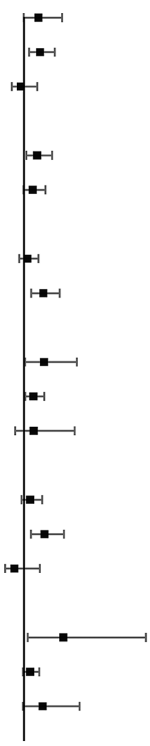

TABLE 4 Association between earthquake bereavement and risk of DM in adulthood.

Model	Nonexposed	Not bereaved by earthquake	Bereaved by earthquake	*P* for trend
Case subjects/total number	140/3,634	165/2,488	22/251	<0.001
Incidence	6.59	10.44	11.35	
Crude Model	1.000	1.63 (1.30–2.04)	1.67 (1.06–2.62)	
Adjusted Model 1	1.000	1.61 (1.29–2.02)	1.74 (1.11–2.73)	
Adjusted Model 2	1.000	1.55 (1.23–1.94)	1.65 (1.05–2.59)	
Adjusted Model 3	1.000	1.51 (1.20–1.89)	1.68 (1.07–2.63)	

Adjusted model 1 was adjusted for gender (male or female). Adjusted model 2 included adjusted model 1 plus body mass index (≥24 or <24 kg/m^2), high education level (less than high school or high school or above), income level (more than 5,000¥), healthy lifestyle (poor, intermediate, ideal). Adjusted model 3 included adjusted model 2 plus systolic blood pressure (continuous variables), diastolic blood pressure (continuous variables), triglycerides (continuous variables), high-density lipoprotein (continuous variables), low-density lipoprotein (continuous variables).

TABLE 5 Association between stratification of earthquake exposure and risk of DM in adulthood.

Model	Nonexposed	Fetal	Infant	Early childhood
Case subjects/total number	140/3,634	57/1,135	95/1,458	73/1,341
Incidence	6.59	8.76	11.29	9.37
Crude Model	1.000	1.31 (0.96–1.78)	1.74 (1.34–2.25)	1.42 (1.07–1.88)
Adjusted Model 1	1.000	1.30 (0.95–1.76)	1.77 (1.37–2.30)	1.48 (1.12–1.97)
Adjusted Model 2	1.000	1.24 (0.87–1.76)	1.64 (1.23–2.20)	1.46 (1.07–2.00)
Adjusted Model 3	1.000	1.21 (0.85–1.72)	1.63 (1.22–2.18)	1.45 (1.06–1.98)

Adjusted model 1 was adjusted for gender (male or female). Adjusted model 2 included adjusted model 1 plus body mass index (≥24 or <24 kg/m^2), high education level (less than high school or high school or above), income level (more than 5,000¥), earthquake bereavement (no, yes), healthy lifestyle (poor, intermediate, ideal). Adjusted model 3 included adjusted model 2 plus systolic blood pressure (continuous variables), diastolic blood pressure (continuous variables), triglycerides (continuous variables), high-density lipoprotein (continuous variables), low-density lipoprotein (continuous variables).

Discussion

To the best of our knowledge, this is the first study investigated associations between earthquake exposure in early life and risk of DM in adulthood in Asian populations. Moreover, it is also the first report about the effect of earthquake bereavement and the interaction of lifestyles and earthquake on the incidence of DM in adulthood. Our findings indicated that participants in the Tangshan earthquake exposed group were inclined to develop DM in adulthood. No interaction effect was observed between earthquake exposure and healthy lifestyle score, but an individual lifestyle factor, alcohol consumption was found that had positive modification effect on DM development. Meanwhile, compared with nonexposed participants, the bereaved survivors had increased risks of DM in adulthood, and the infant and early childhood period were specific susceptible earthquake exposure windows of DM development.

Supported by the DOHaD hypothesis, previous studies have linked exposure to disaster events in early life to metabolic disorders in adulthood. Lumey et al. showed that fetuses and children exposed to the Ukraine famine of 1932–33 was associated with an increased risk of DM in adulthood, with an odds ratio (OR) of 1.47 (95% CI 1.37–1.58) and 1.26 (95% CI 1.14–1.39) in extreme famine regions and severe famine regions (7). Dongfeng-Tongji cohort adequately demonstrated that the exposure to the Chinese famine (1959–1961) was associated with DM in adulthood during the 5 years follow-up period (21). As for earthquake, many studies reported the short-term impact of the Great East Japan Earthquake in Japan on DM development. It has been proved that the glycated hemoglobin (HbA1c) of affected individuals has altered and that glycemic control has worsened in a few months after the Great East Japan earthquake (5, 10, 22). In current study, the long-term impact of earthquake exposure on DM incidence in adulthood was investigated. Our results indicated that the early life stress indeed have impact on DM development, and the incidence of DM in adulthood among individuals who exposed to earthquake in early life was 1.47 times higher than nonexposed individuals, which was consistent with studies above. Moreover, it is worth mentioning that age difference is highly related to the incidence of DM, which may introduce substantial bias in analysis (18). Thus, the age-balance method was emplyeed to overcome this issue. After the age-balance analysis performed, the results still indicated a significant association between exposed group and combined group of pre-earthquake and post-earthquake. However, the development of DM may be affected by many factors, such as lifestyles and psychological stress, which need to be adjusted to obtain more accurate results.

Previous epidemiological and experimental studies have found that lifestyles may have impact on the risk of DM. Based on the China Cardiometabolic Disease and Cancer Cohort, Lu et al. found a significant interaction between ideal cardiovascular health metrics (ICVHMs) and famine exposure in early life on the risk of DM (18). Kautzky-Willer et al. reported that health behavior and physical activity were closely associated with risk of DM (23). In present study, the participants were divided into three quartiles (poor, intermediate and ideal) based on healthy lifestyle score, and we analyzed the interaction of healthy lifestyle score, individual lifestyle factor and earthquake exposure on DM incidence. However, no significant interaction was observed except alcohol consumption, and the results revealed that the increased risk of DM due to earthquake exposure might be modified by alcohol consumption in later life. Elgendy et al. conducted a study using data from the Evaluation of Diabetes Treatment study, an annual telephone survey in Quebec, Canada. The results implied the potential mechanisms between alcohol consumption and DM incidence, the chronic heavy alcohol consumption may induce alteration in glucose levels, insulin resistance, changes in lipid levels and interference in cell signaling (24–26), and individuals with DM who drink heavily were also more likely to have poor self-management behaviors, such as irregular diet, and seldom exercise, compared to those who drink less (27). Thus, alcohol consumption can increase the risk of DM through these metabolic, cell signaling and self-management changes. These findings have strongly supported our results. In addition, many previously epidemiologic studies showed the association between chronic diseases and bereavement stress among earthquake survivors. The prevalence of Post-Traumatic Stress Disorder after earthquakes ranged from 4.10% to 67.07% in adults and from 2.50% to 60.00% in children, and bereavement during the disasters is a predominant predictor (28). A cross-sectional survey showed that the bereaved survivors had a higher tendency to develop prolonged grief disorder (OR, 5.14; 95% CI, 2.72–9.74), compared with non-bereaved group (29). In present study, the bereaved survivors had increased risks of DM in adulthood after multivariable adjustment (*P* for trend <0.001), which indicated that more effective and sustainable mental health services were needed for bereaved survivors.

Amount studies have emphasized that the early life is a vulnerable period of development. Zhang et al. used the data from the Chronic Disease Survey and observed an increased risk of hyperglycemia in early childhood famine exposure cohort compared to the unexposed cohort with an OR of 1.46 (95% CI, 1.04–2.06) (30). Another study in Finland indicated that people evacuated overseas in early life during World War II had increment in the risk of cardiovascular disease and DM in late adulthood (31). To explore the sensitive window of early life, we further stratified the exposed group into fetal-exposed group, infant-exposed, and early childhood-exposed group, the results showed that infant and early childhood-exposed group appeared to have a significant increased risk of DM, compared with nonexposed individuals. However, the association between fetal-exposed group and risk of DM in adulthood was positive but not significant, which might be due to the inadequate sample size.

The mechanisms underlying the observed association between earthquake exposure in early life and DM in adulthood is difficult to determine and should be explored further. Evidence suggests that physiological stress response due to exposure to adversity in early life may be associated with concomitant activations of stress-related biological pathways (6, 32, 33). Although stress-related biological pathways (e.g., oxidative stress and inflammation) have been implicated in the development of diabetes and metabolic disorders (34, 35), the activation process of this system is not clear. It is likely to occur through dialogue with dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis (36–40). Specifically, activation of the HPA axis by stress should generally lead to an increase in glucocorticoid sensitivity, enabling cortisol to inhibit and thus regulate inflammatory responses (39). Inflammation may promote the secretion of cortisol through compensatory mechanisms, and the basal secretion capacity of β cells and HDL-C may regulate the secretion of basal cortisol through negative feedback and lead to the onset and development of DM (36, 38). Nelson et al. reported that 6–12 months is specific time to developmental domains for HPA axis and this specific time is a critical period for the development of chronic metabolic diseases (6). Moreover, Shonkoff et al. found that the response when children exposed to adverse events, which called “toxic stress response”, may prolonged activation of the stress response systems that directly lead to dysregulation of the HPA axis and associated neuro-endocrine-immune as well as epigenetic effects (41). Another behavioral risk factor surveillance system data in U.S showed children exposed to high psychological stress have higher cortisol levels and greater risk of common diseases (33). These findings provided a convincible support to our results. Further studies are needed to follow up these participants continuously to investigate the relationship between earthquake exposure in early life and other metabolic diseases in later life.

The strengths of the current study include the large community-based cohort in northern China covered data on medical examinations, histories of disease, lifestyle factors, which could adjust potential confounding factors at individual level. In addition, the ages of eligible participants exposed to the Tangshan earthquake have been limited from fetal to 2 years old, which minimized the impact of aging on elevated risks of DM outcomes. However, there were several limitations to our study. First, in Kailuan study, the diagnosis of DM was based on a single measurement of FBG rather than oral glucose tolerance testing or the measurement of HbA1c, and therefore, the incidence of DM might have been underestimated. Second, our study did not distinguish between type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). According to the Clinical Guideline for Prevention and Treatment of T2DM in China, T2DM represents 95% of all cases of DM. Third, all participants were employees and retirees of the Kailuan Group, and 82.07% of participants were males, and we did not further stratify the analysis by gender. In addition, the territoriality of our northern occupational population is a restriction, the generalizability of the results is relatively limited. Finally, we acknowledged that the age differences would introduce bias in the development of DM. We have tried to minimize the impact of age differences as possible by using the age-balance method, which was commonly used in previous studies. However, the limitations of combining age group were still exist.

Conclusion

In conclusion, the cohort study among Chinese populations suggests that exposure to earthquake in early life associated with DM in adulthood, and alcohol consumption and bereavement were all have impact on the incidence of DM. Furthermore, the significant association was observed in infant and early childhood-exposed group, which indicated that the infant and early childhood periods might be the sensitive windows of exposure period. These findings provide evidence on the adverse experiences in early life linked to DM in adults and emphasize the importance of enhancing health practice and sustainable mental health services among earthquake survivors to prevent early-stage chronic metabolic disorders.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

XS: conceptualization, methodology, data curation, formal analysis, original draft preparation, writing-reviewing and editing. LZ: conceptualization, methodology, visualization, writing-reviewing and editing, funding acquisition. WL: methodology, writing-reviewing and editing. YJ: methodology, data curation. ZL: reviewing and editing, funding acquisition. CL: data curation, methodology. XY: conceptualization, methodology, reviewing and editing. HH: supervision, reviewing and editing. SW: data curation, investigation, methodology. SC: data curation, investigation. JG: methodology, investigation, reviewing and editing. XL: investigation, reviewing and editing. AW: methodology, investigation. XJ: data curation, reviewing and editing. LG: conceptualization, methodology, supervision, reviewing and editing, funding acquisition. SH: methodology, supervision, reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.1046086/full#supplementary-material.

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Prevalence of waterpipe smoking and its associated factors among adolescents aged 12–16 years in 73 countries/territories

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Introduction: To describe the recent prevalence of, and trends in, waterpipe smoking and to examine its associated factors among adolescents aged 12–16 years in 73 countries/territories (hereafter "countries").

Methods: Data from 72 countries that had conducted a Global Youth Tobacco Survey (GYTS) in 2010–2019 and from the National Youth Tobacco Survey in the United States in 2019 were used to assess the recent prevalence of waterpipe smoking and to examine its associated factors among adolescents aged 12–16 years. Data from 38 countries that had carried out at least 2 surveys from 2000 to 2019 were used to determine trends in the prevalence of waterpipe smoking among adolescents.

Results: The recent prevalence of current waterpipe smoking (on 1 day during the past 30 days) among adolescents was 6.9% (95%CI 6.4–7.5). The prevalence was highest in the European region (10.9%, 9.9–11.8) and Eastern Mediterranean region (10.7%, 9.5–11.9), but lowest in the Western Pacific region (1.9%, 1.4–2.4). The prevalence of current waterpipe smoking increased or remained unchanged in 19 (50%) of 38 countries, but decreased in the remaining 19 countries (50%). Parental smoking, closest friends' smoking, secondhand smoke exposure, tobacco advertisement exposure, not being taught the dangers of smoking, particularly cigarette smoking, were positively associated with adolescent waterpipe smoking.

Discussion: Waterpipe smoking among adolescents remains a major public health issue worldwide, especially in the regions of Europe and the Eastern Mediterranean. Effective prevention and control strategies and measures are needed to curb the epidemic of adolescent waterpipe smoking.

KEYWORDS

waterpipe smoking, trends, risk factors, adolescent, Global Youth Tobacco Survey (GYTS)

Introduction

Waterpipe smoking is a means of tobacco use in which the user inhales smoke from a long, soft tube that pulls smoke through the device and out of a bowl of water. Waterpipe smoking, also known as hookah, narghile, argileh, goza, chica, qalyan, shisha, and hubble-bubble (1), emerged about 500 years ago in India and Iran before spreading to other countries and is now a growing epidemic (2). There is strong evidence that waterpipe smoking is harmful to human health (3, 4). Previous studies have shown that nicotine (the major source of waterpipe addiction) (5), carbon monoxide (which can cause hypoxia and cellular respiratory disorders) (6), polycyclic hydrocarbons (well-known carcinogens or potential carcinogens) (6), and other toxicants (e.g., heavy metals, tar, and particulate matter) (7, 8) were found in mainstream waterpipe smoke. Notably, the amounts of these toxicants mentioned above may even be higher in waterpipe smoke than in cigarette smoke (9, 10). A systematic review and meta-analysis found that waterpipe smoking was associated with a heightened odds of certain types of cancer (11). Another review suggested that regular waterpipe smoking was positively associated with respiratory symptoms, lung disease, and reduced pulmonary function (12). Münzel et al. also found that waterpipe and other tobacco product (tobacco cigarettes and e-cigarettes) use might increase the burden of symptoms in patients with coronavirus disease 2019 and cause more serious health consequences (13).

The harmful effects of waterpipe smoking are not restricted to adults, with adverse health effects such as acute lung infection and injury, carbon monoxide poisoning, and subclinical consequences (e.g., lung function decline, oral and systemic genotoxicity, and the alteration of vascular and hemodynamic functions) found among adolescents (14). Abbadi et al. found that waterpipe nicotine dependence was associated with depressive symptoms among adolescents (15). Alomari et al. reported that waterpipe smoking could inhibit the brain-derived neutrophic factor (which is the pivotal for neuronal survival, migration, dendritic arborization, synaptogenesis and differentiation) among adolescents (16). In addition, Ramôa et al. called on health care and dental care professionals to focus on the increasing popularity of waterpipe smoking among adolescents due to the potential oral hazards (17).

Historically, waterpipe smoking predominated in older men in certain countries. However, waterpipe smoking has become increasingly popular among young adults and has spread to more countries. Salloum et al. found that the prevalence of waterpipe smoking (defined as ≥1 day during the past 30 days) among young adults aged 18–29 years was 60.7% in Egypt, 67.7% in Jordan, and 63.1% in Palestine in 2016 (18). A recent systematic review found that waterpipe smoking was prevalent among university students in some Arab countries, especially in the Kingdom of Saudi Arabia (∼36.4%) (19). In addition, waterpipe smoking is widespread among young adults in South Africa (20), Germany (21), and Syria (22). However, to our knowledge, no previous study has assessed the global prevalence of, and trends in, waterpipe smoking among adolescents aged <18 years, particularly in low- and middle-income countries.

In this study, using the most recent data from the Global Youth Tobacco Surveys (GYTS) collected from 2010 to 2019 and a similar survey conducted in the U. in 2019, we aimed to assess the prevalence of, and trends in, waterpipe smoking among adolescents aged 12–16 years in 73 countries/territories (hereafter "countries"). We also examined the potential factors associated with adolescent waterpipe smoking.

Abbreviations: CIs, confidence intervals; GYTS, Global Youth Tobacco Surveys; NYTS, National Youth Tobacco Survey; OR, Odds Ratio; WHO, World Health Organization.

Methods

Study participants

The most recent data (collected from 2010 to 2019) on waterpipe smoking among adolescents aged 12–16 years were extracted from the self-administered, nationally representative, school-based, and cross-sectional GYTS conducted in 72 countries, which has been described in previous published studies based on the GYTS (23, 24). The protocol of GYTS was developed by the WHO and the US Centers for Disease Control and Prevention (CDC). All countries that conducted the GYTS followed a two-stage sampling strategy. The first stage involved randomly selecting schools in each country, and the second stage involved randomly selecting classes from all selected schools. All students in the selected classes were eligible to complete a standardized, anonymous questionnaire voluntarily. All GYTS were approved by each the respective ethical boards in each country. More details of the GYTS are available from the US CDC website (https://nccd.cdc.gov/GTSSDataSurveyResources/Ancillary/Documentation.aspx?SUID=1&DOCT=1).

For the US, we used data from the National Youth Tobacco Survey (NYTS) performed in 2019, which is similar with GYTS. The NYTS is performed among a representative sample that surveys tobacco use and related factors among U.S. adolescents. The questionnaire items and responses on waterpipe smoking and other related factors are identical between the NYTS and the GYTS. Further details of the NYTS are available from the U.S. CDC website (https://www.cdc.gov/tobacco/data_statistics/index.htm). Both the GYTS and the NYTS are ongoing surveys, with data collection repeated at regular intervals. Verbal or written consent was obtained from both the adolescent participants and their parents/guardians in both surveys.

To assess the recent prevalence of adolescent waterpipe smoking and its associated factors for this study, we used the most recent data that was available from the GYTS conducted in 2010–2019 in 72 countries, and the NYTS that was conducted in 2019 in the US. We also assessed the trends in the prevalence of adolescent waterpipe smoking from 2000 to 2019 based on data from 38 countries that had completed at least two GYTS surveys during this time period. The flowchart of exclusion and inclusion of participating countries is shown in Supplementary Figure S1.

Definition of waterpipe smoking

Current waterpipe smoking was defined as using waterpipe on ≥1 day during the past 30 days. Adolescents were asked to respond to the survey question "During the past 30 days, on how many days did you smoke waterpipe?," with the following frequency options for response: "0 days," "1 to 2 days," "3 to 5 days," "6 to 9 days," "10 to 19 days," "20 to 29 days," and "All 30 days." Ever tried or experimented with waterpipe smoking was assessed by the survey question "Have you ever tried or experimented with waterpipe smoking, even one or two puffs?," with options for response of "Yes" and "No." The location of last place of waterpipe smoking during the past 30 days was assessed by the survey question "The last time you smoked waterpipe during the past 30 days, where did you smoke it?," with the response options of "At home," "At a coffee shop," "At a restaurant," "At a bar or club," and "Other," The age that waterpipe smoking was initiated was assessed by the survey question "How old were you when you first tried smoking waterpipe?," with the response options of "7 years old or younger," "8 or 9 years old," "12 or 13 years old," "14 or 15 years old," and "16 years old." It should be noted that different countries have different waterpipe names (e.g., European countries: shisha; Arab countries: hookah and nargila (nargulia/nargile/nargileh), narguileh; other countries: hubble-bubble, gudugudaa, chicha), with these terms used in place of "waterpipe," as appropriate.

Potential associated factors

Current cigarette smoking was assessed using the survey question: "During the past 30 days, on how many days did you smoke cigarettes?" and defined as a response of smoking a cigarette on ≥1 day during the past 30 days. Secondhand smoke exposure was assessed with the following three questions: "During the past 7 days, on how many days has anyone smoked inside your home, in your presence?"; "During the past 7 days, on how many days has anyone smoked in your presence, inside any enclosed public place, other than in your home?"; and "During the past 7 days, on how many days has anyone smoked in your presence, at any outdoor public place?" with the responses to these questions combined to define exposure to secondhand smoke at home or in enclosed or outdoor places on at least 1 day during the past 7 days. Parental smoking status was assessed using the survey question "Do your parents smoke tobacco?," with the answers of "None," "Father only," "Mother only," and "Both." Closest friends' smoking status was assessed using the survey question "Do any of your closest friends smoke tobacco?," with response options of "None of them," "Some of them," "Most of them," and "All of them." Whether or not being taught dangers of smoking status was assessed by the survey question "During the past 12 months, were you taught in any of your classes about the dangers of tobacco use?," with response options of "Yes" and "No." Exposure to tobacco advertisements was assessed from three questions: "During the past 30 days, did you see any people using tobacco on TV, in videos, or movies?," "During the past 30 days, did you see any advertisements or promotions for tobacco products at points of sale?," and "Do you have something (for example, t-shirt, pen, backpack) with a tobacco product brand logo on it?" with exposure defined as a response of exposure to tobacco advertisements *via* at least one of the above-mentioned avenues. Each country's income level was defined based on the World Bank classification according to the survey year of the GYTS.

Statistical analysis

Prevalence estimates and 95% confidence intervals (CI) of current and ever tried or experimented with waterpipe smoking were calculated using the sampling weights, strata, primary sampling units provided in the GYTS dataset in each country. The weighted prevalence at national level was calculated based on the original sampling weights, and the overall and subgroup (sex, age group, regional, and other) estimates were calculated based on the rescaled weights, with consideration of the sample size of each country. Chi-square test was used to test the differences in the prevalence estimates between groups (sex, age group, WHO region, World Bank income category, cigarette smoking status, secondhand smoke exposure status, and parental smoking status). Poisson regression analyses were used to examine the trends in the prevalence of waterpipe smoking, with consideration of all available GYTS data in all survey years for each country. Multivariable logistic regression analyses were used to examine the association between waterpipe smoking and potential influencing factors (sex, age group, parental smoking status, smoking status of closest friends, cigarette smoking status, secondhand smoke exposure status, tobacco advertisement exposure status, being taught dangers of smoking status, World Bank income category, and survey year). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, US). A two-sided $P < 0.05$ was considered statistically significant.

TABLE 1 Prevalence of waterpipe smoking among adolescents aged 12–16 years by use frequency, sex, age group, WHO region, World Bank income category, cigarette use, secondhand smoke exposure, and parental smoking, 2010–2019.

Group	No. of countries	≥1 day			≥3 days			≥6 days		
		Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls
Total	73	6.9 (6.4–7.5)	8.5 (7.7–9.3)	5.3 (4.7–5.8)*	3.0 (2.7–3.2)	3.9 (3.5–4.3)	1.9 (1.7–2.2)*	1.6 (1.4–1.8)	2.2 (1.9–2.5)	0.9 (0.8–1.1)*
Age group										
12–14 years	73	5.8 (5.3–6.3)	6.9 (6.3–7.6)	4.8 (4.2–5.4)*	2.4 (2.1–2.7)	3.1 (2.7–3.5)	1.7 (1.4–1.9)*	1.2 (1.0–1.3)	1.6 (1.4–1.9)	0.8 (0.6–0.9)*
15–16 years	73	8.7 (7.8–9.7)	11.1 (9.8–12.3)	6.1 (5.2–7.0)*	3.9 (3.4–4.4)	5.2 (4.5–5.9)	2.4 (2.0–2.9)*	2.2 (1.8–2.6)	3.1 (2.5–3.6)	1.2 (0.9–1.5)*
P-value		<0.0001	<0.0001	0.0041	<0.0001	<0.0001	0.0007	<0.0001	<0.0001	<0.0001
WHO region										
Africa	11	4.2 (3.3–5.0)	4.5 (3.2–5.7)	3.9 (3.0–4.8)	1.8 (1.3–2.4)	2.0 (1.2–2.9)	1.6 (1.1–2.2)	1.0 (0.7–1.3)	1.0 (0.6–1.4)	1.0 (0.6–1.4)
Americas	17	4.2 (3.2–5.2)	4.4 (3.3–5.5)	4.0 (2.9–5.1)	1.6 (1.1–2.2)	1.8 (1.2–2.5)	1.5 (0.9–2.0)	0.9 (0.5–1.3)	1.0 (0.5–1.5)	0.8 (0.4–1.2)
Eastern Mediterranean	22	10.7 (9.5–11.9)	13.9 (12.3–15.6)	7.3 (6.1–8.6)*	4.4 (3.8–5.0)	6.5 (5.7–7.3)	2.2 (1.8–2.7)*	2.4 (2.1–2.8)	3.7 (3.1–4.3)	1.1 (0.8–1.4)*
Europe	18	10.9 (9.9–11.8)	12.9 (11.7–14.0)	8.8 (7.9–9.8)*	6.2 (5.5–6.9)	7.2 (6.3–8.0)	5.2 (4.4–6.0)*	2.4 (2.1–2.7)	3.2 (2.8–3.6)	1.5 (1.3–1.8)*
South-East Asia	2	5.4 (3.7–7.2)	7.9 (5.5–10.3)	2.9 (1.3–4.5)*	2.1 (1.3–3.0)	3.3 (1.7–4.9)	1.0 (0.4–1.6)*	1.4 (0.8–1.9)	2.5 (1.4–3.6)	0.2 (0.0–0.5)*
Western Pacific	3	1.9 (1.4–2.4)	2.5 (1.7–3.2)	1.3 (0.8–1.9)*	0.5 (0.3–0.7)	0.7 (0.4–1.0)	0.4 (0.2–0.6)	0.3 (0.1–0.4)	0.2 (0.1–0.4)	0.3 (0.1–0.5)
P-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0049
World Bank income										
Low income	10	4.6 (3.8–5.4)	5.2 (4.0–6.4)	4.0 (3.1–4.9)	1.9 (1.5–2.3)	2.3 (1.5–3.0)	1.5 (1.0–2.1)	1.1 (0.7–1.5)	1.3 (0.8–1.8)	0.9 (0.4–1.4)
Lower-Middle income	23	8.1 (7.1–9.1)	10.5 (9.1–11.9)	5.6 (4.7–6.6)*	3.1 (2.7–3.6)	4.5 (3.8–5.2)	1.7 (1.3–2.0)*	1.6 (1.3–1.8)	2.3 (1.8–2.8)	0.8 (0.6–1.0)*

(Continued)

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TABLE 1 (Continued)

Group	No. of countries	≥1 day			≥3 days			≥6 days		
		Total	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls
Upper-Middle income	23	7.3 (6.3–8.4)	8.7 (7.5–10.0)	5.9 (4.9–7.0)*	3.5 (2.9–4.1)	4.4 (3.5–5.2)	2.6 (2.0–3.1)*	1.8 (1.4–2.2)	2.5 (1.9–3.1)	1.1 (0.8–1.5)*
High income	17	4.7 (4.1–5.2)	5.6 (4.7–6.4)	3.8 (3.2–4.4)*	2.0 (1.7–2.3)	2.5 (2.0–3.0)	1.5 (1.1–1.8)*	1.4 (1.1–1.5)	1.9 (1.4–2.3)	0.9 (0.6–1.1)*
P-value		<0.0001	<0.0001	0.0018	<0.0001	<0.0001	0.0002	0.0065	0.038	0.34
Cigarette smoking										
Yes	73	30.1 (25.9–34.4)	32.8 (28.7–36.8)	25.3 (20.1–30.5)*	15.8 (13.3–18.4)	17.7 (15.1–20.4)	12.3 (9.1–15.4)*	9.2 (7.6–10.9)	10.8 (8.9–12.6)	6.4 (4.5–8.2)*
No	73	4.2 (3.8–4.7)	4.9 (4.3–5.5)	3.6 (3.2–4.1)*	1.5 (1.3–1.7)	1.9 (1.6–2.2)	1.1 (0.9–1.3)*	0.7 (0.6–0.9)	1.0 (0.8–1.2)	0.5 (0.4–0.6)*
P-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Secondhand smoke exposure										
Yes	73	9.8 (9.0–10.7)	12.3 (11.2–13.5)	7.3 (6.4–8.1)*	4.3 (3.8–4.7)	5.8 (5.1–6.5)	2.7 (2.3–3.1)*	2.3 (2.0–2.6)	3.3 (2.8–3.8)	1.3 (1.1–1.5)*
No	73	3.0 (2.6–3.4)	3.5 (3.0–3.9)	2.6 (2.0–3.1)*	1.2 (1.0–1.4)	1.5 (1.2–1.7)	0.9 (0.7–1.2)*	0.6 (0.5–0.7)	0.7 (0.6–0.9)	0.4 (0.3–0.6)*
P-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Parental smoking										
Both	46	23.1 (20.6–25.6)	26.3 (22.7–30.0)	19.6 (17.0–22.2)*	12.3 (10.4–14.2)	14.9 (11.8–17.9)	9.5 (7.7–11.2)*	7.0 (5.4–8.6)	9.7 (6.9–12.4)	4.1 (2.8–5.4)*
Father only	46	11.3 (10.0–12.6)	14.9 (12.6–17.2)	8.0 (6.8–9.1)*	4.4 (3.7–5.0)	6.4 (5.2–7.6)	2.5 (2.0–3.0)*	2.2 (1.8–2.6)	3.3 (2.6–4.0)	1.1 (0.8–1.5)*
Mother only	46	23.9 (19.6–28.2)	30.7 (23.3–38.1)	17.4 (13.4–21.5)*	9.4 (7.5–11.3)	11.2 (8.3–14.1)	7.7 (5.3–10.1)*	4.8 (3.5–6.0)	6.5 (4.5–8.5)	3.1 (1.7–4.6)*
Neither	46	6.1 (5.5–6.6)	7.7 (6.8–8.6)	4.4 (3.9–4.9)*	2.6 (2.2–2.9)	3.5 (3.0–4.1)	1.6 (1.3–1.9)*	1.3 (1.1–1.5)	1.9 (1.6–2.3)	0.6 (0.5–0.8)*
P-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Data are presented as % (95% CI).
WHO, World Health Organization.
*There was a statistically significant difference between sexes.

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Results

Participant characteristics

In this study, 335,062 adolescents aged 12–16 years (boys: 51.1%) from the 73 included countries had data on waterpipe smoking in 2010–2019. Of these 73 countries, 11 (15.1%) were located in the African region, 17 (23.3%) in the American region, 22 (30.1%) in the Eastern Mediterranean region, 18 (24.7%) in the European region, 2 (2.7%) in the South-East Asian region, and 4 (5.5%) in the Western Pacific region (Supplementary Table S1).

Prevalence of and trends in waterpipe smoking

Based on the most recent data conducted in 73 countries in 2010–2019, 6.9% (95% CI 6.4–7.5) of adolescents aged 12–16 years reported to have used a waterpipe on ≥1 day during the past 30 days, 3.0% (2.7–3.2) on ≥3 days, and 1.6% (1.4–1.8) on ≥6 days. The prevalence of current waterpipe smoking (on ≥1 day during the past 30 days) was higher among boys (8.5%, 7.7–9.3) and older adolescents aged 15–16 years (8.7%, 7.8–9.7) than among girls (5.3%, 4.7–5.8) and those aged 12–14 years (5.8%, 5.3–6.3). Sex and age differences remained when waterpipe smoking was ≥3 or ≥6 days during the past 30 days (Table 1). The prevalence of current waterpipe smoking varied significantly across countries even within the same WHO region (Figure 1 and Supplementary Table S2). The prevalence was highest in the European and Eastern Mediterranean regions and lowest in the Western Pacific region. The prevalence was higher in lower-middle income and upper-middle income countries than in low-income and high-income countries. The prevalence was approximately seven times higher among current cigarette users compared with those who did not currently smoke cigarettes, and was three times higher among adolescents who indicated they were exposed to secondhand smoke compared with those not exposed. The prevalence among adolescents whose fathers only, mothers only, and both smoked tobacco was higher than those whose parents did not smoke. Similar patterns were observed in other frequency categories of waterpipe smoking (≥3 or ≥6 days during the past 30 days) (Table 1). We also assessed the prevalence of ever tried or experimented with waterpipe using the most recent data (2010–2019) in 70 countries (Supplementary Tables S3, S4) and the prevalence was much higher (>10%) in most countries (49/70).

Based on the most recent data conducted in 52 countries in 2010–2019, 26.9% (23.4–30.4) of adolescents reported their initially use of waterpipe occurred before age 9 years, 39.5% (36.4–42.6) from age 10–13 years, and 34.2% (30.8–37.5) from age 14–16 years. More details of the distributions of age of initial waterpipe smoking by country, sex, WHO region, World Bank income category, current cigarette use status, secondhand smoke exposure status, and parental smoking status are shown in Supplementary Tables S5, S6.

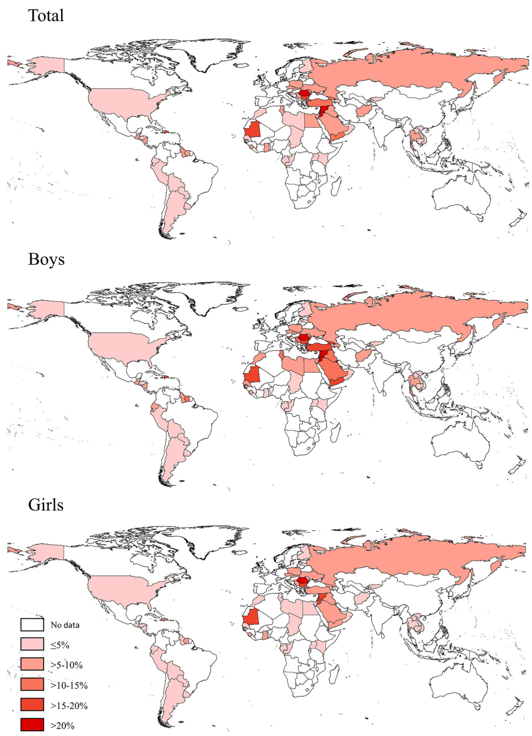

FIGURE 1
Prevalence of waterpipe smoking (on ≥1 day during the past 30 days) among adolescents aged 12–16 years in 73 countries/territories in 2010–2019.

Based on the most recent data from 48 countries in 2010–2019, 37.9% (35.4–40.3) of adolescents reported the last place that they used a waterpipe during the past 30 days was at home, 17.7% (16.0–19.3) at coffee shops, 9.9% (8.1–11.7) at a restaurant, 7.0% (5.8–8.1) at a bar or club, and 27.6% (25.3–30.0) at other places (Table 2). Boys tended to last use a waterpipe at coffee shops compared with girls, while for girls their last use of waterpipe more often occurred at home. The proportions of last waterpipe smoking at a restaurant, bar or club, and other places did not differ significantly between boys and girls in most countries. Young adolescents aged 12–14 years tended to last use waterpipe at home compared with older adolescents aged 15–16 years, while older adolescents aged 15–16 years last use of a waterpipe more often occurred at bars or clubs. The proportion of the last places to use a waterpipe during the past 30 days varied significantly by country, WHO region, and World Bank income category (Table 2 and Supplementary Tables S7, S8).

In this study, 38 countries had conducted ≥2 surveys from 2000 to 2019. 504,686 adolescents aged 12–16 years

TABLE 2 Proportions of the last place of waterpipe smoking during the past 30 days among adolescent waterpipe users by sex, age group, WHO region, World Bank income category, cigarette use, secondhand smoke exposure, and parental smoking, 2010–2019.

Group	No. of countries	Home	Coffee shop	Restaurant	Bar or club	Other places
Total	48	37.9 (35.4–40.3)	17.7 (16.0–19.3)	9.9 (8.1–11.7)	7.0 (5.8–8.1)	27.6 (25.3–30.0)
Sex						
Boys	48	33.9 (31.0–36.8)	21.2 (18.9–23.5)	9.0 (7.1–10.9)	6.8 (5.2–8.5)	29.1 (25.9–31.2)
Girls	48	43.9 (40.0–47.9)	12.2 (10.2–14.2)	11.3 (7.5–15.0)	7.2 (5.2–9.2)	25.4 (21.7–29.1)
P-value		<0.0001	<0.0001	0.27	0.79	0.14
Age group						
12–14 years	48	41.0 (37.5–44.5)	17.0 (14.4–19.5)	10.2 (7.8–12.5)	4.9 (3.9–5.9)	27.0 (23.9–30.1)
15–16 years	48	34.3 (30.9–37.6)	18.5 (15.6–21.3)	9.6 (7.1–12.0)	9.4 (7.4–11.4)	28.3 (24.8–31.7)
P-value		0.0053	0.48	0.71	<0.0001	0.57
WHO region						
Africa	7	35.4 (27.4–43.4)	24.1 (17.5–30.6)	13.1 (8.2–18.0)	10.0 (7.2–12.7)	17.4 (8.5–26.3)
Americas	9	27.8 (22.9–32.6)	10.1 (6.9–13.4)	4.2 (2.3–6.1)	14.9 (10.8–19.0)	42.9 (37.7–48.2)
Eastern Mediterranean	21	41.7 (38.4–44.9)	19.9 (17.6–22.1)	11.3 (8.7–14.0)	2.9 (2.2–3.6)	24.2 (21.4–27.0)
Europe	7	28.5 (24.5–32.6)	24.2 (19.8–28.6)	10.0 (7.8–12.1)	16.4 (13.9–18.8)	21.0 (17.3–24.6)
South-East Asia	1	40.9 (30.5–51.2)	3.8 (0.4–7.2)	4.9 (1.3–8.5)	14.3 (7.4–21.2)	36.1 (27.4–44.9)
Western Pacific	3	20.9 (13.9–27.8)	22.5 (13.8–31.2)	18.7 (14.3–23.2)	12.2 (5.5–18.9)	25.7 (16.8–34.4)
P-value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
World Bank income						
Low income	7	46.9 (41.4–52.3)	23.8 (19.0–28.6)	9.7 (6.8–12.7)	3.3 (2.5–4.1)	16.3 (13.8–18.8)
Lower-Middle income	18	37.1 (33.4–40.7)	21.2 (18.7–23.6)	14.5 (11.3–17.8)	4.5 (3.5–5.5)	22.7 (19.4–26.1)
Upper-Middle income	15	38.8 (34.7–42.8)	12.8 (10.2–15.4)	4.8 (3.5–6.2)	10.4 (8.1–12.8)	33.2 (29.6–36.8)
High income	8	34.6 (30.1–39.1)	17.0 (12.2–21.7)	4.5 (3.2–5.8)	7.1 (4.9–9.2)	36.8 (29.0–44.7)
P-value		0.19	<0.0001	<0.0001	<0.0001	<0.0001
Cigarette smoking						
Yes	48	29.8 (25.5–34.0)	23.6 (19.5–27.7)	8.3 (4.7–11.8)	8.4 (6.0–10.8)	30.0 (26.3–33.7)
No	48	40.7 (38.0–43.5)	15.4 (13.3–17.5)	9.9 (7.9–11.8)	6.4 (5.0–7.8)	27.6 (24.2–31.1)
P-value		<0.0001	0.0002	0.45	0.12	0.41
Secondhand smoke exposure						
Yes	48	38.0 (35.4–40.6)	18.3 (16.3–20.2)	9.8 (7.8–11.8)	6.7 (5.4–7.9)	27.2 (24.9–29.5)
No	48	37.8 (33.5–42.1)	15.2 (12.0–18.4)	10.2 (7.7–12.6)	8.1 (5.8–10.5)	28.7 (24.1–33.3)
P-value		0.94	0.11	0.82	0.25	0.51
Parental smoking						
Both	28	47.9 (41.9–54.0)	16.1 (12.7–19.6)	8.4 (4.8–12.1)	4.2 (2.6–5.7)	23.4 (18.6–28.1)
Father only	28	42.4 (38.0–46.8)	12.2 (9.9–14.5)	9.1 (5.9–12.4)	6.3 (4.3–8.3)	29.9 (25.9–34.0)
Mother only	28	33.6 (23.6–43.5)	11.8 (6.1–17.4)	12.0 (4.9–19.0)	4.9 (2.0–7.9)	37.7 (23.6–51.9)
Neither	28	38.3 (34.9–41.7)	16.0 (13.8–18.2)	9.9 (7.8–11.9)	4.9 (3.6–6.2)	30.9 (27.2–34.7)
P-value		0.029	0.039	0.82	0.28	0.099

Data are presented as % (95% CI).
WHO, World Health Organization.

were included to assess trends in the prevalence of current waterpipe smoking from 2000 to 2019. The trends in the prevalence of waterpipe smoking varied across countries (Supplementary Table S9). From 2000 to 2019, the prevalence of waterpipe smoking decreased in 19 (50.0%) countries, increased in 18 (47.4%) countries, and remained unchanged in 1 (2.6%) country (Table 3). In addition, the overall and subgroup (e.g., sex, WHO region, World Bank income category, cigarette smoking status, secondhand smoke exposure status, and parental smoking status) prevalence of waterpipe smoking (calculated as per 5 calendar-years) remained unchanged from 2000 to 2019 (Supplementary Table S10).

TABLE 3 Proportions of countries with upward, downward, and unchanged trends in waterpipe smoking (on ≥ 1 day during the past 30 days) among adolescents aged 12–16 years from 2000 to 2019.

Group	No. of countries	Total			Boys			Girls		
		Downward**	Upward**	Unchanged*	Downward**	Upward**	Unchanged*	Downward**	Upward**	Unchanged*
Total	38	50.0	47.4	2.6	52.6	42.1	5.3	47.4	47.4	5.3
WHO region										
Americas	6	67.0	33.0	0.0	66.7	16.7	16.7	66.7	33.3	0.0
Eastern Mediterranean	20	45.0	50.0	5.0	50.0	45.0	5.0	45.0	45.0	10.0
Europe	11	54.6	45.5	0.0	54.6	45.5	0.0	45.5	54.6	0.0
South-East Asia	1	0.0	100.0	0.0	0.0	100.0	0.0	0.0	100.0	0.0
World Bank income										
Low income	4	50.0	50.0	0.0	50.0	50.0	0.0	50.0	25.0	25.0
Lower-Middle income	14	57.1	42.9	0.0	57.1	42.9	0.0	57.1	42.9	0.0
Upper-Middle income	9	44.4	44.4	11.1	55.6	44.4	0.0	33.3	55.6	11.1
High income	11	45.5	54.5	0.0	45.5	36.4	18.2	45.5	54.6	0.0

Data are presented as %.
WHO, World Health Organization.
Poisson regression analysis was used to examine the trend in prevalence across all survey years (detailed results are listed in Supplementary Table S9, **P for trend <0.05; *P for trend >0.05).

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Association between waterpipe smoking and potential factors

As shown in Table 4, boys (vs. girls, OR = 1.31, 95% CI = 1.16–1.48), older adolescents aged 15–16 years (vs. younger adolescents aged 12–14 years, OR = 1.22, 95% CI = 1.07–1.38), parental smoking (father alone: OR = 1.51, 95% CI = 1.33–1.71; mother alone: OR = 2.76, 95% CI = 2.09–3.64; both: OR = 2.26, 95% CI = 1.91–2.66), closest friends' smoking (some: OR = 2.10, 95% CI = 1.84–2.40; most: OR = 2.74, 95% CI = 2.34–3.20; all: OR = 4.12, 95% CI = 3.16–5.37), current cigarette smoking (vs. not, OR = 4.76, 95% CI = 4.10–5.53), secondhand smoke exposure (vs. not, OR = 1.58, 95% CI = 1.39–1.80), tobacco advertisement exposure (vs. not, OR = 1.19, 95% CI = 1.07–1.33), and not being taught dangers of smoking (vs. being taught, OR = 1.23, 95% CI = 1.10–1.38) were associated with higher odds of adolescents waterpipe smoking. Subgroup analyses by sex, national income level and current cigarette smoking status showed similar results (Supplementary Tables S11–S13).

Discussion

Based on the most recent GYTS data (2010–2019) from 73 countries, 6.9% (6.4–7.5) of adolescents aged 12–16 years reported waterpipe smoking on ≥1 day during the past 30 days. The prevalence was highest in the European and Eastern Mediterranean regions. The most common places of last use of waterpipe were home (37.9%) and coffee shop (17.7%). In addition, the prevalence of current waterpipe smoking increased or remained unchanged in 19 (50%) of 38 countries. We found that the prevalence was higher in boys (vs. girls) and older adolescents (vs. younger ones). Parental smoking, closest friends' smoking, current cigarette smoking, secondhand smoke exposure, and not being taught the dangers of smoking were positively associated with waterpipe smoking among adolescents.

In this study, the overall prevalence of current waterpipe smoking was highest in Romania (36.9%) and lowest in Chad (0.7%) and Peru (0.7%), with more than 30% (22/73) of included countries having a prevalence of >10%. Previous studies in some specific countries also showed large differences in the prevalence of current waterpipe smoking, e.g., 46.1% in 2019 among Iraq male adolescents aged 15–18 years (25), 59.1% in 2018 among Jordan adolescents (mean age 14.6 years) (26), and 2.5% in 2017 among US middle and high school students aged 10–17 years (27). Since the age distributions of these previous studies were different from our study, direct comparison is not suitable. Nevertheless, these findings suggest that the prevalence of waterpipe smoking is already high among adolescents in many countries, underlying the need for more effort to prevent and control waterpipe smoking among adolescents.

To our knowledge, this is the first study to assess the prevalence of waterpipe smoking according to different use frequencies. We found that the prevalence was much lower when based on ≥3 days (3.0%) and ≥6 days (1.6%) vs. ≥1 day (6.9%) during the past 30 days, which was consistent with the prevalence of cigarette smoking based on different frequencies of use (28). This suggests that most waterpipe users (on ≥1 day) in adolescents are experimental. However, it is suggested that more than 10% of irregular smokers would become regular smokers after 1 year of follow-up (29). We also found that most adolescents first tried smoking a waterpipe before 13 years old. Given the addictive nature of waterpipe smoking, health education programs and regulatory frameworks to prevent waterpipe smoking among adolescents at an early age should be given priority.

We found that the prevalence of waterpipe smoking was highest in the Eastern Mediterranean and European regions. A systematic review that included 129 studies from 68 countries also reported that the prevalence of waterpipe smoking among adults was highest in the Eastern Mediterranean region, and the prevalence was also higher among youth in Eastern Mediterranean and European regions (although the prevalence estimates were mainly based on data collected before 2010) (30). Salloum et al. also reported that the prevalence of waterpipe smoking among young adults (18–29 years) in three Eastern Mediterranean countries was high (Egypt: 60.7%; Jordan: 67.7%; Palestine: 63.1%) (18). The main reason might be that waterpipe smoking is popular at social gatherings and has become ingrained in culture in these countries and regions (31). These findings suggest the need for more effective strategies and measures aimed at waterpipe smoking in Eastern Mediterranean and European countries.

Our study showed that the most common place for last waterpipe smoking was at home (37.9%), especially for girls and younger adolescents (aged 12–14 years), followed by coffee shops (17.7%). One study reported that the proportion of waterpipe smoking in coffee shops among young adults (18–29 years) was highest in three Eastern Mediterranean countries (Egypt: 74.0%, Palestine: 44.8%, Jordan: 43.0%) (18). Another study reported that home, friends' houses, coffee shops, and hookah bars were the most popular places for US young adult users aged 18–24 years (32). Widespread waterpipe cafe culture in some countries coupled with peer pressure might cause more adolescents to smoke waterpipe at coffee shops. Our data might be useful to inform policymakers of where targeted prevention might be directed to prevent adolescents from initiating or regularly smoking of a waterpipe.

Worryingly, the prevalence of current waterpipe smoking increased or remained unchanged in 50% (19/38) of countries. Similar unchanged trends were found in German adolescents aged 11–17 years from 2014 to 2017 (21) and Great Britain adolescents aged 11–18 years from 2013 to 2016 (33). Although a previous study showed a downward trend of waterpipe smoking

TABLE 4 Factors associated with waterpipe smoking (on ≥1 day during the past 30 days) among adolescents aged 12–16 years in 73 countries/territories, 2010–2019.

Variable	Prevalence (%)	β	OR (95% CI)
Sex			
Girls	5.3		1.00
Boys	8.5	0.273	1.31 (1.16–1.48)
Age group			
12–14 years	5.8		1.00
15–16 years	8.7	0.197	1.22 (1.07–1.38)
Parental smoking status			
Neither	6.1		1.00
Father only	11.3	0.411	1.51 (1.33–1.71)
Mother only	23.9	1.014	2.76 (2.09–3.64)
Both	23.1	0.814	2.26 (1.91–2.66)
Smoking status of closest friends			
None	4.2		1.00
Some	12.1	0.741	2.10 (1.84–2.40)
Most	21.0	1.006	2.74 (2.34–3.20)
All	36.9	1.416	4.12 (3.16–5.37)
Cigarette smoking			
No	4.2		1.00
Yes	30.1	1.561	4.76 (4.10–5.53)
Secondhand smoke exposure			
No	3.0		1.00
Yes	9.8	0.459	1.58 (1.39–1.80)
Tobacco advertisements exposure			
No	4.4		1.00
Yes	7.7	0.174	1.19 (1.07–1.33)
Being taught about dangers of smoking			
Yes	6.5		1.00
No	7.9	0.210	1.23 (1.10–1.38)
World Bank income			
Low income	4.6		1.00
Lower-Middle income	8.1	0.565	1.76 (1.39–2.22)
Upper-Middle income	7.3	1.716	5.56 (4.25–7.28)
High income	4.7	0.164	1.18 (0.90–1.54)
Survey year			
2016–2019	5.6		1.00
2010–2015	8.4	0.437	1.55 (1.32–1.81)

All variables listed in the table were introduced into logistic regression models.
OR, odds ratio; CI, confidence interval.

among US adolescents aged 10–17 years from 2011 to 2017 (27), we observed a slight upward trend in waterpipe smoking among US adolescents from 2011 to 2019. The prevalence of waterpipe smoking did not decrease in half of the included countries, which might be due to the wrong perceptions that the smoke was "filtered" through water, and that the associated risks might be minimal (34). In addition, the number of cafes or bars providing waterpipe has increased significantly as waterpipe smoking is increasingly popular among young adults (35). These findings highlight that health education programs should be strengthened to help control waterpipe smoking among adolescents.

In this study, we identified several important factors associated with waterpipe smoking. Cigarette smoking was strongly associated with waterpipe smoking. However, the causal relationship between waterpipe smoking and cigarette smoking should be made with caution because of the cross-sectional design of our study. Two other cross-sectional studies also showed that cigarette smoking was a determinant of adolescent waterpipe smoking, with OR of 3.18 (95% CI = 1.89–5.34) (36), and 6.06 (95% CI = 3.12–11.74) (37). However, a systematic review and meta-analysis based on six prospective cohort studies indicated that waterpipe smoking increased the risk of later initiation of cigarette smoking among young adults, although the definitions were not strict (the definition of waterpipe smoking was based on ever used waterpipe in four studies and cigarette use was also defined based on ever used cigarette in three studies) (38). These findings suggest policymakers should integrate waterpipe smoking with existing tobacco products when implementing policies and regulations on tobacco control.

We also found that parental smoking, closest friends' smoking, secondhand smoke exposure, tobacco advertisement exposure, and not being taught the dangers of smoking were positively associated with waterpipe smoking among adolescents. One study found that smoking of mothers or close friends were significantly associated with adolescent waterpipe smoking (39). Another study found that waterpipe smoking of family members and friends were positively associated with adolescent waterpipe smoking (37). Evidence from Lebanon suggested that secondhand smoke exposure and parental smoking were positively associated with adolescent waterpipe smoking (40). In addition, students who believed that waterpipe smoking was less harmful than cigarette smoking had a higher risk of engaging in waterpipe smoking (36). These findings highlight the importance of prevention strategies and measures that focus on providing adolescents with information about the dangers of waterpipe smoking (41). To comprehensively prevent adolescents from waterpipe smoking, waterpipe advertisements and promotions also should be monitored and restricted (42), including limiting the use of fruit flavors in waterpipe and adding labels of accurate nicotine content (43). In addition, use of education and interventions to improve adolescents' self-efficacy is also an effective way for adolescents to refuse waterpipe smoking by increasing young people's knowledge and perception of the dangers of waterpipe smoking (44).

Strengths and limitations

There are two strengths of our study. First, the same standardized questionnaire was used in all countries on national or sub-national representative data, making the estimates directly comparable across countries. Second, we assessed the frequency of waterpipe smoking (e.g., ≥1, ≥3, and ≥6 days during the past 30 days) in 73 countries, helping distinguish between regular use and experimentation. However, several limitations of our study should be noted. First, data on waterpipe smoking were self-reported, thus there might be recall bias. Second, the GYTS data did not provide information on the types and flavors of waterpipes. Further studies are needed to better describe which types and flavors of waterpipe are more commonly used by adolescents. Third, only adolescents aged 12–16 years were included in our study, thus the estimates should not be generalized to youths of other ages. Fourth, our study was based on data collected using a cross-sectional design, thus we could not determine causal relations between waterpipe smoking and related factors. Fifth, only 8 (11.0%) of 73 countries conducted the GYTS across several cities, thus the results might not be representative of the whole country. Sixth, only 73 countries were included in our study, most countries which have higher number of adolescents population (e.g., countries from South-East Asia) were not included due to unavailable GYTS data.

Conclusion

We found that waterpipe smoking among adolescents, especially in the European and Eastern Mediterranean regions, remains high-representing an important public health issue. It is important to establish effective prevention and control strategies to curb the epidemic of adolescent waterpipe smoking.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Ethics statement

Data from the GYTS and the NYTS are de-identified and do not include any data that allow participant identification. The country data sets are publicly available and have complied with a corresponding national ethical board review. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

BX designed the study and led the writing of the paper and was the principal investigator. CM drafted the first version of the manuscript. HY did the data analysis. HY and CM accessed and verified the data. BX, CGM, and MZ critically revised the manuscript. All authors critically revised the manuscript and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1052519/full#supplementary-material

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The influence of outdoor play spaces in urban parks on children's social anxiety

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Urban green spaces are critical to the healthy development of children's social interactions and activities. However, the relationship between urban green spaces for children's activities and the alleviation of children's social anxiety remains unclear. In this study, we aimed to explore the link between spatial characteristics and social anxiety in children. To explore the coupling relationships among green space, play space, and social anxiety, an assessment of children's play spaces and levels of social anxiety was performed using self-reported data, OpenStreetMap captured the characteristic indicators of urban parks, and the ArcGIS and SPSS softwares were used for the mathematical analysis. The results showed that (1) both the NDVI and 10-min accessibility were significantly negatively related to children's social anxiety; (2) the diversity of service facilities, surfacing materials, and the attractiveness and challenge of the environment were negatively related to children's social anxiety; (3) there were significant differences between activity types and social anxiety. These results provide design references and a theoretical basis for improving the benefits of urban green space on children's health and wellbeing.

KEYWORDS

urban park, play space, children, social anxiety, children's health

Introduction

Social anxiety disorder (SAD) is the most common type of anxiety disorder that contributes to other mental health disorders (1, 2) such as anxiety and depression (3). An estimated 9–46.7% of young people suffer from anxiety symptoms (4, 5), and the level of social anxiety among young people is rising (6). Social impairment in children predicts higher levels of depression (7). Prejudiced perceptions of social functioning in socially anxious children result from repeated exposure to unpleasant social interactions or a lack of positive interactions (8).

Socially anxious children's biased perceptions of social functioning are the result of repeated exposure to unpleasant social interactions or a lack of positive interactions. Studies have found that young people perform poorly in social situations, especially in negative interactions with peers, and this poor outcome, in turn, leads to anxiety, which, in turn, provides fewer opportunities for social skills, leading to poorer social performance (9). If not taken seriously, childhood social anxiety typically persists into adolescence or adulthood and increases the risk of psychological disorders (10, 11). SAD in childhood is associated with a wide range of negative outcomes, including disruption of social relationships, physical symptoms, substance abuse, and other psychiatric problems (12, 13). The main research tool used to assess social anxiety is the Social Anxiety Scale for Children-Revised (SASC-R) (14), which is a widely used self-report instrument of children's subjective feelings of social anxiety that has been used to assess the clinical and symptomatic levels of children's social anxiety (15).

With the advancement of urbanization, the benefits of green space have also been magnified. The impact of urban green spaces on physical and mental health has been extensively demonstrated (16). Research theories supporting this conclusion include the attention restoration theory (ART) (17), stress recovery theory (SRT) (18), and the biophilia theory (19). Among these theories, the SRT considers a non-threatening natural environment to be a restorative environment, which promotes improving people's positive emotional state and offers the best physiological arousal level (20). Some studies have found that a natural environment, no matter what type, can increase psychological wellbeing, including positive emotions, subjective life satisfaction, positive affect, subjective life satisfaction, and meaning in life (21). The ART describes natural settings as having soft fascination, in which nature can hold people's attention, thus, resting executive systems that regulate directed attention, holding back pessimistic thoughts, and reducing or eliminating negative emotions to be replaced by positive emotions (22). For example, studies have shown that bird songs and water sounds in nature have obvious positive regulating effects on children's stress recovery (23). According to the biophilia theory, the most basic human need is to communicate with nature (24). For example, when people hear words such as forest, green space, landscape, and wildflowers, it has a positive effect on improving mental health and life satisfaction (19). Even brief contacts with natural environments such as gardens and green spaces can improve psychological states (25) and are critical to "public mood" (26). Contact with a natural environment has a positive effect on children's mental health (27, 28) and also leads to better cognitive, mental health, and immune function (29). Nature exposure—in particular, the amount of physical contact that an individual has with nature (30) in childhood—is thought to develop habits, preferences, and mental health (31, 32). More nature exposure during childhood is thought to foster better habits, preferences, and mental health (32), for example, providing more nature exposure in daily life leads to a greater understanding of the biosphere and greater empathy for other organisms (33). In addition, the level of nature exposure during childhood is positively correlated with children's perceptions of the natural world as adults, as well as influencing their environmental behavior and awareness of environmental issues (34). Therefore, more outdoor activities in urban parks contribute positively to children's physical and mental development. Outdoor play areas can also develop children's language and comprehension, physical activity, and social skills (35, 36). This confirms the link between activity space design and value (37, 38). At the same time, children's positive or supportive interactions with playmates may be a protective factor that can help socially anxious children to develop more realistic views of their social functioning (38). However, the intrinsic link between urban green space characteristics and children's social anxiety is still not sufficiently understood.

In addition, children prefer to play with friends and partners when engaging in outdoor activities (39). Social distance, as proposed by research scholars, has been defined as the degree to which an individual is willing to interact or spend time with others outside of his or her own group (40). At the same time, social distance has been used as an important tool to assess the degree of closeness between individuals (41). Therefore, the distance between children and each other should be considered. Moreover, studies have found that social distance included close distance, individual distance, social distance, and public distance. When participating in activities with friends, adults' social distances are typically within 1.2–3.5 meters (42). These scales are often more appropriate for the design of specific elements within a space. This can provide a more rational and effective basis for the design of the interior of children's activity spaces.

Landscape features, facilities, amenities, and maintenance in urban parks indicate the quality of a green space (43). Various relationships between health and urban green space characteristics have been proposed, such as area size (44), space type (45), vegetation cover (46), and the normalized difference vegetation index (NDVI) (47) (the most commonly used plant cover index) that reflects plant growth, vegetation type and biomass, and is linearly related to vegetation cover (48). Urban parks provide places for children to play, especially in highly urbanized environments, and are essential outdoor resources for children's wellbeing (49, 50). The focus of urban planning has been to build child-friendly cities that promote children's development. Children's playgrounds should be fully integrated into urban open space systems and should be evenly distributed and easily accessible (51). Therefore, many studies have proposed that accessibility is the criterion to measure whether an urban space is child oriented (52), while, at the same time, evaluating the fairness and suitability of services provided by urban green spaces.

In this study, we aimed to investigate the effect of urban green spaces on children's social anxiety. We analyzed the relationship between children's social anxiety and spatial environments and explored the need for spatial environments to alleviate the level of social anxiety. In this work, we ask the following research questions:

Research Question 1 (RQ1) Is there a significant relationship between urban green space characteristics and children's social anxiety?
Research Question 2 (RQ2) If the answer to RQ1 is positive, is there a significant relationship between playing fields in green spaces and children's social anxiety?
Research Question 3 (RQ3) If the answer to RQ2 is positive, then, do the characteristics of children's activities in the playing field affect the patterns that have been observed?

Materials and methods

Study area

The study was conducted in Changchun, Northeast China, which is a developing megacity in China, with a population of more than 8 million. The urbanization level is relatively high (53), and the urban green coverage rate exceeds 40%. The selection of urban park green space involved the directory of urban parks and an actual investigation. According to the sampling selection, 15 community parks near children's daily living areas were selected, which were widely distributed, as shown in Appendix A.

Participants

In our study, based on child psychologist Jean Piaget's theory of cognitive development (54) and our previous research protocols (55), children were divided into three age groups: 4–7 years, 8–11 years, and 12–15 years. The field investigations were carried out on the site of children's play activities in urban green spaces. The field research was conducted every weekend in July, which was during the summer vacation period for children. According to a preliminary study, the number of children's activities on weekends was more than that on average working days. Therefore, we randomly set the time for recruiting interviewees to be every Saturday and Sunday in the urban parks. Questionnaires were distributed using sample surveys. Among the children aged 4–7, due to their limited cognitive ability (38), the children and guardians completed the questionnaire together. At the same time, and by trained observers, behavioral characteristics of the children's activities were recorded. After the subjects filled out the questionnaires, they returned them immediately. A total of 300 questionnaires were distributed. After excluding the missing questions and other problems, there were 254 valid questionnaires, and the effective rate of the questionnaires was 83%.

Measurement procedures

In terms of measurement indicators, the OpenStreetMap platform was used to obtain the park POI data, and the ArcGIS software was used to calculate green space characteristic indicators such as 10-min walkability and the NDVI. Regarding children's play areas, the Woolley and Lowe assessment tool was used to evaluate the spatial and environmental characteristics of children's play space in urban parks (38, 56), as shown in Appendix B.

To assess social anxiety in children, we used the Social Anxiety Scale for Children-Revised (SASC-R) (14) because of its good validity and wide application (15, 57). Three dimensions were included, i.e., fear of negative evaluation (SAD-FNE), social avoidance and distress to novelty (SAD-NEW), and general social avoidance and distress (SAD-GEN). Each adopted item was assessed on a seven-point rating scale from "never" (7) to "always have" (1).

Green space metrics

To select relevant urban park indicators, we referred to a previous research scheme (27), and to express the characteristics of urban green spaces we included area scale and the normalized difference vegetation index (NDVI) of the urban green spaces. The NDVI further indicated the plant coverage in the urban green spaces. The accessibility of park green space is one of the basic indicators for evaluating service efficiency. Generally, the walking proximity index of an urban green space is used, that is, the appropriate walking distance and walking time. The walking distance or time threshold was based on the law regarding the appropriate distance for an urban green space[1] or the survey and research results of walking preference time designated in (58–60). In this paper, because the research object was children in urban parks and green spaces, their walking distance to the park was closer to a 10-min walking distance. The accessible area based on a 10-min walk is a specific 10-min walking distance, that is, a distance of about 500 meters that creates a circular buffer zone representing the service area of each corresponding point (61). Therefore, our study used the ArcGIS network analysis and network service area analysis methods to calculate the accessibility coverage area, where the accessibility area of pedestrians in the park referred to the 10-min coverage area.

1 https://www.mohurd.gov.cn/gongkai/fdzdgknr/tzgg/201811/20181130_238590.html

Data analysis

We also tested the reliability and validity of the Children's Social Anxiety Scale and the Woolley and Lowe's play space assessment tool. The SPSS software was used to standardize the factors involved in the questionnaire. A reliability analysis was used to study the reliability and accuracy of the quantitative data. First, the alpha coefficient was determined. If this value was higher than 0.8, the reliability was high. The Cronbach's alpha coefficients of the SASC-R and Woolley and Lowe's assessment tool in this study were 0.848 and 0.819, respectively. The KMO and Bartlett tests were used to verify validity. If the KMO value was higher than 0.8, the research data were considered to be suitable for extracting information (excellent validity from the side reaction). The KMO for the SASC-R and Woolley and Lowe's assessment tool were 0.842 and 0.816, respectively. Therefore, the validity of the study data was good, and it could be inferred that the validity and reliability of the questionnaire were reasonable, indicating that the data were accurate and useful.The survey data were analyzed using the SPSS software based on the collection of game activity site assessments and questionnaires for each green space. The Spearman and Pearson correlation tests calculated the relationship between urban green space characteristics and children's social anxiety, the relationship between play activity space characteristics and children's social anxiety, and the relationship between activity characteristics and children's social anxiety. The tests were performed at $p < 0.01$ and $p < 0.05$ to test for significant differences. A stepwise regression analysis was also carried out to test the relationships among particular children's play space elements, environmental elements, and social anxiety in the green space. In addition, an analysis of variance (ANOVA) was used to test for significant differences in children's activity types and social anxiety.

Results

Descriptive statistics

The personal attributes and activity characteristics of the children are shown in Table 1. In terms of age, the proportion of the three age groups is similar, among which, the proportion of the 4–7-year-old age group is slightly higher (35.57%) and the proportion of the 12–15-year-old age group is slightly lower (29.90%). This shows that the populations in city parks are relatively equal in age and can accommodate the activity needs of children of different ages. In terms of gender, there is a slightly higher proportion of boys, i.e., 14.44% higher than girls, which may be related to different gender play habits, with boys preferring outdoor activities. In terms of activity frequency, the lowest proportions are less than once a week and more than five times a week; the highest proportion is 3–4 visits a week to a city park. In terms of the length of activities in urban parks, the lowest proportions are shorter than 30 min and more than 120 min, while a common activity duration is between 30 and 120 min, the activity duration between 60 and 90 min accounts for the highest proportion of 39.37%. Regardin activity distance, it can be seen that 1–2 m is the most common distance, accounting for 46.46%. The lowest proportion of activity distances are <0.5 m or more than 4 m, which are 2.36 and 7.48%, respectively. In our study, the most appropriate children's social distance when playing outdoor games was 1–2 m.

TABLE 1 Description of the study samples.

Item	Option	Amount	Proportion (%)
Age (years)	4–7	87	34.25
	8–11	91	35.83
	12–15	76	29.92
Gender	Boys	149	58.66
	Girls	105	41.34
Activity frequency (times/week)	<1	8	3.15
	1–2	50	19.69
	3–4	103	40.55
	4–5	78	30.71
	>5	15	5.91
Activity duration (min)	<30	24	9.45
	30–60	56	22.05
	60–90	100	39.37
	90–120	60	23.62
	>120	14	5.51
Activity distance (m)	<0.5	6	2.36
	0.5–1	41	16.14
	1–2	118	46.46
	2–4	70	27.56
	>4	19	7.48

TABLE 2 Correlation results of social anxiety and spatial environment.

	FNE	SAD-NEW	SAD-G
Green space area	−0.117	−0.089	−0.054
10-min accessibility	−0.227**	−0.146*	−0.159*
NDVI	−0.354**	−0.281**	−0.297**

* $p < 0.05$, ** $p < 0.01$.

TABLE 3 Correlation results of social anxiety and spatial environment.

	FNE	SAD-NEW	SAD-G
Spatial characteristics	−0.489**	−0.468**	−0.452**
Environmental characteristics	−0.390**	−0.357**	−0.346**

* $p < 0.05$, ** $p < 0.01$.

Results of the relationship between children's social anxiety and green space characteristics

Research Question 1 mainly explores the relationship between urban green space characteristics and social anxiety. In this study, we calculated the relationship between the urban green space index and children's social anxiety, as shown in Table 2. A correlation analysis was used to study the correlations among FNE, SAD-NEW, SAD-G, green space area, 10-min accessibility, and the NDVI. The Spearman correlation coefficient was used to indicate the strength of the correlation. The children's social anxiety factors significantly negatively correlated with the 10-min accessibility and the NDVI. Among them, FNE had the greatest influence on accessibility based on a 10-min walk and the NDVI, and the influence coefficients were −0.227 and −0.354, respectively ($p < 0.01$).

The results of the relationships among children's social anxiety and play field characteristics

The relationship between spatial environment and social anxiety

To explore the relationships between urban green play spaces and children's social anxiety, a correlation analysis was conducted to study the correlations among FNE, SAD-NEW, SAD-G, spatial, and environmental characteristics. As shown in Table 3, spatial and environmental characteristics both have significant negative relationships with the three factors of social anxiety. Among them, spatial environment significantly influenced FNE, and the correlation coefficient value was −0.489 ($p < 0.01$). Similarly, environmental characteristics also had the greatest impact on FNE, and the correlation value was −0.390 ($p < 0.01$). Moreover, spatial and environmental characteristics both had the least influences on SAD-G.

Spatial elements affecting social anxiety

To further answer Research Question 2, a stepwise regression analysis was performed with 11 spatial features as independent variables and social anxiety as the dependent variable, as shown in Table 4. Finally, the number of remaining immovable facilities, the seats, and the material of the ground are identified as three items in the model, and the R-square value is 0.246, which means that these three elements of spatial characteristics can explain 24.6% of the changes in social anxiety. The stepwise regression model did not include the other eight spatial characteristic variables. In the green space, fixed play equipment has the highest impact on social anxiety ($B = -0.250$, $p < 0.01$), and surfacing materials have the lowest impact on social anxiety ($B = -0.187$, $P < 0.01$). Moreover, the model passed the F-test ($F = 27.128$, $p = 0.000 < 0.05$). Through the regression model analysis, the model formula is: social anxiety = 4.444–0.186 * fixed play equipment-0.181 * seats-0.145 * surfacing materials.

Environmental elements affecting social anxiety

A stepwise regression analysis was performed with five game environmental characteristic elements as independent variables and social anxiety as a dependent variable, as shown in Table 5. Finally, two items, i.e., attractiveness and challenges, are identified in the model, and the R-square value is 0.143, which means that these two environments can explain 14.3% of the changes in social anxiety. In addition, the three environmental features, including visual stimulation, providing learning opportunities, and being suitable for all ages, were not included in the stepwise regression model. The attractiveness and challenge of the environment have similar effects on social anxiety, and the model passed the *F*-test ($F = 25.746$, $p = 0.000 < 0.05$), indicating that the model is valid. The model formula is social anxiety = 4.099–0.195 * attractiveness-0.212 * challenging.

Results of the relationships among social anxiety and activity characteristics in children

The relationships among activity characteristics and social anxiety

To answer Research Question 3, a correlation analysis was performed to study the correlations among FNE, SAD-NEW, and SAD-G and the frequency, duration, and distance of outdoor activities, as shown in Table 6. All three assessment factors of social anxiety are negatively related to children's activities. FNE has a significant relationship with activity frequency, duration, and distance; the correlation coefficient values are −0.151, −0.199, and −0.136, respectively. The SAD-NEW items, i.e., activity frequency and distance, both show significant relationships, and the correlation coefficient values are −0.132 and −0.159, respectively. SAD-G only has a significant relationship with activity frequency.

Differences in activity types and social anxiety

A one-way analysis of variance was performed to study the differences in activity types for FNE, SAD-NEW, and SAD-G. Table 7 shows that samples of the different activity types all show significant relationships ($p < 0.05$) with FNE, SAD-NEW, and SAD-G. Social activities, such as playing seesaw and slides, correlate with low social anxiety scores. Rule-based games

TABLE 4 Stepwise regression results of social anxiety and spatial elements.

	Unstandardized coefficients		Standardized coefficients	*t*	*p*	VIF	R^2	Adjusted R^2	F
	B	Standard error	Beta						
Constant	4.444	0.188	-	23.609	0.000**	-			
Number of non removable facilities	−0.186	0.045	−0.250	−4.161	0.000**	1.195	0.246	0.237	$F_{(3,250)} = 27.128, p = 0.000$
Seats	−0.181	0.048	−0.226	−3.759	0.000**	1.196			
Surfacing materials	−0.145	0.047	−0.187	−3.063	0.002**	1.229			

Dependent variable: social anxiety.
D-W value: 1.131.
* $p < 0.05$, ** $p < 0.01$.

TABLE 5 Stepwise regression results of social anxiety and environmental factors.

	Unstandardized coefficients		Standardized coefficients	*t*	*p*	VIF	R^2	Adjusted R^2	*F*
	B	Standard error	Beta						
Constant	4.099	0.186	-	22.065	0.000**	-			
Attractiveness	−0.195	0.050	−0.245	−3.882	0.000**	1.208	0.170	0.164	$F_{(2,251)} = 25.746, p = 0.000$
Challenging	−0.212	0.055	−0.245	−3.880	0.000**	1.208			

Dependent variable: social anxiety.
D-W value: 1.053.
* $p < 0.05$, ** $p < 0.01$.

TABLE 6 Correlation results of social anxiety and children's activity.

	FNE	SAD-NEW	SAD-G
Activity frequency	−0.151*	−0.132*	−0.162**
Activity duration	−0.199**	−0.126*	−0.089
Activity distance	−0.136*	−0.159*	−0.057

* $p < 0.05$, ** $p < 0.01$.

such as hide-and-seek have relatively high scores for social anxiety. This is followed by functional and imaginative activities. In contrast, social activities score lower on social anxiety. Furthermore, others conduct multiple comparison analyses, as shown in Appendix C. There is a significant difference between social anxiety groups regarding activity type. This is a further answer to Research Question 3.

Discussion

First, in this study, we investigated the relationships between children's social anxiety in 15 urban community parks and play space environments and explored the relationships between children's activities and social anxiety under the influence of space. Children's social anxiety was significantly negatively correlated with the NDVI, 10-min accessibility, play space characteristics, and environmental characteristics of urban green spaces. The accessibility of an urban green space is also considered to be one of the essential indicators to measure the efficiency of the design for children (52), and the higher the green space NDVI, the lower the social anxiety of children, which is further proof of the positive benefits of the NVDI (27). The findings also provide empirical evidence for the impact of urban green space planning on the park design–children's social anxiety relationship. Our results can help urban planners and policy makers to better understand what types of urban green spaces and outdoor play spaces can better alleviate children's social anxiety and can affect children's health.

Second, urban community parks are outdoor play spaces that are frequently visited by children (62). In our research, we found that the number of immovable facilities and seats in the play space and the variety of surfacing materials were negatively correlated with children's social anxiety. Especially, these facilities in the play space are more closely related to social interaction (63). These findings provide support for children's outdoor social interactions, activities, and other needs (64). The attractiveness and challenge of environmental features also reduce the level of social anxiety in children (65). Previous studies have shown the importance of natural elements in cities for children's health and activity (66). On this basis, our research shows that, in urban green spaces, the design of the environment and the impact of services on children are also particularly important. The combination of natural and artificial elements

TABLE 7 Correlation results of social anxiety and children's activity.

	Activity type (mean ± standard deviation)					F	p
	Rule class ($n = 58$)	Function class($n = 87$)	Social class ($n = 64$)	Construction class ($n = 11$)	Imagination class ($n = 43$)		
FNE	3.60 ± 0.68	2.81 ± 0.71	2.33 ± 0.60	2.39 ± 0.66	2.74 ± 0.79	27.895	0.000**
SAD-NEW	3.21 ± 0.58	2.79 ± 0.61	2.36 ± 0.63	2.33 ± 0.73	2.56 ± 0.69	16.123	0.000**
SAD-G	3.37 ± 0.66	2.82 ± 0.72	2.51 ± 0.65	2.48 ± 0.69	2.74 ± 0.78	12.867	0.000**

* $p < 0.05$, ** $p < 0.01$.

may provide greater benefits for children's wellbeing. Extending the time of children's activities, promoting the frequency of children's visits to green space, and promoting children's social activities are effective ways to reduce the level of social anxiety. This is particularly important for early-rise interventions for social anxiety in children (67).

Thirdly, in terms of the influence of children's social anxiety, we found that children engage in many activities in outdoor play space, such as running, jumping, seesaw, and ball games, and these aerobic exercises have been confirmed to reduce social anxiety, which is consistent with the results of our study. At the same time, we also found that the frequency and duration of activity and the distance between children's activities were closely related to social anxiety. Play spaces are more closely related to children's activities (39). It should be pointed out that, in our study, the most common value of the social distance of children in the outdoor play space of urban parks was 1–2 m, which was different from the common social distance of adults, i.e., 1.2–3.5 meters. To explain this difference, we found that some studies have shown that children's social distance is closer than that of adults (68). This also supports the validity of our experimental results. Activities to support this distance are mainly focused on ball games and activities with facilities such as seesaws and slides. In our study, social play was found to be negatively correlated with social anxiety scores. This was consistent with existing manifestations of social anxiety in children; often, the more socially anxious and less accepting of peers that children are, the less likely they are to engage in social play (69). It can be concluded that strengthening children's outdoor activities, and encouraging collectivism and group wellbeing (70) provide a new solution for alleviating children's social anxiety (71), and has positive guiding significance for the design and optimization of children's play spaces in urban parks.

Existing research on children's social anxiety has mostly focused on psychological medicine and social sciences, with a detailed classification of their living environments; major studies have explored the effects of family factors, school factors, and social factors on children's anxiety. The impact of family on children is the most direct and widely researched, and research on the psychological impact of green activity spaces on children is less well documented than adult health research, but should still be an important focus of current research because children are in a period of rapid growth and development and are more sensitive to the effects of natural exposure (72). Most of the studies are about children's psychological depression and anxiety, and there are almost no studies that have specifically focused on the effects of urban park play spaces on children's social anxiety. Our study was conducted from this aspect. It expands on the benefits of urban green spaces in terms of mental health. Our study belongs to the initial exploration of this field.

Finally, the limitations of the current study should be acknowledged. On the one hand, this study is a cross-sectional design, which limits the understanding of the causal relationship between children's play fields in urban green spaces and children's social anxiety and play space-based activities. The current study focused on the relationship between an urban green space and children's health benefits in summer, a relationship that may change with the season. As a result, longitudinal and experimental studies are recommended as future research to establish causal inferences about the effects of year-round children's play places in urban green spaces on children's social anxiety and social interactions. In addition, perhaps due to the limited number of people studied, we cannot derive demographic attributes such as gender differences with children's play space assessment. Additionally, local and social anxiety about children's activities were self-reported. It may have varied due to green space attachment economics and regional differences (73), which may have contributed to the study's findings. Moreover, due to the limitation of sample size, our study cannot be extended to the differences in age and gender of children.

Conclusions

This study explores the benefits of children's play space in urban green spaces and the relationship between the space environment and children's levels of social anxiety. Based on our findings, several conclusions can be drawn as follows:

First, the NDVI and accessibility of urban green spaces affect children's social anxiety. However, the relationship between the NDVI and children's social anxiety was a more significant degree of correlation. Secondly, among the spatial elements of children's play spaces in green spaces and the model constructed by social anxiety, three elements, i.e., the number of immovable facilities, seats, and surfacing materials, were the most significant. Environmental features significantly associated with children's social anxiety were the attractiveness and challenge of the environment. Finally, children's activity frequency, duration, and distance from each other were all related to social anxiety. This study expects to create a higher-quality outdoor activity environment in urban green spaces for children to play and socialize in public places and to provide valuable help in improving child-friendly cities.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Jilin Agricultural University Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Conceptualization and writing–review and editing: YB, MG, and DL. Methodology and visualization: MG. Formal analysis: XZ. Investigation and data curation: YB and XZ. Resources and supervision: YB, XZ, and DL. Writing—original draft preparation: YB. Funding acquisition: DL. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1046399/full#supplementary-material

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Short-term effect of ambient air pollution on outpatient visits for children in Guangzhou, China

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This study examined the short-term relationship between ambient air pollutants and children's outpatient visits, and identified the effect of modifications by season. Daily recordings of air pollutants (CO, NO_2, O_3, SO_2, PM_{10}, and $PM_{2.5}$) and children's outpatient visit data were collected in Guangzhou from 2015 to 2019. A generalized additive model adjusted for potential confounding was introduced to verify the association between ambient air pollution and outpatient visits for children. Subgroup analysis by season was performed to evaluate the potential effects. A total of 5,483,014 children's outpatient visits were recorded. The results showed that a 10 $\mu g/m^3$ increase in CO, NO_2, O_3, SO_2, PM_{10}, and $PM_{2.5}$ corresponded with a 0.19% (95% CI: 0.15–0.24%), 2.46% (2.00–2.92%), 0.27% (0.07–0.46%), 7.16% (4.80–9.57%), 1.16% (0.83–1.49%), and 1.35% (0.88–1.82%) increase in children's outpatient visits on the lag0 of exposure, respectively. The relationships were stronger for O_3, PM_{10}, and $PM_{2.5}$ in the warm seasons, and for CO, NO_2, and SO_2 in the cool seasons. When adjusting for the co-pollutants, the effects of CO, NO_2, and PM_{10} were robust. The results of this study indicate that six air pollutants might increase the risk of children's outpatient visits in Guangzhou, China, especially in the cool season.

KEYWORDS

time-series study, outpatient, air pollution, short-term, children

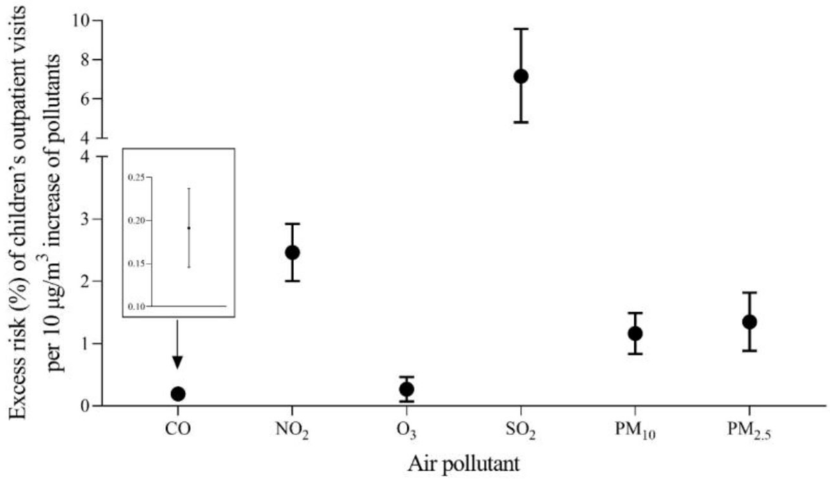
Highlights

- The air pollutants were associated with children's outpatient visits.
- The E–R curves between pollutants and outpatient visits sometimes were positive.
- The links between air pollution and outpatient visits were different in seasons.
- Most robust associations of CO, NO_2, and PM_{10} with children's outpatient risk.

1. Introduction

Ambient air pollution is a major global health issue with significant impacts worldwide, especially in developing countries. According to the Global Disease Burden, air pollution is a main cause of the global disease burden (1). Air pollution is a serious problem in China (2) due to rapid industrialization and urbanization over the past few decades. As the fourth largest environmental risk factor, air pollutants caused about 1.58 million deaths in China in 2016 (3).

Many epidemiological studies have demonstrated that exposure to air pollution, including carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), particulate matter with an aerodynamic diameter <10 µm (PM_{10}), and particulate matter with an aerodynamic diameter <2.5 µm ($PM_{2.5}$), can cause a range of adverse health effects. PM_{10} and $PM_{2.5}$ are significantly associated with cardiorespiratory mortality risks, and even an increased risk of respiratory mortality (4). SO_2, PM_{10}, and $PM_{2.5}$ are positively correlated with lung cancer



GRAPHICAL ABSTRACT

mortality in Guangzhou (5). One study showed that ambient NO_2 and $PM_{2.5}$ exposure are significantly contacted with aggrandized all-cause non-accidental mortality (6). The adverse impacts of $PM_{2.5}$ on cardiovascular emergency have been observed in previous studies (7, 8). Studies have also shown a positive correlation between $PM_{2.5}$ exposure and daily medical treatment for respiratory diseases (9, 10). Moreover, SO_2 and PM_{10} exposure are linked to increasing the risk of hospitalization for mental disorders (11). In short, previous studies have mostly reported the relationships between some of the six major air pollutants and human health effects, whereas there are few studies on the short-term relationships between six ambient air pollutants and health impacts.

Ambient outdoor and indoor air pollution caused the death of ~660,000 children in 2012 (12). Children are perhaps more sensitive than adults to the adverse health influences of air pollutants due to biological, behavioral, and environmental reasons (12). Children's exposure to ambient air pollution can have harmful and irreversible affections on organ systems because of their immature immune systems and developing lung functions (13). Compared with adults, children may inhale higher doses of air pollutants because they breathe more frequently and spend more time outdoors engaging in physical activity (14). Exposure to air pollution in infancy can cause lasting damage to cells and tissues, increase the risk of disease in children, and may have lifelong effects (15). Ambient air pollution exposure can affect child's development, so it is necessary to study the impacts of air pollutants on children's health.

Associations between children's health effects, specifically respiratory diseases, and ambient air pollutants have been well established. For example, lower respiratory diseases (16), upper respiratory tract infection (17), acute bronchitis (18), acute respiratory infections (14), pneumonia (19), and asthma (20) are significantly correlated with ambient air pollution. However, most studies have generally focused on a specific outpatient disease, and there is a lack of studies on the relationship between air pollution and children's outpatient visits for general diseases. In addition, many previous time-series studies lasted 2–4 years (18, 19, 21–23), and 5-year time-series studies have been limited.

Therefore, this study uses the time-series analysis method of quasi-Poisson generalized additive model to evaluate the acute effects of ambient air pollution (CO, NO_2, O_3, SO_2, PM_{10}, and $PM_{2.5}$) on outpatient visits for children in Guangzhou, China from 2015 to 2019.

2. Materials and methods

2.1. Study location

Guangzhou (113°17′E 23°8′N), a crucial central city in China, is a comprehensive transportation hub and an international trade center (Supplementary Figure S1). Guangzhou has an oceanic subtropical monsoon climate, with a yearly average relative humidity of 77%, an average temperature of 23°C, and annual rainfall of about 1,720 mm. It has high temperatures and much rain water in the summer, and is mild and comparatively dry in winter (24). Guangzhou covers an area of 7,434.4 km^2 and is divided into 11 municipal districts, with a resident population of 18.81 million by 2021.

2.2. Outpatient data

The data of children's outpatient visits were collected from January 1, 2015 to December 31, 2019 from the Guangdong Provincial Center for Disease Control and Prevention. The outpatient visits for children were obtained from six hospitals: Guangzhou Conghua District Hospital of Traditional Chinese Medicine, Guangzhou Panyu Central Hospital, Guangzhou First People's Hospital, The First Affiliated Hospital of Guangzhou Medical University, He Xian Memorial Affiliated Hospital of Southern Medical University, and the Clifford Hospital (Supplementary Figure S1).

2.3. Ambient air pollutants and meteorological data

During the study period, daily 24-h average concentrations of CO, NO_2, SO_2, PM_{10}, and $PM_{2.5}$, and maximum daily 8-h average concentration for O_3 were obtained from the Urban Air Quality Real-Time Release Platform (https://air.cnemc.cn:18007/) of the Ministry of Ecology and Environment of the People's Republic of China. The routine average concentrations of these air pollutants were from 21 air monitoring stations spread in the urban area of Guangzhou (Supplementary Figure S1). Meteorological indicators, including the daily mean temperature and average relative humidity, were collected from the Guangdong Meteorological Service at the same time. Those two parameters were included in the model to adjust for the effects of confounding factors.

2.4. Statistical analyses

A children's outpatient visit is a low probability event, conforming to the Poisson distribution. A time-series quasi-Poisson generalized additive model was introduced to verify the relationships between ambient air pollution and children's outpatient visits. According to the results of previous time-series studies (25, 26), several covariates were adjusted in the model. In this main smoothing model, degrees of freedom (df) were set on the basis of previous studies (24, 27):

$$\begin{aligned} Log\left[E\left(Y_t\right)\right] = & \ \beta Z_t + ns\left(time,\ df = 7/year\right) \\ & + \ ns\left(temperature,\ df = 6\right) \\ & + \ ns\left(relative\ humidity,\ df = 3\right) \\ & + \ DOW_t + \ intercept, \end{aligned}$$

where $E\left(Y_t\right)$ is the expected number of routine children's outpatient visits on everyday t, β is the regression coefficient, Z_t represents the pollutant concentration at day t, *ns()* is the natural cubic curve, and DOW_t is the dummy variable indicating the day of the week of day t.

The potential delay effect was analyzed using various delay effect constructions. These lag models were divided into two classifications: single lag effects (lag0–lag5) and cumulative lag effects (lag01–lag05). Then, by adding a natural spline function with 4 df to the above GAM model, the exposure–response association between children's outpatient visits and ambient air pollutants were plotted. In addition, stratified analysis was carried out according to the season. The cool period was from October 1 to April 30, and the warm period was from May 1 to September 30.

The significance of a difference between two groups was examined by determining the 95% confidence interval (CI) as follows: $(\beta_1 - \beta_2) \pm 1.96\sqrt{(SE_1)^2 + (SE_2)^2}$, where SE_1 and SE_2 are their

TABLE 1 Daily air pollutants, meteorological data, and children's outpatient visits during the study.

	Mean	SD	MIN	P25	P50	P75	MAX
Air pollution concentration ($\mu g/m^3$)							
CO	892.8	224.0	400.0	700.0	900.0	1,000.0	2,100.0
NO_2	46.8	19.1	8.0	34.0	42.5	55.0	168.0
O_3	90.1	52.3	0.0	49.0	84.0	122.0	287.0
SO_2	10.4	4.4	3.0	7.0	10.0	13.0	37.0
PM_{10}	55.3	27.3	9.0	36.0	48.0	70.8	212.0
$PM_{2.5}$	34.5	19.1	5.0	21.0	30.0	44.0	155.0
Meteorological measures							
Humidity (%)	80.3	10.3	31.0	75.0	82.0	88.0	100.0
Temperature (°C)	22.3	5.9	3.6	17.9	23.5	27.3	31.2
No. of daily children's outpatient visits	3,003	632	221	2,632	3,014	3,390	5,225
Season (N)							
Cool	3,029	663	221	2,694	3,074	3,416	5,225
Warm	2,966	584	1,465	2,577	2,930	3,354	4,816

TABLE 2 Spearman's correlations between daily average air pollution concentrations and meteorological factors during the study period.

	CO	NO_2	O_3	SO_2	PM_{10}	$PM_{2.5}$	Humidity
NO_2	0.57**						
O_3	−0.17**	0.10**					
SO_2	0.39**	0.55**	0.29**				
PM_{10}	0.52**	0.75**	0.37**	0.67**			
$PM_{2.5}$	0.59**	0.74**	0.30**	0.64**	0.96**		
Humidity	0.09**	0.03	−0.45**	−0.35**	−0.34**	−0.30**	
Temperature	−0.39**	−0.34**	0.43**	−0.04	−0.23**	−0.31**	0.16**

**$P < 0.01$.

standard errors, and β_1 and β_2 are estimate value for every subgroup (28, 29). To test the robustness of the estimated relationships, we changed the df with 4–10 per year (30, 31). Furthermore, co-pollutant models were constructed to check the stability of the results.

We regulated all statistical analyses with R software (version 4.1.1) using the *mgcv* package. The effects are expressed as the excess risk (ER), figured out by the (relative risk – 1) × 100%, and 95% CI of children's outpatient visits per 10 $\mu g/m^3$ increase in ambient air pollutants. $P < 0.05$ was considered statistically significant.

3. Results

Supplementary Figure S2 shows the time-series distributions of CO, NO_2, O_3, SO_2, PM_{10}, $PM_{2.5}$, and children's outpatient visits from 1 January 2015 to 31 December 2019 in Guangzhou. A total of 5,483,014 children's outpatient visits were recorded in the six hospitals. Table 1 shows the descriptive statistics of daily ambient air pollutants, children's outpatient visits, and meteorological conditions. The daily average concentrations of CO, NO_2, O_3, SO_2,

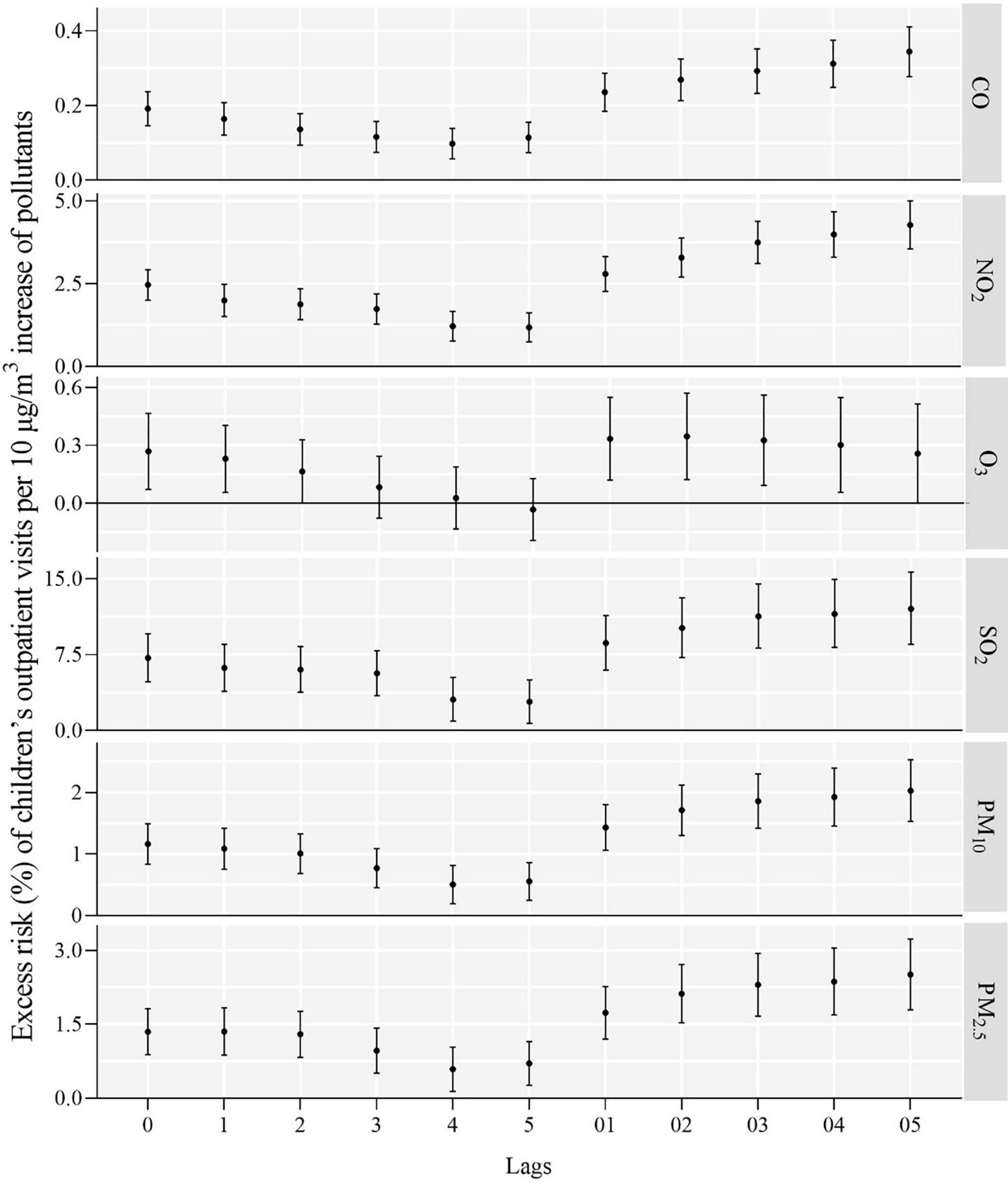


FIGURE 1
Excess risk (%) and 95% confidence intervals of children's outpatient visits a 10 $\mu g/m^3$ increase in various ambient air pollutant concentrations along different lag days.

PM_{10}, and $PM_{2.5}$ were 892.8, 46.8, 90.1, 10.4, 55.3, and 34.5 μg/m^3, respectively. These values for CO, NO_2, SO_2, PM_{10}, and $PM_{2.5}$ were about 0.2, 1.2, 0.2, 0.8, and 1.0 times the secondary standard limits of GB 3095-2012 set by China (4,000.0, 40.0, 60.0, 70.0, and 35.0 μg/m^3 annually), and 0.2, 4.7, 0.3, 3.7, and 6.9 times the ambient air quality standards in World Health Organization (WHO) (4,000.0, 10.0, 40.0, 15.0, and 5 μg/m^3 annually), respectively. O_3 concentrations on 193 and 699 days exceeded the daily criteria set by China (160 μg/m^3) and the WHO (100 μg/m^3), respectively. The daily average value of relative humidity was 80.3%, and the annual mean temperature was 22.3°C in Guangzhou.

Table 2 displays the Spearman correlation coefficients among ambient air pollution and meteorological elements in Guangzhou, China. The six air pollutants were positively correlated with each other, except O_3 and CO, and negatively correlated with temperature, except O_3. Moreover, relative humidity was negatively correlated with O_3, SO_2, PM_{10}, and $PM_{2.5}$, and positively correlated with temperature, CO, and NO_2. Significant correlations were observed between the exposure variables, except between SO_2 and temperature and between NO_2 and relative humidity.

As shown in Figure 1, a 10 μg/m^3 increase in CO, NO_2, SO_2, PM_{10}, and $PM_{2.5}$ was connected with excess risk of outpatient visits

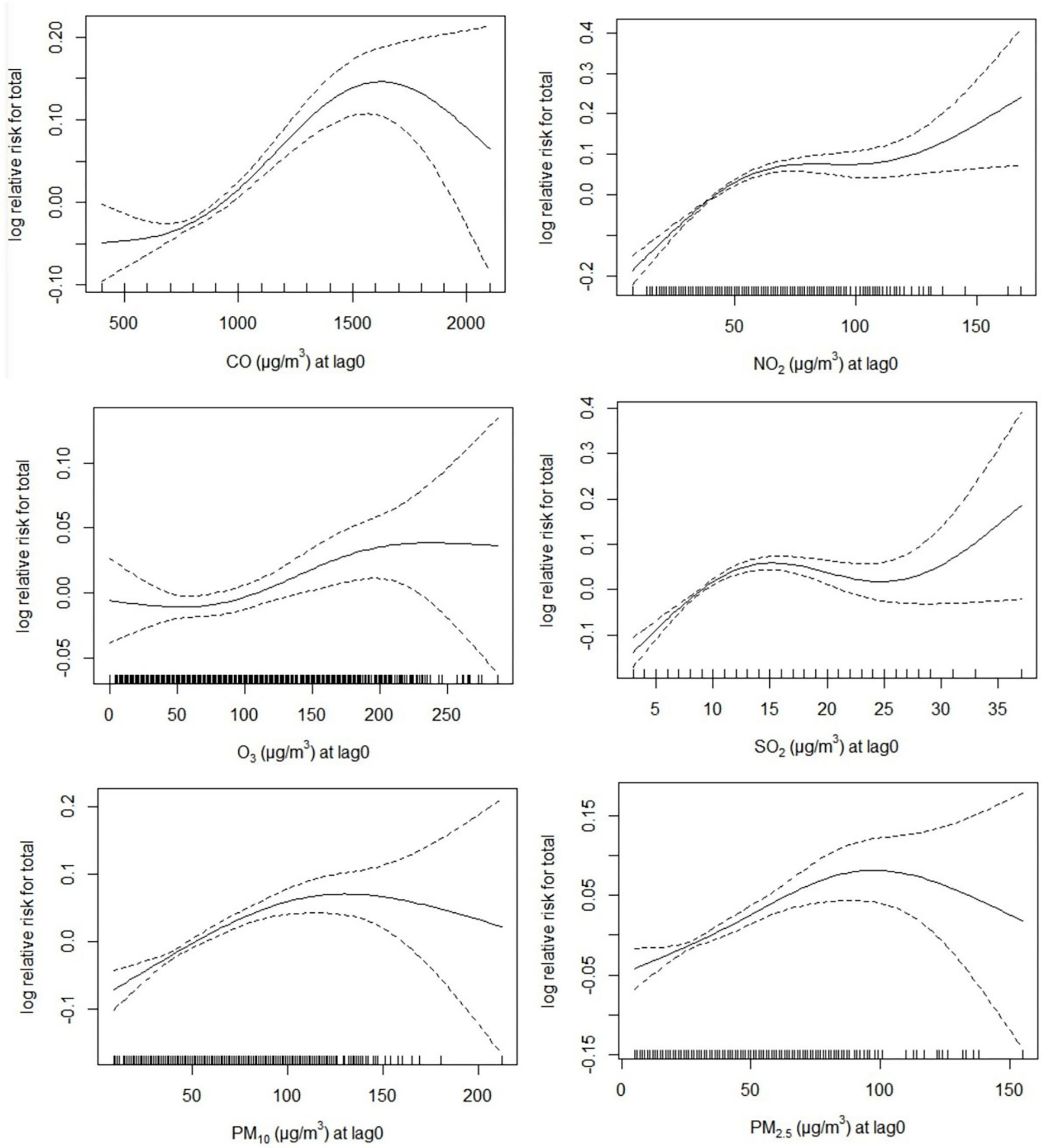


FIGURE 2
The exposure–response curves of the associations of different air pollution with the risk of children's outpatient visits in single-pollutant model. The black line represents the average relative risk of the pollutant concentration, and the dashed lines are the 95% confidence interval of the risk estimates.

TABLE 3 Estimated ER and 95% CI of children's outpatient visits a 10 μg/m^3 increase in the concentrations of air pollution stratified by season.

Pollutant	Whole	Season	
		Cool	Warm
CO	0.19 (0.15 to 0.24)	0.16 (0.10 to 0.21)*	0.08 (0.01 to 0.16)*
NO_2	2.46 (2.00 to 2.92)	2.03 (1.52 to 2.55)*	1.82 (0.86 to 2.80)*
O_3	0.27 (0.07 to 0.46)	0.15 (−0.14 to 0.45)*	0.29 (0.08 to 0.50)*
SO_2	7.16 (4.80 to 9.57)	5.67 (2.86 to 8.57)*	4.82 (0.95 to 8.85)*
PM_{10}	1.16 (0.83 to 1.49)	0.74 (0.36 to 1.11)*	1.00 (0.37 to 1.63)*
$PM_{2.5}$	1.35 (0.88 to 1.82)	0.82 (0.29 to 1.36)*	1.30 (0.41 to 2.20)*

*The difference between groups was statistically significant.

for children after adjusting for relative humidity and temperature. The estimated effects on risk of air pollutant concentrations were tested using models with different single lag days. The relationships between air pollution and children's outpatient visits were statistically significant, except for O_3 in the model with lag3–5 in the single-pollutant. According to the model fit statistics, this means that each 10 μg/m^3 increase in ambient CO, NO_2, SO_2, PM_{10}, and $PM_{2.5}$ corresponded to a 0.19% (95% confidence interval:0.15–0.24%), 2.46% (2.00–2.92%), 0.27% (0.07–0.46%), 7.16% (4.80–9.57%), 1.16% (0.83–1.49%), and 1.35% (0.88–1.82%) increase in children's outpatient visits on the day (lag0) of exposure, respectively. The cumulative lag days, like single lag days, ranging from lag01 to lag05. Overall, the influences of six air pollutants on the cumulative lag days were stronger than on the single days. The maximum cumulative effects were observed on lag02 for O_3, 0.35% (0.12–0.57%), and lag05 for CO, 0.34% (0.28–0.41%), NO_2, 4.27% (3.55–5.00%), SO_2, 12.01% (8.50–15.64%), PM_{10}, 2.03% (1.53–2.53%), and $PM_{2.5}$, 2.51% (1.79–3.23%).

The exposure–response curves of the correlations between ambient air pollution and children's outpatient visits are given in Figure 2. The curves of the ambient air pollution were obviously positive in the meaningful exposure range. The exposure–response curves of CO, PM_{10}, and $PM_{2.5}$ displayed a sharp pitch at concentrations <1,500 μg/m^3, <100 μg/m^3, and <100 μg/m^3 and then a decrease. The curves of O_3 were nearly S-shaped, sharply rising at concentrations ≥100 μg/m^3 and flattening for concentrations ≥200 μg/m^3. The exposure–response curves of NO_2 and SO_2 showed steep hill at concentrations <50 and <15 μg/m^3, rapidly ascended at concentrations ≥100 and ≥25 μg/m^3, and became flattened at mid-range concentrations.

Table 3 shows the estimated ER of children's outpatient visits and 95% CI by season breakdown of the concentrations of ambient air pollution. Season stratification revealed significant differences in the links between ambient air pollutants and the risk of children's outpatient visits. The associations with O_3, PM_{10}, and $PM_{2.5}$ were more prominent in warm than in cool seasons, and the links with CO, NO_2, and SO_2 were much stronger in cool seasons. Specifically, relationships between O_3 and children's outpatient visits were non-significant in the cool seasons.

In the sensitivity analysis, when we use df to adjust the smoothness of time from 5 to 9, the results did not change substantially, except for O_3 (Figure 3). Table 4 establishes the relationships between all ambient pollutants and children's outpatient visits in two-pollutant models, as assessed by another sensitivity analysis. In the two-pollutants analysis, the Spearman's correlation coefficients <0.7 were introduced into the co-pollutant models. The correlations of CO, NO_2, and PM_{10} in the risk of children's outpatient visits remained robust in the co-pollutant models. However, after adjusting for four air pollutants, the effects of O_3 became non-significant, while the adjustment for NO_2 yielded significant results. When adjusting for NO_2 and PM_{10}, the influences of SO_2 decreased and became not significant, respectively. After adjusting for CO, the effects of $PM_{2.5}$ decreased and became non-significant. Together, these results indicate that CO, NO_2, and PM_{10} may play more alone role in children's outpatient risk.

4. Discussion

We conducted a time-series study to assess the short-term relationships between ambient air pollution and children's outpatient visits and observed significant relationships. Exposure–response relationships between six ambient air pollutants and the risk of children's outpatient visits were positive in the meaningful exposure range. The associations with O_3, PM_{10}, and $PM_{2.5}$ were more prominent in warm than in cool seasons, and the links with CO, NO_2, and SO_2 were stronger in cool than in warm seasons. The correlations of O_3, SO_2, and $PM_{2.5}$ with children's outpatient visits were likely affected by other air pollutants, whereas CO, NO_2, and PM_{10} appeared to play more alone role in the risk of children's outpatient visits. This analysis provides the latest evidence to establish the relationships between air pollutants and harmful health effects.

Significant relationships between CO, NO_2, O_3, SO_2, PM_{10}, $PM_{2.5}$, and children's outpatient visits were found in this research, which was commonly consistent with previous time-series studies (22, 32–34). Each 10 μg/m^3 increase of O_3 and $PM_{2.5}$ corresponded to 0.27% (0.07–0.46%) and 1.35% (0.88–1.82%) increments in the risk of children's outpatient visits in the single-pollutant model, respectively, but these were not significant in the co-pollutant models, match with previous studies (31, 35). In the co-pollution model, the adverse effects of O_3 disappeared or even reversed may be explained by the relative instability of ozone (36). A weak but significant relationship between CO and children's outpatient visits was found, in line with a previous study (30, 37). In the analysis of the two pollutant models, the associations with NO_2 and PM_{10} remained robust, which may reveal that NO_2 and PM_{10} had more independent effects on children's outpatient visits. Previous studies have indicated that the level of significance did not increase when SO_2 be analyzed in co-pollutant model (38, 39).

Although exposure–response relationships may change due to a variety of limitations, including climatic characteristics, geographical location, air pollution mixtures, and population sensitivity (11, 31), the results still have reminders for human health assessment. In this research, a linear and limitation association between CO, PM_{10}, and $PM_{2.5}$ the risk of children's outpatient visits were identified within a certain range, whereas a linear and not threshold association between O_3, NO_2, SO_2 and children's outpatient visits were confirmed. The curve for NO_2 tended to plateau at mid-range concentrations. The S-shaped curve for O_3 tended to plateau at high concentrations. As a result, ambient air pollutant concentrations should be constantly reduced to protect human health and reduce the risks of outpatient visits among children.

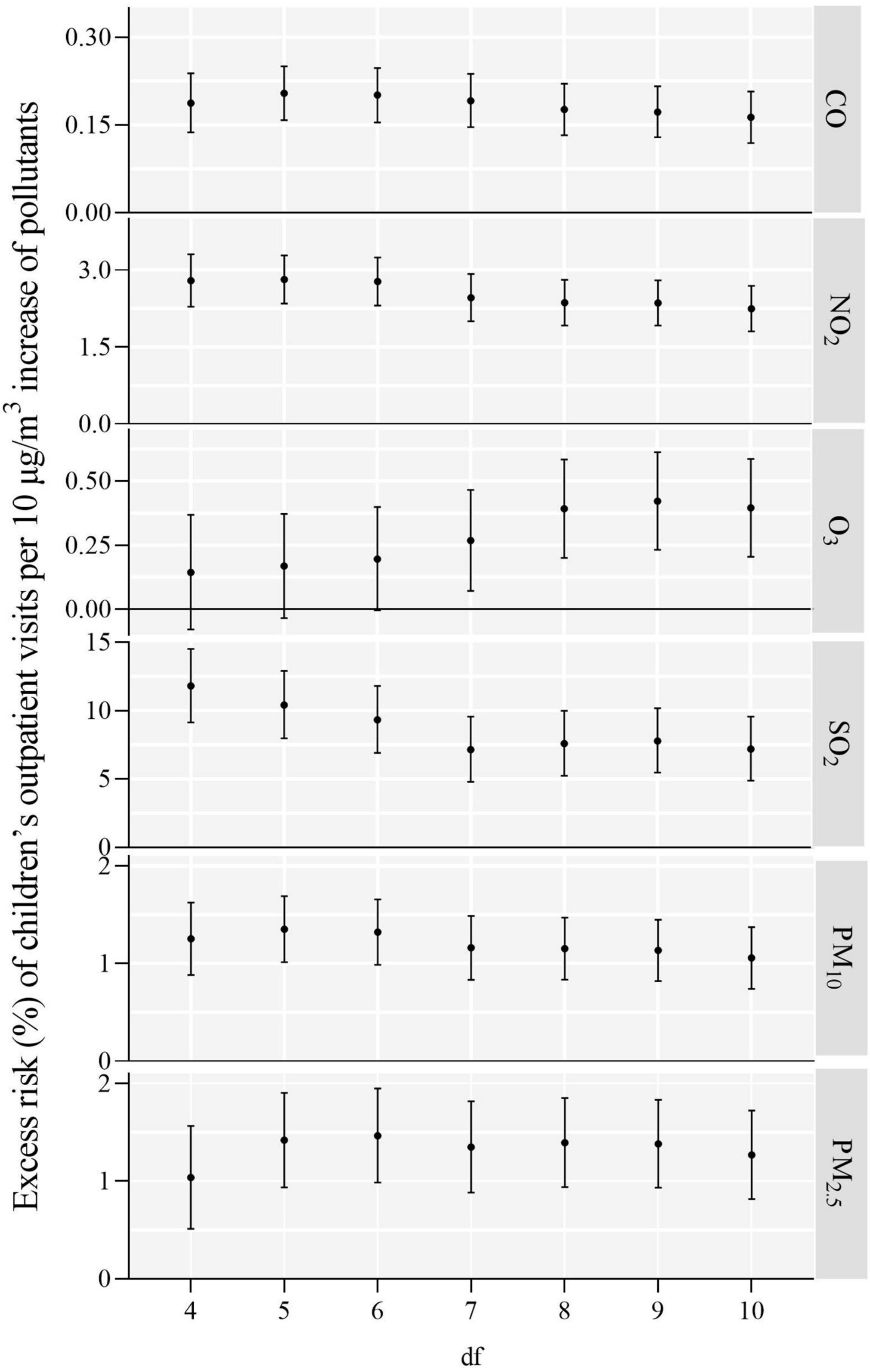


FIGURE 3
ER (%) and 95% CI of children's outpatient visits a 10 μg/m^3 increase in air pollution concentrations on the day of exposure.

The differences in the effects of CO, NO_2, O_3, SO_2, PM_{10}, and $PM_{2.5}$ on the risk of children's outpatient visits between cold and warm seasons were statistically significant. The influences of PM_{10} and $PM_{2.5}$ on this risk were significantly stronger in warm seasons, consistent with previous studies (31, 40). The possible reason may be that children spend more time outdoors in warm than in cold seasons. So their exposure dose perhaps lower during the cold seasons (31). The relationships of SO_2 and NO_2 with children's outpatient

TABLE 4 ER (%) and 95% CI of children's outpatient visits in co-pollutant models.

Two-pollutant models		Estimates
CO	–	0.19 (0.15 to 0.24)*
	$+NO_2$	0.08 (0.02 to 0.13)*
	$+O_3$	0.19 (0.14 to 0.23)*
	$+SO_2$	0.16 (0.11 to 0.21)*
	$+PM_{10}$	0.15 (0.09 to 0.21)*
	$+PM_{2.5}$	0.18 (0.12 to 0.24)*
NO_2	–	2.46 (2.00 to 2.92)*
	+CO	2.01 (1.46 to 2.56)*
	$+O_3$	2.73 (2.22 to 3.25)*
	$+SO_2$	2.85 (2.21 to 3.50)*
O_3	–	0.27 (0.07 to 0.46)*
	+CO	0.06 (−0.14 to 0.26)
	$+NO_2$	−0.25 (−0.46 to −0.04)*
	$+SO_2$	0.04 (−0.17 to 0.25)
	$+PM_{10}$	−0.10 (−0.33 to 0.12)
	$+PM_{2.5}$	−0.01 (−0.23 to 0.22)
SO_2	–	7.16 (4.80 to 9.57)*
	+CO	3.51 (0.98 to 6.10)*
	$+NO_2$	−2.64 (−5.59 to 0.39)
	$+O_3$	6.98 (4.43 to 9.59)*
	$+PM_{10}$	2.53 (−0.74 to 5.91)
	$+PM_{2.5}$	4.82 (1.58 to 8.16)*
PM_{10}	–	1.16 (0.83 to 1.49)*
	+CO	0.50 (0.09 to 0.92)*
	$+O_3$	1.25 (0.87 to 1.63)*
	$+SO_2$	0.89 (0.41 to 1.37)*
$PM_{2.5}$	–	1.35 (0.88 to 1.82)*
	+CO	0.17 (−0.43 to 0.77)
	$+O_3$	1.36 (0.83 to 1.89)*
	$+SO_2$	0.65 (0 to 1.31)*

*$P < 0.05$.

visits were stronger in the cool season. This finding was in agreement with several studies (41, 42) but contradictory to others (33, 35). The specific reason for these differences between warm and cool seasons must be clarified in the future.

The observed influences of ambient air pollution on children's outpatient visits are biologically plausible. NO_2 and SO_2 can augment the permeability of airway mucosa and increase allergic diseases (43). NO_2 can also induce airway inflammation and may restrict the smaller airways and terminal bronchioles (44). $PM_{2.5}$ and PM_{10} can be deeply inhaled into the lungs (45), causing various inflammatory reactions (46–48), and local inflammation of alveoli can further develop into systemic inflammatory (49). O_3 affects airway inflammation in children by increasing the levels of cationic proteins associated with leukocytes and eosinophils (50). $PM_{2.5}$, SO_2, and NO_2 can increase airway oxidative stress and reduce small airway function (51).

This study has a few limitations. First, we used in average pollutant concentrations from fixed-site monitors rather than individual monitoring data, which might have resulted in exposure errors (52). Second, although we used data on children's outpatient visits from six hospitals in the study city, selection bias might have existed. Third, due to the limitations of the collected children's outpatient records, we can only get the number of children's outpatients per day, without studying other stratification analyses and finding multiple visits during a course of illness (26). Fourth, none of the hospitals is a children's hospital which has the largest number of children's outpatient visits in the city. In addition, the matching between environmental exposure and illness is not enough because of the lack of the children's residential address and monitoring data from the nearest monitoring stations according to the location of hospitals, which is also the inadequacy of this study. Finally, we did not include confounding factors at the personal level (e.g., lifestyles and indoor pollution exposure) (53), which might affect the relationships between ambient air pollution and individual vulnerability.

5. Conclusions

This time-series analysis suggests that ambient air pollution, especially CO, NO_2, and PM_{10}, can significantly increase the risk of children's outpatient visits in Guangzhou, China. The relationships were stronger for CO, NO_2, and SO_2 in the cool seasons, and for O_3, PM_{10}, and $PM_{2.5}$ in the warm seasons. The findings of this study suggest that persistent efforts to reduce air pollution levels in Guangzhou would have health benefits, resulting in a decrease in children's outpatient visits. These results can only be generalized to cities with similar populations, societies, and environments.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

QY designed the study and supervised the research, including funding, text review, and overall quality assurance and control. SC helped with the formulation of research methods, software analysis, and wrote the original draft of the text. BX helped with the investigation and review of the data and assisted in the preparation of the original draft of the text. TS assisted in the implementation of research, data management, investigation, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1058368/full#supplementary-material

SUPPLEMENTARY FIGURE S1
The locations of 21 ambient air monitoring stations and 6 hospitals in Guangzhou between 1 January 2015 and 31 December 2019.

SUPPLEMENTARY FIGURE S2
The time-series distributions of CO, NO_2, O_3, SO_2, PM_{10}, $PM_{2.5}$ and outpatient visits from 1 January 2015 to 31 December 2019 in Guangzhou.

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Seasonal differences in the effects of local concentrations of atmospheric substances and meteorological elements on asthma exacerbation of children in metropolitan area, Korea: A 13-year retrospective single-center study

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Purpose: Air pollutants contribute to asthma exacerbation, and the types of air pollutants involved in acute asthma exacerbation may differ depending on climate and environmental conditions. This study aimed to identify factors affecting asthma exacerbation in each of the four seasons so that to prevent acute asthma exacerbation and to establish effective treatment strategies for each season.

Methods: Pediatric patients aged 0–18 years old hospitalized or admitted to the emergency room for asthma exacerbation at Hanyang University Guri Hospital between January 1, 2007, and December 31, 2019 were recruited. The number of asthma exacerbations comprised the total number of patients admitted to the emergency room or hospitalized for asthma and treated with systemic steroids. The association between the number of asthma exacerbations/week and average concentrations of atmospheric substances and meteorological elements in that week were analyzed. Multiple linear regression analyses were performed to examine the association between various atmospheric variables and the number of asthma exacerbations.

Results: The number of asthma exacerbations was found to be associated with the concentration of particulate matter with an aerodynamic diameter of ≤10 µm in that week in autumn. No atmospheric variables exhibited an association in other seasons.

Conclusions: Air pollutants and meteorological factors affecting asthma exacerbation vary by season. Moreover, their effects may change *via* their interaction with each other. The results of this study suggest that it will be helpful to establish differentiated measures for each season to prevent asthma exacerbation.

KEYWORDS

air pollutants, asthma exacerbation, meteorological element, mold, pollen

Abbreviations
CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; PM, particulate matter; SO_2, sulfur dioxide.

1. Introduction

The World Health Organization defines air pollution as contamination of the indoor or outdoor environment by any chemical, physical, or biological agent that adversely modifies the natural characteristics of the atmosphere (1). These agents directly affect human health (2, 3). Metropolitan areas are characterized by high population densities and high levels of transportation and industrial activities that jointly deteriorate the atmospheric environment (4, 5). Moreover, most residential areas and schools are located near roads, which can frequently present a threat of exposure to air pollutants such as particulate matter (PM), ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) (4–6). Recently, there has been a growing interest in PM, which has been reported to adversely affect patients with asthma by increasing their hospitalization rate, worsening respiratory symptoms, and hindering lung function (3, 7, 8). Pollen is a seasonal aeroallergen that causes allergies; accordingly, increased pollen concentration cause asthma exacerbation (9, 10).

Asthma is the most common chronic respiratory disease in childhood globally (11). Despite specific guidelines for the treatment of childhood asthma and improvements in asthma management, acute asthma exacerbations continue to occur, placing a considerable burden on both medical finances and pediatric patients and their families (12). Therefore, prevention of exacerbation is an important part of the treatment goal for asthma. Acute asthma exacerbation is defined as rapid worsening of asthma symptoms, such as coughing, shortness of breath, wheezing, and chest tightness (11–13).

PM with an aerodynamic diameter of ≤10 µm (PM_{10}), SO_2, NO_2, O_3, and CO plays a major role in asthma occurrence and exacerbation, as well as the course of this disease (14, 15). Other factors such as humidity, temperature, and temperature differences, all of which depend on seasonal variations, also contribute to asthma exacerbations (13). Weather changes increase emergency department visits and hospitalizations among patients with asthma (16). Extremely high temperatures are associated with increased emergency room visits by patients with asthma (17, 18). A previous study conducted in the United States found that summer heat significantly increased hospitalization rate for asthma, as well as that a decrease in winter temperature and an increase in SO_2 concentration were significantly associated with acute asthma exacerbation (19).

Types of air pollutants and meteorological elements involved in acute asthma exacerbation could be differ depending on climate and environmental conditions. Therefore, in the present study, we divided the year in Korea into four seasons and explored the factors that may be manipulated to prevent asthma exacerbations and establish seasonal-effective treatment approaches. The results of this study will contribute to the development of seasonal strategies for coping with exacerbations in patients with asthma.

2. Materials and methods

2.1. Ethical considerations

This study was approved by the Institutional Review Board (IRB) of the Hanyang University Guri Hospital, Gyeonggi-do, South Korea (IRB No. 2022-07-029). The requirement for written informed consent was waived owing to the retrospective nature of the study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Participant recruitment

Concentration of air pollutants greatly varies across regions. Therefore, we limited our study to a suburban area of Seoul (Gurisi, Gyeonggi-do, South Korea), which provides good access to the Hanyang University Guri Hospital for nearby residents. Gurisi is a city with 188,550 residents occupying an area of 33.31 km^2 (population density: 5,670.25/km^2). The city has a small mountain with a green index of 43 and a relatively small area of 211,699 m^2. There are no industrial complexes or large highways nearby, and most of the city's territory is taken by residential buildings that are 20–30 years old.

To analyze the association between asthma exacerbation and atmospheric substances to which the patients were locally exposed, only patients with no major difference between their place of residence and the main place of stay, such as school and workplace, were included in this study. Since most adults spend considerable time working, the separation between their home and working areas should be taken into account, as concentrations of atmospheric substances and pollen (in the external environment) of their residence areas may not represent their true exposure. In Korea, children attend kindergartens and schools in close vicinity from their home address. Therefore, most children living in Gurisi attend kindergartens and schools in the same area, so there is no difference between their place of residence and the place where they spend most of their daytime. Accordingly, we recruited only the patients aged <19 years old living in the designated study areas. Children aged 0–18 years old admitted to the emergency room or hospitalized for asthma at Hanyang University Guri Hospital between January 1, 2007, and December 31, 2019 were recruited. The patients were recruited only until the end of 2019 because, with the outbreak for COVID-19 pandemic, the exposure to air pollution has decreased due to reduced vehicle traffic and outdoor activity, which could interfere with the study analysis (20, 21).

2.3. Definition of asthma exacerbation

Asthma exacerbation was defined as admittance to the emergency room or hospitalization for asthma and treated with systemic steroids.

2.4. Exclusion

Respiratory diseases such as respiratory viral infections cause asthma exacerbation, constituting a variable that should be evaluated. However, considering that viral confirmatory tests are not performed in the emergency room, it was difficult to confirm whether the patients had respiratory viral infections. Therefore, we excluded patients with respiratory infectious diseases, such as bronchiolitis, bronchitis, or pneumonia, in addition to asthma.

Furthermore, we also excluded the patients who did not reside in Gurisi after confirming their residence through a chart review.

2.5. Air pollutants

PM and air pollutant concentrations were measured in Gurisi. Daily and weekly average concentration data for PM_{10}, $PM_{2.5}$, O_3, NO_2, CO, and SO_2 were collected from January 1, 2007, to December 31, 2019 using the data published by the Ministry of Environment (www.airkorea.or.kr).

There was one center in Guri, Gyeonggi-do, to measure air quality and two centers to measure air pollutants in the region. The distance between the two measuring stations was 2.3 km.

Among these centers, the data measured at a station near the hospital were used. Given that pollen and mold are being measured in the hospital, we attempted to measure the concentration of atmospheric substances in the same area. The concentration of SO_2 was measured using the pulsed UV-fluorescence method. CO concentration was measured with the non-dispersive infrared method and nitrogen dioxide (NO_2 concentration) concentration using the chemiluminescence method. The concentration of fine dust (PM-10) was assessed using the x-ray absorption method, while that of ozone (O_3 concentration) was evaluated using the UV photometric method.

2.6. Pollen and mold

Pollen was collected at Hanyang University Guri Hospital from January 1, 2007, to December 31, 2019. Pollen distribution was measured daily by installing a 7-day recording volumetric spore trap (Burkard Manufacturing Co., Hertfordshire, UK) at the height of 1.5 m from the surface of the hospital roof. We collected weekly drums that collected pollen from the air, and these were further examined by two specialists. The glycerin-adhesive vinyl was stained with Calberla fuchsin solution (10 ml of glycerin, 20 ml of 95% alcohol, 30 ml of distilled water, and 0.2 ml of basic fuchsin) and identified under an optical microscope with 400-fold magnification (OLYMPUS/BX43, Tokyo, Japan). The number of pollen grains/species/m^3 was calculated and recorded. Pollen was categorized according to its size, shape, and surface pattern depending on the allergy-related plants distributed in each region.

The number of mold/spores/m^3 was also recorded and calculated. The mold was categorized according to its size and shape.

2.7. Meteorological elements

The meteorological elements were measured in Gurisi. Daily and weekly average temperature, humidity, and precipitation data were collected from January 1, 2007, to December 31, 2019 using the data published by the Meteorological Agency (www.weather.go.kr).

2.8. Statistical analyses

In order to reduce the possible effect of variation in atmospheric environmental variables, such as temperature and humidity, we performed our analysis within a period of similar environmental variables. Therefore, correlations between atmospheric factors and asthma exacerbation were analyzed per each of the four seasons (spring, summer, autumn, and winter). Spring was defined from March to May, summer from June to August, autumn from September to November, and winter from December to February. For each individual week, we analyzed the association between the weekly number of asthma exacerbations and the average weekly concentration of air pollutants, pollen, and meteorological elements. First, cross-correlation coefficients between weekly measures of each environmental substance and asthma exacerbation were computed to determine which time point (t, t-1, t-2, or t-3) had the most influence. The time point abbreviations were as follows: (t) for that week, (t-1) for 1 week prior, (t-2) for 2 weeks prior, and (t-3) for 3 weeks prior. The associations between atmospheric factors that showed correlation during that period and the number of asthma exacerbations/week were investigated by multiple linear regression analysis to identify the factors with the greatest influence. Statistical significance in all analyses was set at p-value < 0.05, and all analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

3. Results

3.1. Demographic characteristics

A total of 633 patients (mean age, 6.58 ± 4.19 years; $n = 391$ males) experienced asthma exacerbations in the past 13 years.

The numbers of exacerbations in spring, summer, autumn, and winter in the data were 168 (26.5%; mean age, 7.32 ± 3.11 years; $n = 92$ males), 157 (24.8%; mean age, 4.98 ± 2.65 years; $n = 85$ males), 292 (46.1%; mean age, 6.79 ± 5.27 years; $n = 102$ males), and 131 (20.7%; mean age, 7.24 ± 2.96 years; $n = 79$ males), respectively. The number of exacerbations was the highest in autumn.

3.2. Spring

In spring, the average levels of O_3, CO, temperature, and humidity in a week (t) had the greatest correlation with the number of asthma exacerbations in that week (t). Moreover, the average concentration of PM10 1 week prior (t-1) also strongly correlated with the number of asthma exacerbations in a given week (t) (Table 1). The concentrations of other substances showed no correlation. The results of computing the association between the number of asthma exacerbations at (t)/week and the average concentrations of atmospheric substances at (t)/week using multiple linear regression revealed no correlation between asthma exacerbations and substance concentrations in that week (t) and 1 week prior (t-1).

3.3. Summer

In summer, concentrations of PM_{10}, O_3, and tree pollen during that week affected asthma exacerbation. The concentrations of other substances showed no correlation (Table 2). The results of multiple regression analysis with the concentrations and the number of asthma exacerbations in that week revealed no correlation between the number of asthma exacerbations and substance concentrations during that week (t).

3.4. Autumn

In autumn, concentrations of most environmental substances (PM_{10}, O_3, weed pollen, mold) in that week correlated with the number of asthma exacerbations in a given week (t). Concentrations of other substances showed no correlation (Table 3). The results of computing the association between the number of asthma exacerbations at (t)/week and the average concentrations of atmospheric substances that showed correlation at (t)/week using multiple linear regression revealed that the number of asthma exacerbations was associated with PM_{10} during that week (adj. $R^2 = 0.273$) (Table 4).

TABLE 1 Cross-correlation coefficients between the number of asthma exacerbations (t) and atmospheric substance (t-n) in spring.

In spring	t-3	t-2	t-1	t
PM_{10} ρXY (*h*)	0.018	0.069	**0.110**	0.070
O_3 ρXY (*h*)	0.021	0.063	−0.011	**0.124**
CO ρXY (*h*)	−0.109	−0.091	−0.035	**0.111**
Temperature ρXY (*h*)	0.064	.0031	0.104	**0.143**
Humidity ρXY (*h*)	−0.089	−0.017	0.042	**0.119**

Bold values represent highest cross-correlation coefficients.
t-n: n weeks ago.
ρXY (*h*): cross-correlation coefficient.
O_3, ozone; CO, carbon monoxide.

TABLE 2 Cross-correlation coefficients between the number of asthma exacerbations (t) and atmospheric substance (t-n) in summer.

In summer	t-3	t-2	t-1	t
PM_{10} ρXY (*h*)	0.002	−0.037	−0.053	**0.122**
O_3 ρXY (*h*)	0.055	−0.042	−0.068	**0.194**
Tree pollen ρXY (*h*)	0.024	−0.132	0.046	**0.159**

Bold values represent highest cross-correlation coefficients.
t-n: n weeks ago.
ρXY (*h*): cross-correlation coefficient.
PM_{10}, particulate matter 10; O_3, ozone.

TABLE 3 Cross-correlation coefficients between the number of asthma exacerbations (t) and atmospheric substance (t-n) in autumn.

In autumn	t-3	t-2	t-1	t
PM_{10} ρXY (*h*)	0.030	0.007	0.057	**0.137**
O_3 ρXY (*h*)	0.055	−0.110	0.044	**0.164**
Weed pollen ρXY (*h*)	0.005	0.010	0.039	**0.129**
Mold ρXY (*h*)	0.046	0.086	0.055	**0.177**

Bold values represent highest cross-correlation coefficients.
t-n: n weeks ago.
ρXY (*h*): cross-correlation coefficient.
PM_{10}, particulate matter 10; O_3, ozone.

TABLE 4 A multiple linear regression analysis of the number of asthma exacerbations (t)/week (y) and correlated atmospheric substance (t) in autumn.

	Estimate (b_i)	Std. error	*p*-value
PM10	**0.0182**	**0.002013**	**<0.001**
O_3	21.2514	18.532169	0.1341
Weed pollen	3.5299	11.378256	0.8290
Mold	697.1223	881.575954	0.4639

Bold values represent highest cross-correlation coefficients.
PM_{10}, particulate matter 10; O_3, ozone.
The number of asthma exacerbation (t) = $b0 + b1 \times$ PM10(t) + $b2 \times O_3$ (t − 1) + b3 × Weed pollen (t) + b4 × Mold (t).

3.5. Winter

In winter, the average levels of O_3, humidity, and weed pollen in that week (t) exhibited the greatest correlation with the number of asthma exacerbations in a given week (t). Moreover, average concentrations of NO_2 and CO at 1 week prior (t-1) showed the greatest correlation with the number of asthma exacerbations in a given week (t). Concentrations of other substances showed no correlation (Table 5). The results of computing the association between the number of asthma exacerbations at (t)/week and the average concentrations of atmospheric substances at (t)/week using multiple linear regression revealed that the number of asthma exacerbations showed no association with substance concentrations in that week (t) and 1 week prior (t-1).

TABLE 5 Cross-correlation coefficients between the number of asthma exacerbations (t) and atmospheric substance (t-n) in winter.

In winter	t-3	t-2	t-1	t
O_3 ρXY (*h*)	0.009	0.085	−0.065	**0.131**
NO_2 ρXY (*h*)	0.055	0.068	**0.163**	0.058
CO ρXY (*h*)	0.010	0.015	**0.103**	0.009
Humidity ρXY (*h*)	−0.022	−0.019	0.066	**−0.126**
Weed pollen XY (*h*)	0.006	0.045	0.027	**0.121**
Mold XY (*h*)	0.064	0.016	0.001	**0.186**

Bold values represent highest cross-correlation coefficients.
t-n: n weeks ago.
ρXY (*h*): cross-correlation coefficient.
O_3, ozone; NO_2, nitrogen dioxide; CO, carbon monoxide.

4. Discussion

We found that, in most seasons, asthma exacerbations were greatly influenced by the mean concentrations of environmental substances in that week and the previous week; however, the impact of the substances differed by season. Accordingly, for each season, we ran multiple linear regression analyses to identify the association between asthma exacerbations and environmental substance concentrations in that week and 1 week prior. In autumn, PM_{10} concentrations in that week (t) were associated with asthma exacerbation at time (t). In spring, summer, and winter, no substances were associated with asthma exacerbation at both time (t) and time (t-1).

Our finding on the varying impact of atmospheric substances on asthma exacerbation suggests that different seasons have different actions and require distinctive precautions to prevent asthma exacerbations. Unlike in the other three seasons, in autumn, there was a correlation between the increased PM10 concentration and asthma exacerbation. Therefore, in the autumn season, patients with asthma should carefully check the air pollution forecast system and respond accordingly.

The number of asthma exacerbations patients in autumn was the highest ($n = 292$) across all four seasons. The larger the number of asthma exacerbations, the more correlated the analysis results would be. In future research, further well-characterized, longitudinal, and large-scale cohort studies would be needed to clarify seasonal differences in asthma exacerbation. Future research should also establish an appropriate countermeasure against asthma exacerbations for each season.

Air pollution worsens asthma symptoms, and there is robust evidence showing its associations with increased airway hyperresponsiveness, use of symptom relievers, and emergency room visits and hospitalizations (22, 23). According to the results of previous time series studies, air pollution in urban areas is also associated with an increase in the number of deaths from respiratory diseases (24–26). In Korea, pollen and air pollutant concentrations vary largely by region, with a significant difference between Seoul and Busan (10, 27). While several recent studies on asthma exacerbation have been conducted on significant amounts of data (28), analyses using local concentrations remain scarce, highlighting the need for research the correlation between local exposure and asthma exacerbation. Contrary to existing investigations involving big data, such as on a national scale, in this study, we examined the concentrations of atmospheric substances as close to the site of exposure as possible (28). Therefore, this was a single-center study conducted at a secondary hospital with good accessibility, and only the patients living in a certain area were examined.

In our results, we found differences in factors affecting each season, and the time point was also different. Air pollution aggravates the symptoms in patients with asthma, increasing emergency room visits and hospitalizations. Weather factors, such as temperature and humidity, adversely affect the course of asthma, and factors contributing to the exacerbation of asthma symptoms interact with each other to produce different effects. Therefore, there is a difference in the timing and degree of influence by season. In the present study, when each factor was analyzed individually, the concentration of atmospheric substances in that week or the previous week for each season exhibited a strong correlation with the number of asthma exacerbations. However, when all substances were analyzed together by multiple regression analysis, no association between the number of asthma exacerbations and atmospheric substances was noted in most seasons, except for in autumn.

This study has several limitations. First, the study was conducted on children, and the results should not be generalized to adults. To analyze the association between the number of asthma exacerbations and atmospheric substances to which the patients were exposed locally, only the patients with no significant difference between their residence and their main living radius were included in the study. Most adults spend considerable time working, and their exposures in living and working areas can considerably vary. Accordingly, the concentrations of atmospheric substances and pollen in adult patients' residences may not represent exposure. Therefore, we recruited only the patients aged <19 years old living in the designated study areas. In the future, we will conduct a larger cohort study to recruit adults with no difference in the radius of action and analyze the correlation between local exposure and asthma exacerbation in adults. Second, respiratory diseases such as respiratory viral infections cause asthma exacerbation and can contribute to asthma exacerbation. However, since viral confirmatory tests are not performed in the emergency room, it was difficult to confirm whether the patients had respiratory viral infections. However, effort was made to exclude exacerbation conditions due to viral infections to a significant extent by excluding patients with respiratory infectious diseases, such as bronchiolitis, bronchitis, or pneumonia, in addition to asthma at the time of admission to the emergency room and/or hospitalization. We intend to supplement the present results with further larger-scale research that would involve multiple centers, broader time, and patient scope.Third, we did not factor in the variable of indoor air pollutant concentrations. To date, several previous studies showed that indoor air quality can be worse than outdoor air quality (29). However, indoor air quality improved with the development of ventilation systems (29, 30). Therefore, it would also be useful to define air pollutant concentrations with respect to the level to which the patients are locally exposed indoors. Fourth, in order to clarify the local influence of atmospheric substances, we designated a characteristic small area called Gurisi and recruited only the patients from that area. Gurisi is a metropolitan area characterized by a low green area ratio and abundance of residential buildings. Several studies suggest that increased green space reduces allergy occurrence and exacerbation (31). So, our results could be biased. Finally, there were more environmental variables that interacted with each other than just those analyzed in this study. The amount of green space also affects asthma exacerbation (31). To reduce the effect of differences in atmospheric environmental variables, we attempted as to perform our analysis strictly within a period when such factors were similar. Therefore, correlations among air pollution, pollen concentration, and asthma exacerbation were analyzed by studying spring, summer, autumn, and winter separately. We also recruited only those patients who lived in a certain state area in a similar environment with no significant difference in land conditions, such as the amount of green space.

Despite these limitations, our results revealed seasonal differences in the correlation between asthma exacerbation and local concentrations of environmental substances, including allergic pollen and meteorological elements.

In conclusion, air pollution and meteorological factors interact with each other in asthma exacerbation. Air pollution causes worsening of symptoms in patients with asthma, and meteorological factors, such as temperature and humidity, can also affect the course of the disease. However, their effects may change through interaction with air pollutants (32, 33). Accordingly, our results show that air pollutants and meteorological factors that affect asthma exacerbation vary by season. In autumn, controlling PM10 concentrations was important to prevent asthma exacerbation. No significant correlation was found in other seasons; however, further well-characterized, large-scale cohort studies are expected to demonstrate seasonal differences in the effects of local concentrations of atmospheric factors on asthma exacerbation in children.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB no. 2022-07-029) of Hanyang University Guri Hospital, Gyeonggi-do, South Korea. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Y-JC and JKH: conceptualized and designed the study, designed the data collection instruments, collected the data, and drafted the initial draft of the manuscript. Y-JC and JYN: designed the data collection instruments, collected data, and performed the initial analyses. Y-JC and J-WO: conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript. Y-JC, KSL and J-WO: reviewed the manuscript and revised it. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Relationship between birth weight and ambient temperature during pregnancy in a cross-sectional study of the residents of Suzhou, China

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Objective: The association between birth weight and ambient temperature during pregnancy remains inconclusive, and data from Chinese populations are scarce. We conducted a cross-sectional study to investigate the association between birth weight and ambient temperature during pregnancy among the residents of Suzhou Industrial Park, Suzhou, China.

Methods: Information regarding 10,903 infants born between January 2018 and December 2018 who were born at the hospitals in Suzhou Industrial Park, Jiangsu province was obtained via public birth records.

Results: This study found that the ambient temperature during the first trimester of pregnancy was negatively correlated with birth weight, suggesting that elevated temperature may be related to lower birth weight. However, the ambient temperatures during the second and third trimesters of pregnancy were positively correlated with birth weight. Moreover, when the ambient temperature was below 15°C during the second trimester of pregnancy, the birth weight increased with temperature. However, when the temperature was higher than 15°C, the birth weight decreased with temperature. The relationship between ambient temperature in the third trimester and birth weight presented an inverted "U" curve. When the ambient temperature was lower than 20°C, the birth weight increased with ambient temperature, but when the ambient temperature was higher than 20°C, the increase of ambient temperature showed no significant relationship with the increase of birth weight.

Conclusion: The ambient temperature was correlated with birth weight. The ambient temperature during the first trimester of pregnancy was negatively correlated with birth weight. The relationship between ambient temperature in the third trimester and birth weight presented an inverted "U" curve.

KEYWORDS

birth weight, pregnancy, temperature, trimester, cross study

Introduction

Birth weight is an important indicator for evaluating fetal growth and development, which is related to early cognition, metabolism, and risk of cardiovascular disease during life (1). It is also one of the important factors influencing the mortality rate of newborns (2). Moreover, Birth weight is associated with the risk of many chronic disease, such as hypertension, cardiovascular disease, and diabetes in adulthood. Epidemiological studies show that children born with body weight that is small for gestational age (SGA) are at a greater risk of primary hypertension (3, 4). Liang et al. (5) reported that there are non-linear inverse associations between birth weight and CVD risk, with a threshold of 3.41–3.79 kg for the lowest risk, and low birth weight may interact with adult obesity to increase the risk of CHD and heart failure. A recently published birth cohort study indicated a correlation between birth weight and brain volume in the elderly above 70 years of age (6). Lilja et al. (7) found that an inverse association between birth weight and the risk of adult stroke, IS, and ICH independent of young adult BMI, suggest that low birth weight should be included in assessments of stroke risk in adults. The above research suggests that birth weight, as a common body measurement index, has great significance, but it is often ignored.

The known influencing factors of birth weight include race, socioeconomic situation, maternal energy intake during pregnancy, and maternal weight gain during pregnancy, maternal body size, and maternal disease status, maternal nutrition before pregnancy, gestational weeks, and maternal smoking history. Numerous studies have focused on the effects of seasonal or ambient temperature on birth weight, although the results have been inconsistent. Some investigators have found seasonal variations in birth weight (possibly attributed to seasonal variations in ambient temperature), while others have not (8–13). Therefore, this study investigated the birth weight of newborns registered in the Maternal and Child Health System in Suzhou Industrial Park in 2018 in order to examine the relationship between birth weight and ambient temperature during pregnancy.

Materials and methods

Subjects

Information regarding 10,903 infants born between January 2018 and December 2018 who were born at the hospitals in Suzhou Industrial Park, Jiangsu province was obtained via public birth records. Pregnant women in our study are all permanent residents. The establishment of cards during pregnancy, prenatal examination, post-natal visit, and child health care of the subjects were completed in the local hospital. The information included date of birth, sex, birth weight (g), and gestational age (weeks). Information for infants who had died since the time of birth was not included. Each participant signed an informed consent form at the interview. According to the definition of WHO, infants whose birth weight is <2,500 g are called low birth weight infants.

Methods

Meteorological data were collected from China Meteorological Data Network including daily average temperature (°C) and daily average relative humidity (%) in Suzhou from March 20, 2017 to March 27, 2018. The data of Suzhou Air Quality Index (Daily Average) are from the National Environmental Monitoring Station. The baby weight measuring instrument is used for birth weight measurement. The unit is Kg, accurate to 2 decimal places, and the measuring accuracy is ±10 g. The measuring instrument is sent to the measurement department for calibration every year. The average temperature, relative humidity, and air quality index of early pregnancy (the last menstruation to the 12th week of pregnancy), middle pregnancy (the 13th week to the 27th week of pregnancy) and late pregnancy (the 28th week to the delivery) were calculated according to the daily average of the air quality index in Suzhou.

Statistics

The clinical characteristics of the continuous variables were expressed as the mean ± SD and were tested using a two-sample *t*-test or ANOVA. A value of $P < 0.05$ for two-sided tests was considered statistically significant. A generalized linear model and a logistic regression model were used respectively to evaluate the effects of ambient temperature during different trimesters on the birth weight of newborns. Model 1: Adjust maternal age, pregnancy order and baby sex. Based on Model 1, the gestational age was adjusted in Model 2. Based on Model 2, environmental relative humidity and air quality index are adjusted in Model 3. A natural cubic spline with three degrees of freedom were defined for the environmental mean temperature and relative humidity in the generalized linear model. The exposure-effect curves of the environmental mean temperature and birth weight in different pregnancies were fitted. Data analyses were conducted using the SPSS Statistics 21.

Results

Baseline information of the study subjects

The basic information of pregnant women and newborns in the Suzhou Industrial Park 10,903 is shown in Table 1. Among the newborns with normal birth weight, significant differences in birth weight were found between mothers aged < 25 years, aged 25–30 years and aged > 30 years ($p = 0.013$), and mothers aged > 30 years had newborns with the highest birth weight. Moreover, significant differences in birth weight were found between women with 1, 2 or more pregnancies ($p < 0.001$), and women with more pregnancies had a higher newborn weight. Significant differences in birth weight were also found between newborn genders ($p < 0.001$), and males had higher birth weight than females. Furthermore, significant differences in birth weight were found between different modes of delivery (natural labor vs. cesarean section) ($p < 0.001$), and the birth weight was higher in cesarean section. Significant differences in birth weight were also found between the newborns

TABLE 1 Basic information of pregnant women and newborns.

Characteristics	*N*	Birth weight (*n* = 10,427)			Low birth weight (*n* = 476)		
		Mean ± SD	F/t	*P*	Number	F/t	*P*
Maternal age (years)			4.32	0.013		0.967	0.381
<25	1,692	3376.14 ± 394.85			66	2014.12 ± 454.59	
25∼30	5,020	3396.21 ± 395.01			214	2108.88 ± 413.11	
>30	3,715	3410.09 ± 402.75			196	2060.26 ± 427.91	
No. of pregnancies			30.1	<0.001		2.398	0.092
1	4,896	3361.12 ± 389.59			253	2085.30 ± 428.95	
2	5,262	3424.77 ± 401.17			201	2052.79 ± 433.71	
3∼	269	3450.52 ± 438.22			22	2259.09 ± 216.93	
Infant gender			133	<0.001		0.422	0.516
Male	5,502	3440.17 ± 400.44			223	2093.09 ± 430.75	
Female	4,925	3350.67 ± 389.66			253	2067.71 ± 420.56	
Delivery mode			14.9	<0.001		0.48	0.489
Natural labor	6,611	3386.97 ± 377.85			185	2096.54 ± 444.19	
Cesarean section	3,816	3417.67 ± 429.75			291	2068.83 ± 412.93	
Gestational weeks			463	<0.001		39.02	<0.001
<37	939	3038.35 ± 339.88			408	2031.79 ± 438.05	
37∼	9,439	3432.67 ± 385.22			68	2366.47 ± 134.58	
>41	49	3589.80 ± 383.03			0	-	
Total	10,427				476		

with gestational weeks < 37, 37–41, and > 41 weeks ($p < 0.001$), and the newborns with longer gestational weeks had higher birth weight. Among the low-birth-weight newborns, no significant difference was found in maternal ages, gestational weeks, infant gender, or delivery mode ($p > 0.05$). There was a significant difference between the newborns with gestational weeks < 37 and 37–41 weeks ($p < 0.001$), and newborns with longer gestational weeks had a higher birth weight.

Ambient monitoring

The daily mean temperature, daily mean relative humidity, and air quality index of pregnant women are shown in Table 2. The dispersion of daily mean temperature in the third trimester was greater than that in the first and second trimesters of pregnancy. The air quality indices in all three trimesters were good. There were significant differences in the daily mean temperature, daily mean relative humidity, and air quality index between the three trimesters.

Effect of ambient temperature during pregnancy on birth weight

The results of logistic regression analysis between ambient temperature during pregnancy and birth weight in 10,471 newborns with normal birth weight are shown in Table 3. After adjusting for maternal age, parity and infant gender, Model 1 showed no significant correlation between ambient temperatures in the first, second and third trimesters of pregnancy and birth weight. After adjusting the gestational weeks based on Model 1,

TABLE 2 Ambient characteristics of pregnant women.

Ambient database	Mean ± SD	T12, p1T13, p2T23, p3	Minimum	P_{25}	P_{50}	P_{75}	Maximum
Daily mean temperature							
First trimester of pregnancy:	18.20 ± 8.15	6.073, <0.001	5.4	10.36	18.98	25.98	29.10
Second trimester of pregnancy:	17.52 ± 7.76	2.997, 0.003	6.0	9.88	17.49	25.42	28.33
Third trimester of pregnancy:	17.19 ± 8.19	6.567, <0.001	1.8	9.14	17.98	24.88	30.30
Daily mean relative humidity (%)							
Second trimester of pregnancy:	75.29 ± 1.73	16.93, <0.001	72	73.72	75.29	76.77	79
Third trimester of pregnancy:	74.93 ± 2.26	11.88, <0.001	54	73.2	73.20	76.61	89
Air index							
First trimester of pregnancy:	84.72 ± 10.55	4.761, <0.001	66	74.55	85.87	92.31	105
Second trimester of pregnancy:	83.93 ± 9.99	0.276, 0.783	68	74.43	85.06	91.15	103
Third trimester of pregnancy:	84.77 ± 11.95	5.034, <0.001	54	74.46	84.16	93.59	133

TABLE 3 Correlation between ambient temperature (°C) during pregnancy and normal birth weight of newborns.

Trimester of pregnancy	Model 1		Model 2		Model 3	
	b (95% CI)	*P*	b (95% CI)	*P*	b (95% CI)	*P*
First trimester of pregnancy:	0.249 (-0.871 to 1.369)	0.663	0.345(-0.744 to 1.433)	0.535	−3.134(-4.997 to−1.271)	0.001
Second trimester of pregnancy:	0.004 (-1.153 to 1.161)	0.995	−0.084(-1.208 to 1.040)	0.883	−0.249(-2.017 to 1.519)	0.782
Third trimester of pregnancy:	0.278 (-0.801 to 1.357)	0.614	0.155(-0.898 to 1.208)	0.774	0.302(-1.168 to 1.772)	0.688

Model 1 was adjusted for maternal age, parity and infant gender. Model 2 was adjusted for gestational weeks based on Model 1. Model 3 was adjusted for the relative humidity and air quality index based on Model 2.

Model 2 also showed no correlation between ambient temperature during pregnancy and birth weight. After further adjusting the ambient relative humidity and air quality index based on Model 2, Model 3 showed a significant negative correlation between the ambient temperature in the first trimester of pregnancy and birth weight ($p < 0.001$), wherein the birth weight decreased by 3.134 g (1.271–4.997 g) for every 1°C increases in temperature. There was no significant correlation between ambient temperatures in the second and third trimesters of pregnancy and birth weight.

The results of logistic regression analysis between ambient temperature during pregnancy and birth weight in 476 newborns with low-birth weight are shown in Table 4. After adjusting for maternal age, parity, and infant gender, Model 1 showed no significant correlation between ambient temperature in the first, second and third trimesters of pregnancy and birth weight. There was no significant correlation between ambient temperature and during pregnancy and newborn birth weight whether further adjusting gestational weeks on Model 2 or further adjusting temperature ambient relative humidity or air quality index on Model 3.

The relationship between birth weight and ambient temperatures during first, second and third trimesters of pregnancy was analyzed by the generalized non-linear curve in 10,471 pregnant women and newborns. The results showed no non-linear relationship between birth weight and ambient temperature in the first trimester of pregnancy. A significant non-linear correlation was found between birth weight and ambient temperatures in the second and third trimesters of pregnancy, with *p*-values of correlation coefficients of 0.0066 and 0.0318, respectively (Figure 1).

Discussion

This study found that the ambient temperature during the first trimester of pregnancy was negatively correlated with birth weight, suggesting that elevated temperature may be related to lower birth weight. However, the ambient temperatures during the second and third trimesters of pregnancy were positively correlated with birth weight. Moreover, when the ambient temperature was below 15°C during the second trimester of pregnancy, the birth weight increased with temperature. However, when the temperature was higher than 15°C, the birth weight decreased with temperature. The relationship between ambient temperature in the third trimester and birth weight presented an inverted "U" curve. When the ambient temperature was lower than 20°C, the birth weight increased with ambient temperature, but when the ambient temperature was higher than 20°C, the increase of ambient temperature showed no significant relationship with the increase of birth weight. The results of this study were consistent with several large cohort studies worldwide. Lawlor et al. (14) studied the Aberdeen children cohort in the 1950's and found that the mean outdoor temperature in the first trimester of pregnancy was negatively correlated with birth weight, while the mean outdoor temperature in the third trimester was positively correlated with birth weight. Some retrospective cohort studies

TABLE 4 Correlation between ambient temperature (°C) during pregnancy and low birth weight of newborns.

Trimester of pregnancy	Model 1		Model 2		Model 3	
First trimester	1.007 (0.994–1.019)	0.2970	1.004 (0.986–1.021)	0.6981	0.994 (0.965–1.025)	0.7030
Second trimester	0.990 (0.978–1.003)	0.1285	0.992 (0.973–1.010)	0.3757	1.005 (0.975–1.035)	0.7535
Third trimester	0.989 (0.977–1.001)	0.0615	0.999 (0.982–1.016)	0.9020	0.998 (0.976–1.022)	0.8963

Model 1 was adjusted for maternal age, parity and infant gender. Model 2 was adjusted for gestational weeks based on Model 1. Model 3 was adjusted for the relative humidity and air quality index based on Model 2.

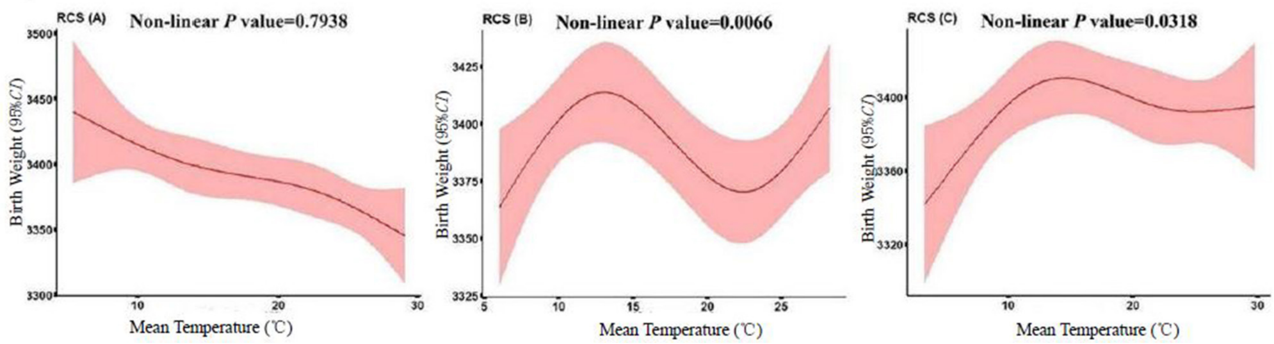

FIGURE 1
Dose-response relationship between ambient temperature during pregnancy and normal birth weight of 10,471 newborns. Correlation between ambient temperature during pregnancy and birth weight of newborns estimated using the generalized non-linear model. The model controls for maternal age, education level, number of pregnancies, and mode of delivery, gestational weeks, infant gender, relative humidity, and air quality index. From left to right: first trimester of pregnancy **(A)**; second trimester of pregnancy **(B)**; third trimester of pregnancy **(C)**. The light pink region is the 95% CI.

(15–19) and ecological studies (20–25) have found that hotter weather was associated with lower birth weight. In contrast, other studies have found that hot weather was associated with higher birth weight (26), or birth weight decreased with decrease in temperature (27, 28). A recent large cohort study reported that temperatures both above and below the mean temperature were correlated with reduced full-term birth weight (although the decrease below the mean temperature was small), suggesting an inverted U-shaped relationship (29). Similarly, another recent cohort study found that low full-term birth weight was correlated with high and low ambient temperatures (30). One study found that the correlation between body weight and ambient temperature may be associated with exposure gestational weeks (14). However, some studies reported no correlation between the temperature during pregnancy and birth weight or low birth weight (31–33).

An animal study indicated that chronic heat stress during pregnancy may reduce blood flow in the uterus and umbilical cord and placental weight, resulting in lower birth weight of many species (24). However, the correlation of the potential mechanism in humans remains unclear. Some studies have reported the correlation between temperature change and inflammatory markers. Although many of them have observed evidence of inflammation with decrease in temperature (21, 34–36), other studies have suggested that lower temperature reduces the production of inflammatory markers (37) or inflammatory markers increase with increase in temperature (38). However, these results suggested that temperature variation may correlate with inflammatory markers. Inflammatory mechanisms may play a role in the correlation between weather and fetal growth. Besides, heat stress can induce oxidative stress, and placental oxidative stress may be one of the causes of intrauterine growth restriction (39–41). However, these potential mechanisms cannot explain the possible impact of temperature changes on birth weight as a concept, independent of the mean temperature. Continuous temperature changes may interfere with the body's ability to recover from heat stress-induced inflammatory changes or blood flow patterns. Moreover, given the changes in the cardiovascular system and other physiological processes during pregnancy (42), pregnant women may have lower thermoregulatory capacity and adaptability to rapid temperature changes.

This study had some limitations. First, the indoor and outdoor activity times and real-time ambient temperatures of pregnant women were not monitored, which may have led to inaccurate estimation of real exposure temperature. Second, confounding factors, such as maternal living habits and nutritional status, were unavailable. Third, our study didn't analyze the relationship between humidity and newborn birth weight. Humidity is known to reduce the body's ability to release heat, its potential independent effects on health are unclear (24, 25). These limitations may have led to bias. However, this study had a large sample size, and the records of birth weight and maternal indicators were directly obtained from the regional information system, which led to high reliability and accuracy of the data. Thus, the results of this study have scientific value and clinical guiding significance.

In conclusion, our study has examined the association between the ambient temperature and birth weight based on normal and low birth weight population analyses. We found that the ambient temperature during the first trimester of pregnancy was negatively correlated with birth weight, suggesting that elevated temperature may be related to lower birth weight. Moreover, the ambient temperatures during the second and third trimesters of pregnancy were positively correlated with birth weight. Additionally, the relationship between ambient temperature in the third trimester and birth weight presented an inverted "U" curve. Independent replications in large sample sizes are needed to confirm the role of the ambient temperature with newborn birth weight found in this study for normal and low birth weight population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

YD and LW conceived and designed the research. YD wrote the manuscript. LW, YD, MT, YM, and XC revised it critically for important intellectual content. YD and HZ performed the data analysis. All authors contributed to the interpretations of the findings, reviewed the manuscript, contributed to the article, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Lead poisoning in a 6-month-old infant: a case report

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Background: Lead is a toxic element of the environment that leads to major complications once it enters the blood stream, affecting multiple organs and systems of the body.

Methods: We present a case of a 6-month-old female infant diagnosed with lead poisoning after presenting for routine child health care. The child's mother denied that the infant had a history of exposure to lead-containing substances. After a month of calcium supplementation, the patient's blood lead level remained elevated. We then tested the blood lead level of the mother and father. The results showed that the blood lead level of the mother was 77.0 μg/L and that of the father was 36.9 μg/L. The high blood lead level of the mother attracted our attention. We found that the mother had been using an external traditional Chinese medicine, Hu Wang Fen, which contains lead. After the mother's discontinuation of use of the traditional medicine, the child was treated with symptomatic treatment and chelation therapy. Subsequently, the patient's blood lead level decreased significantly.

Results: Lead toxicity can be a life-threatening problem because of its potential for severe complications. In children, there is no safe blood lead level, and the toxic effects of lead can be prevented by the awareness and avoidance of traditional Chinese medicines that may contain lead.

Conclusion: Even though the diagnosis of lead poisoning remains difficult in children, it must be taken into consideration by the clinician when treating a child using traditional Chinese medicines.

KEYWORDS

lead, lead poisoning, blood lead level, traditional Chinese medicine, Hu Wang Fen

Introduction

The problem of lead poisoning in children has existed for a long time, and sporadic cases of lead poisoning are reported every year. It is generally believed that the exposure source of lead is most commonly from industry (1) or occupational pollution (2). However, lead poisoning from other sources should not be ignored. Lead poisoning in children is an important health problem; it can lead to growth retardation, intellectual disability and irreversible damage to the nervous system (3), blood system, digestive system and other areas (4), accounting for nearly half of the 2 million lives lost to known chemical exposure in 2019 according to the World Health Organization (5). According to the National Health and Nutrition Examination Survey data, from 2007 to 2010, ~535,000 children aged 1–5 years, or 2.6% of the population, have blood lead levels above 5 μg/dL. More recently, lead exposure has ascribed mainly to household lead contamination. In addition, cases of lead poisoning caused by the use of traditional Chinese medicine have been reported. We report a case of infant lead poisoning due to the mother's use of traditional Chinese medicine. The aim of our work is to sensitize practitioners and parents to the abuse of traditional Chinese medicine in general and draw their attention to potential problems arising from lead poisoning.

Case report

The patient was a 6-month-old female infant who had been exclusively breastfed. Neither of the parents was engaged in lead-related work. Since birth, the child lived in Longquanyi District, Chengdu, Sichuan Province, China. There was no known environmental lead pollution around her residential area. There was no previous medical history and no history of drug or food allergies. She underwent routine health care at the local public hospital on May 18, 2020. Her general examination was unremarkable, and her height and weight were normal. However, her blood lead level was more than 200.0 μg/L. The results of routine blood examination showed RBC = 5.44 × 10^{12}/L, HGB = 115 g/L, MCV = 68.4 fl, MCH = 21.1 pg, and MCHC = 309 g/L. Her doctor diagnosed the patient with lead poisoning, and upon questioning, the mother denied that the infant had a history of exposure to any lead-containing substances such as medicine, food, paint and so on. Shengxuebao and zinc calcium gluconate oral liquid were given for 1 month. Following this, the patient's blood lead level was measured once again, and the result was 429.9 μg/L on June 4, 2020. After oral calcium supplementation for 1 month, the blood lead level remained elevated.

The infant came to our hospital on June 28, 2020. The blood lead level and routine blood examination were re-evaluated. Her blood lead level was 454.0 μg/L. The results of routine blood examination showed RBC = 4.82 × 10^{12}/L, HGB = 101 g/L, MCV = 63.9 fl, MCH = 20.9 pg, and MCHC = 327 g/L (microcytic hypochromic anemia). Because the infant was exclusively breastfed, we also checked the blood lead level of the mother and father. The results showed that the blood lead level of the mother was 77.0 μg/L and that of the father was 36.9 μg/L. The high blood lead level of the mother attracted our attention. After further probing the history of medication usage, we found that the mother had been using a kind of external traditional Chinese medicine—Hu Wang Fen (Figure 1). The lead content of the medicine was measured. The result was 180.1 ± 0.6 mg/kg, which exceeded the National Food Safety Standard (5 mg/kg) and the National Cosmetics Hygiene Standard (40 mg/kg). The mother was advised to stop using the medicine. In addition, we also tested the lead level of the mother's breast milk, and the result was 10.0 ± 0.7 μg/L, which was not significantly different from that of normal breast milk. Considering that the infant was too young for this topical medication, the pediatrician suggested that after stopping the exposure source, the infant should continue to take oral calcium supplementation to treat the elevated lead level and be reassessed 1 month later. The blood lead level was tested again on July 31, and the result was 435.0 μg/L.

As the blood lead could not be reduced by oral calcium supplementation, the infant was admitted to the hospital. Chelation therapy was initiated, and edetate calcium disodium was administered at a dose of 200 mg by 12-h continuous intravenous infusion per day for 4 consecutive days for three cycles in total, with a 3-day rest period between cycles. 250 mg/d Calcium gluconate supplementation was also given every day. After three cycles of treatment, her blood lead level was tested again, and it was found that the level was reduced to 272 μg/L. The infant was discharged on August 24. She continued to take oral calcium supplementation after discharge. We also provided education to the mother about the common sources of lead exposure and the ways to prevent further lead exposure, for the health of both the infant and herself. Moreover, we made some suggestions on diet and nutrition, especially on calcium and iron intake. We re-tested the blood lead level after 5 months, and found that it was reduced to 84.29 μg/L on January 27, 2022. The changes in the patient's blood lead level are summarized in Figure 2.

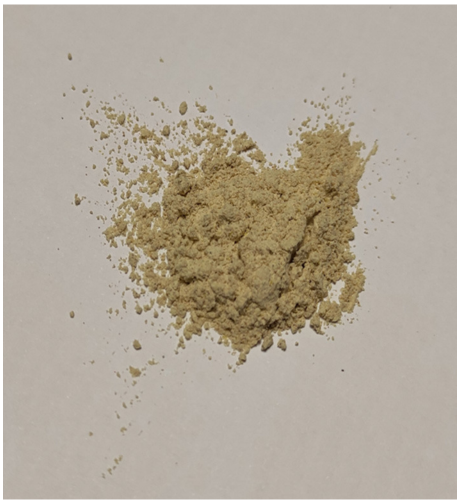

FIGURE 1
Samples of traditional Chinese medicine (TCM) were obtained from the patient.

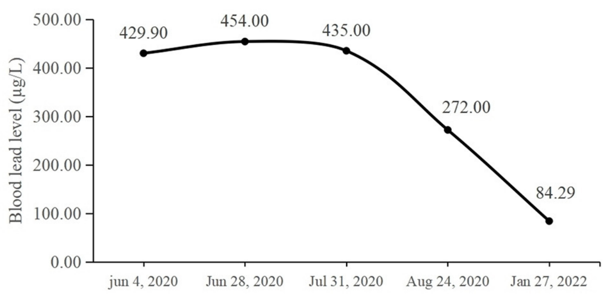

FIGURE 2
The blood lead levels of the patient were measured at different time points.

Discussion

Two documents entitled "The Children Lead Acidosis and Lead Poisoning Prevention Guide" and "Children's Blood Lead and Lead Poisoning Classification Principles" were issued by the Ministry of Health in China. It is emphasized that intervention is necessary when the blood lead level is more than 100 μg/L (6). The absorption rate of lead is high, and the excretion rate is low, which results in lead being more easily accumulated in children than in adults (7). The infant reported in this case had a hidden history of lead exposure and had no obvious symptoms. Infants and young children cannot express their own physical discomfort, and in addition to the more serious symptoms of toxic encephalopathy, general symptoms such as abdominal pain, irritability and memory loss are difficult to detect. The discovery of lead poisoning in this case was accidental, in that her child care program fortunately included a blood lead level test (there is no routine lead screening for children in China). Early screening of blood lead levels made this finding of lead poisoning as early as possible, thus avoiding the potential occurrence of serious complications and risk of damage to the nervous system.

The mother had applied Hu Wang Fen to her own armpit and the lower edge of her breast for a long time to keep these areas dry and refreshed. When the mother was asked whether the infant had a history of lead exposure, this medicine was not mentioned because it was not directly given to the infant. Child care doctors should endeavor to learn more about the possible sources of exposure to infant lead poisoning cases. In particular, they should be vigilant about the use of traditional medicines, and the parents' blood lead levels should be measured to further explore the source of lead intake. In this case, we were led to the discovery of the medicine that caused lead exposure because of the mother's high blood lead level, and subsequent test results confirmed that the topical medicine used by the mother contained lead. Due to hand-to-mouth and toy-to-mouth activities in children, the medicine may enter the human body through the digestive tract or skin-to-skin contact (8). The patient's blood lead level was much higher than her mother's, possibly because lead is more easily stored in children than in adults. Another reason is that lead is distributed differently in their bodies; 95% of lead is stored in bones in adults (9), while only 70% is stored in bones in children (10).

The antagonistic relationship between lead and calcium plays a critical role in the treatment of lead poisoning. Lead binds to the sites at which calcium typically acts and enters the cells through calcium channels. Therefore, calcium supplementation is beneficial to lead excretion (11). In the early stage, our patient was treated by oral calcium supplementation, but this proved ineffective. We postulate that the ineffectiveness of this treatment may have been for two reasons: first, the child remained exposed to the source of lead at the time, resulting in poor treatment effect, followed by anemia. The most important element in the treatment of lead toxicity is to disengage from the source as soon as possible. Second, the child was too young to have fully developed excretory functions, therefore the rate of effectiveness of the commonly used calcium supplement treatment was too slow. We no longer recommend this treatment to be used in patients of very young age who are being treated for high blood lead levels. For patients who are symptomatic or have a blood lead level of 450 μg/L or more, chelation treatment is generally recommended (12). Subsequently, when we added chelation therapy to the treatment program, the patient's blood lead level decreased rapidly. It should be noted that succimer is the first choice for chelation therapy in children since a weight of 8 kg and oral chelation therapy is safer. However, because only edetate calcium disodium was available at the hospital at the time of the patient's presentation, the doctor used edetate calcium disodium to remove lead.

According to the literature, the use of traditional medicine has become the main cause of lead poisoning in China. Ba-Baw san, Po-Ying-Tan, Jin Bu Huan, Hai Ge Fen, "Yi shao guang" ointment, and other traditional Chinese medicines all contain excessive lead levels (13). In Jiangxi, Fujian, Zhejiang, and Jiangsu provinces, Hong Dan Fen was used to prevent and treat diaper rash, infantile eczema, heat rash and other skin disorders. The children with lead poisoning caused by Huang Dan Fen mainly came from Shanghai and Hunan Province, where Huang Dan Fen was commonly used to prevent heat rash and symptoms of red buttocks in infants. The main components of these two lead-containing traditional Chinese medicines are lead trioxide and lead monoxide. On the basis of appearance and purpose, we speculated that the Hu Wang Fen used in this case was a type of Dan Fen.

Lead has no biologic role in the body, and any detectable level is abnormal. The deleterious effects of lead ingestion on children's neurocognitive and behavioral development are irreversible (8). Through awareness of this case, we appeal to women considering pregnancy and those who have young babies <6 months of age to urge their medical providers to monitor children for blood lead levels for the early detection of lead poisoning. We suggest that in young children with high blood lead levels, the often used first line therapy of oral calcium supplementation should not be utilized as the sole therapy because the lead excretion capacity of young children is limited, and therefore the treatment benefit of calcium supplementation will be relatively slow. Infants, as well as their lactating mothers, should avoid using any unnecessary traditional Chinese medicine that may contain lead. Because blood lead testing is not a component of the routine child health care program, it is important for clinicians to have a more comprehensive understanding of the living habits, working environment, and drug history of children as well as that of their parents.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the patients legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article. Written informed consent was obtained from the participant/patient(s) for the publication of this case report.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Association of SO_2/CO exposure and greenness with high blood pressure in children and adolescents: A longitudinal study in China

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Introduction: We aimed to investigate the association between greenness around schools, long-term gaseous air pollution exposure (SO_2 and CO), and blood pressure in children and adolescents.

Methods: From 2006 to 2018, a total of 219,956 Chinese children and adolescents aged 7–17 years in Beijing and Zhongshan were included in this longitudinal study. Annual average concentrations of SO_2 and CO and the mean values of normalized difference vegetation index around schools were calculated. We used the generalized estimation equation model, restricted cubic spline model, and Cox model to analyze the health effects.

Results: Among all the subjects, 52,515 had the first onset of HBP. During the follow-up, HBP's cumulative incidence and incidence density were 23.88% and 7.72 per 100 person-year respectively. Exposures to SO_2 and CO were significantly associated with SBP [$\beta = 1.30$, 95% CI: (1.26, 1.34) and 0.78 (0.75, 0.81)], DBP [$\beta = 0.81$ (0.79, 0.84) and 0.46 (0.44, 0.48)] and HBP [HR = 1.58 (1.57, 1.60) and 1.42 (1.41, 1.43)]. The risks of HBP attributed to SO_2 and CO pollution would be higher in school-aged children in the low greenness group: the attributable fractions (AFs) were 26.31% and 20.04%, but only 13.90% and 17.81% in the higher greenness group. The AFs were also higher for normal-BMI children and adolescents in the low greenness group (AFs = 30.90% and 22.64%, but 14.41% and 18.65% in the high greenness group), while the AFs were not as high as expected for obese children in the low greenness group (AFs = 10.64% and 8.61%), nor was it significantly lower in the high greenness group (AFs = 9.60% and 10.72%).

Discussion: Greenness could alleviate the damage effects of SO_2/CO exposure on the risks of HBP among children and adolescents, and the benefit is BMI sensitivity. It might offer insights for policymakers in making effective official interventions to prevent and control the prevalence of childhood HBP and the future disease burden caused by air pollution.

KEYWORDS

sulfur dioxide, carbon monoxide, blood pressure, greenness, body mass index

1. Introduction

High blood pressure (HBP) in children was once considered a rare disease, but it is now a public health concern worldwide (1). Today, childhood HBP affected over 1.13 billion people worldwide as it significantly increases the risks of heart attack, stroke, and other complications (2). In recent years, the incidence of HBP has increased constantly in developing countries. Environmental and lifestyle changes might contribute to its prevalence (3, 4).

Evidence indicated that air pollutants sulfur dioxide (SO_2) and carbon monoxide (CO) might be important risk factors for hypertension (5, 6) and other CVDs in adults (7, 8). Animal experiments also showed that short- and long-term exposure to SO_2 could cause functional damage to the cardiovascular system (9, 10). Its possible mechanisms could be explained by oxidative stress, alterations in the autonomic nervous system, or ion concentration change in body fluids (9, 11, 12). However, this evidence was limited (13) compared to similar studies about PM_{10}, $PM_{2.5}$, ozone, and NO_2, especially in cohort studies and large populations of children and adolescents in developing countries (14–19). Moreover, the limited evidence supported inconsistent conclusions. For example, 5-day short-term exposure to SO_2 was reported to have no association with BP increase (20). The long-term exposure investigation, however, observed a strong correlation between SO_2/CO exposure and hypertension (16). Greenness plays another important role in cardiovascular health, according to the assessment of the beneficial impact of greenspace on a dozen health outcomes, including BP (21). Cross-sectional and retrospective studies mostly focused on the potential benefits of plants to attenuate the respiratory and cardiovascular health risks of PM_{10}, $PM_{2.5}$, and NO_2 pollution in adults or seniors (22–26). Few of them focused on SO_2 and CO. A cross-sectional study in Northern China found a 10-$\mu g/m^3$ increase in SO_2 was responsible for a 2.43% increase in mean arterial pressure among adults. These identified harmful effects of SO_2 mainly occurred among people who lived in low-greenness environments (27). Subgroup analysis of greenness may provide a concise illustration of the role of greenness on health outcomes. Although the association may be non-linear, higher greenness is probably to have a more positive effect on hypertension (28). In terms of biological mechanisms, exposure to better green space can increase immunoregulation, lowering the risk of inflammatory and cardiovascular diseases. Greenness can also improve physical activities and reduce noise effects (29) to counteract the negative effects of environmental pollution by improving stress resilience (30). In addition, children and adolescents of different genders, ages and BMIs have various physiological, psychological, and socio-environmental differences. The blood pressure in different subgroups may be influenced by growth and development characteristics, for example, sex-related differences in hormone secretion, age-related differences in puberty timing (31), obesity-related differences in endocrine regulation/insulin resistance, and environment sensitivity (32, 33). Previous findings on these subgroups' sensitivity to SO_2, CO and greenness exposure are limited (18, 27) and therefore further validation and supplementation are still needed.

In this multicenter, longitudinal, prospective open cohort study in China, we hypothesized that SO_2 and CO were risk factors for HBP in school-aged children and adolescents, while greenness protected blood pressure. We also aimed to investigate whether a high level of greenness can reduce this risk, and whether different BMIs groups had different sensitivities.

2. Materials and methods

2.1. Design and population

This study was based on an open cohort covering all school-age students attending primary, junior, and senior high schools aged 7–17 years in Beijing and Zhongshan from 2006 to 2018. They were enrolled through an annual medical examination survey, similar to a census for local children and adolescents, except for school dropouts, as described in detail in the previous study (34). Students were included in the study from 1,839 schools, and we matched individual data for each year based on unique codes. In this open cohort, participants were free to enter and leave as they liked. There was no specific selection of participants and no strict definitions of inclusion and exclusion criteria. Participants were included in the open cohort if they had their first medical examination records from their first year of primary school to their second year of high school.

A total of 3,290,046 participants entered the open cohort. During data processing, we excluded participants with missing information on weight, height, birthday, and blood pressure (N = 261,122), those with abnormal data (N = 920,095), and those diagnosed with HBP at baseline or with only one record of blood pressure (N = 1,484,725). Therefore, the eligible participants included in the study had more than twice completed annual medical examinations. The annual follow-up with medical check-ups was usually between September–November or April–June. We further excluded another 404,148 subjects with missing data on SO_2/CO/NDVI around schools after linking the annual physical examination survey to the gaseous pollution data. Eventually, we enrolled 219,956 participants in the final analysis (Beijing: 46,652, Zhongshan: 173,304). The subjects were followed up annually until the onset of HBP, loss, and the end of the study, whichever came first. Children and adolescents are automatically out of the cohort when they reach the age of 18 or graduate from high school. The flow chart is shown in Supplementary Figure A1 and the characteristics of the included and excluded participants are shown in Supplementary Table A1. The study was approved by the Biomedical Ethics Committee of Peking University Health Science Center (Reference Number: IRB00001052-20033).

2.2. Anthropometric measurement and outcomes definition

Anthropometric data, including height (cm), weight (kg), and systolic and diastolic blood pressure (SBP, DBP; mmHg) were measured and recorded by trained physicians. Height was accurately measured to 0.1 cm with portable stadiometers and weight was accurately measured to 0.1 kg with a standardized scale. All participants were required to stand barefoot with light clothing, naturally straight torsos, straight heads, and eyes straight in front, as well as upper limbs hanging naturally and the legs straight. Height and weight were measured twice, and the mean was recorded. Body Mass Index (BMI, kg/m^2) is calculated as the weight (kg) divided by the square of height (m). BMI groups were categorized into three levels (normal weight, overweight, and obesity) according to growth reference data for 5–19 years old children from the WHO definition (35).

Right arm brachial BP in a sitting position was used for BP measurement, with appropriate cuff sizes according to the actual situation. Auscultation mercury sphygmomanometer was uniformly used. SBP (mmHg) and DBP (mmHg) were measured 3 times, respectively, by Korotkoff I sound and V sound (vanishing sound), and the average value was calculated and recorded. After each measurement, the cuff was loosened for about 2 mins. Systolic and diastolic high blood pressure (SHBP and DHBP) were defined as SBP and DBP above or equal to the 95th percentile of the reference population by age, sex, and height. HBP was defined as the presence of either SHBP or DHBP (36).

2.3. Assessment of SO_2/CO concentration and estimation of greenness

SO_2 and CO concentrations were calculated at a spatial resolution of 10 km from 2014 to 2018 in the CHAP dataset (available at: https://weijing-rs.github.io/product.html). The dataset is generated using a space-time extremely randomized trees (STET) model from big data, including satellite remote sensing, meteorology, multi-resolution emission inventory, and land utilization data (37, 38). The annual average concentrations of SO_2 and CO around schools 1 year before the occurrence of HBP or the end of follow-up were used to indicate gaseous pollutants exposure. The distributions of SO_2 and CO in Beijing and Zhongshan in 2014 are shown in Figure 1.

Greenness was estimated with a normalized difference vegetation index (NDVI) with a resolution of 30 m by 30 m. The formula of NDVI is: $NDVI = \frac{\text{Near Infrared} - \text{RED}}{\text{Near Infrared} + \text{RED}}$, where Near Infrared (NIR) denotes the land surface reflectance of near-infrared, and RED denotes the surface reflectance in red regions of the electromagnetic spectrum. NDVI values range between −1.0 to 1.0. It is assumed that a negative value indicates a water area, and a value close to 0.0 may be bare ground without vegetation (39). A low positive value indicates a barren area with vegetation, a medium positive value indicates low vegetation, and a high positive value indicates dense vegetation such as trees. The annual mean of NDVI within a 1 km radius of each school in 1 year before the onset of HBP or the end of follow-up was used as an individual's greenness exposure. A higher NDVI value indicates a higher green vegetation density. In our study, NDVI values ranged from 0.1023 to 0.7199, indicating various green environments surrounding schools. The data was divided into two NDVI levels using the median (0.2816) as a cut-off line.

2.4. Statistical analysis

Categorical variables were described by frequencies and rates, and continuous variables were described by means and standard deviation (SD).

The cumulative incidence of HBP was calculated as the number of new HBP during the follow-up period divided by the total number of participants. The incidence density (ID) was calculated by: $\text{ID} = \frac{N_{new}}{\sum(Y_i \times n_i)}$, where N_{new} was the number of new HBP incidents during the follow-up, Y_i was the year between entry into the cohort and the onset of HBP, loss, and the end of the study, whichever came first; n_i represented the number of participants corresponding to Y_i.

We created a Cox regression with restricted cubic splines (RCS, Figure 2) to describe the qualitative relationship between SO_2/CO/greenness and the HBP risks. The Event Status of participants was recorded as "1" when they were diagnosed with HBP, and "0" when HBP subsided or was not present until the end of the study. Event Time was calculated in years, from the entry of the cohort to the latest event status record. The Cox model can also evaluate the hazard ratio (HR) of HBP attributable to SO_2/CO/NDVI by sex. We also considered that a participant's blood pressure at annual follow-up was correlated with that at baseline. Although participants having HBP at baseline were excluded, it is still necessary to consider the impact of multiple measurements on risk assessment, which potentially overestimated the role of risk factors on outcomes. We, therefore, used the generalized estimation equation (GEE) model to address the problem of correlation between individuals repeating multiple measurements at baseline, follow-up, and ending. For estimating the quantitative association between SO_2/CO/NDVI and SBP/DBP, β represents the regression coefficient obtained after adjusting age, sex, BMI, and city, results of which could also be validated with Cox regression results for HBP. We also tested for interactions using GEE regression with robust standard errors. Given interactions between NDVI and SO_2/CO (Supplementary Table A2), we further divided greenness levels into low and high NDVI groups based on the median value of NDVI and created a Cox model to evaluate the HR of HBP induced by NDVI grouped pollutants. The attributable fraction (AF) of SO_2 or CO-induced HBP risk and the whole samples from the dynamic cohort were calculated to estimate the benefits of SO_2 and CO control in reducing HBP at different greenness levels. The calculation methods were shown in previous research, $AF = 1 - \frac{1-S0t}{1-St}$, where S_{0t} denoted the counterfactual survival function for the event if the exposure was eliminated at baseline and S_t denoted the factual survival function (34). Covariates in our models included age, sex, BMI, and city. Additionally, we considered that the individuals with different BMIs have different sensitivity to the effect of environmental exposure on blood pressure and that this difference is important, so we performed a subgroup analysis for BMI and obtained as a secondary outcome.

All statistical analyses were completed using R version 4.1.1. All p-values were two-tailed, and <0.05 was considered statistically significant unless otherwise stated.

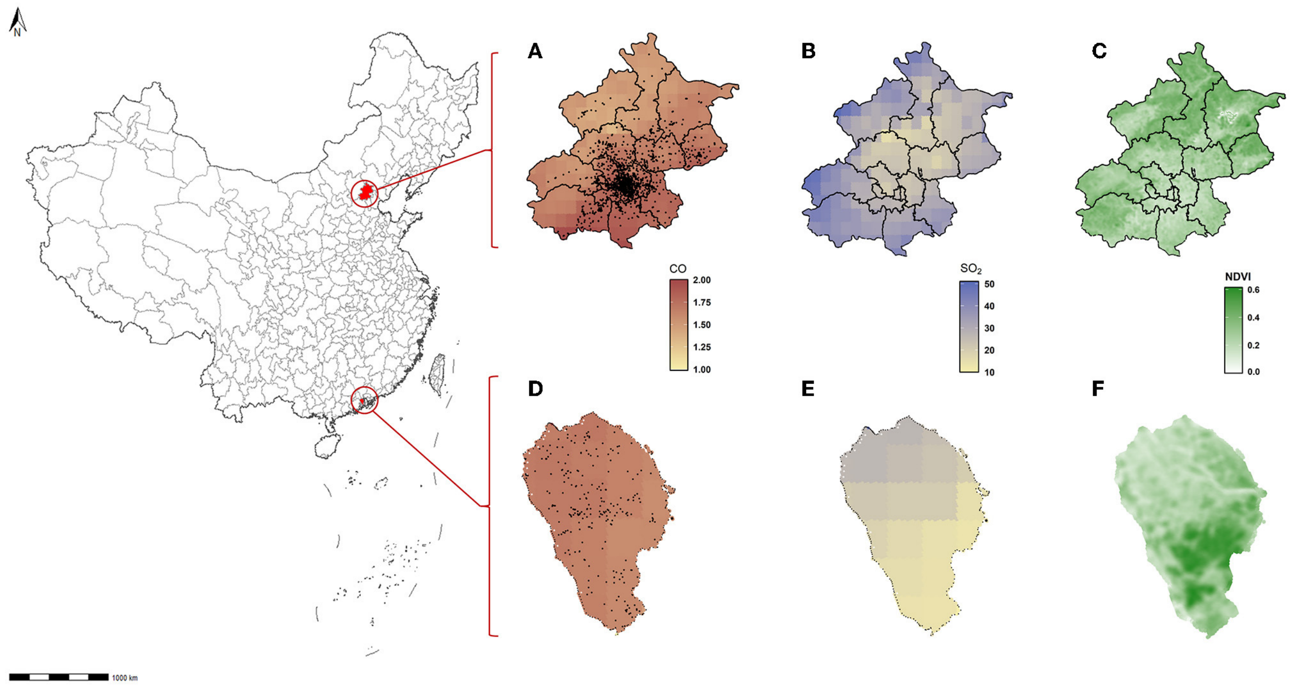

FIGURE 1
Location of schools surveyed, the SO_2/CO concentration, and NDVI distribution in Beijing and Zhongshan. **(A)** Mean concentration of CO in Beijing 2014. **(B)** Mean concentration of SO_2 in Beijing 2014. **(C)** Annual NDVI in Beijing 2014. **(D)** Mean concentration of CO in Zhongshan 2014. **(E)** Mean concentration of SO_2 in Zhongshan 2014. **(F)** Annual NDVI in Zhongshan 2014.

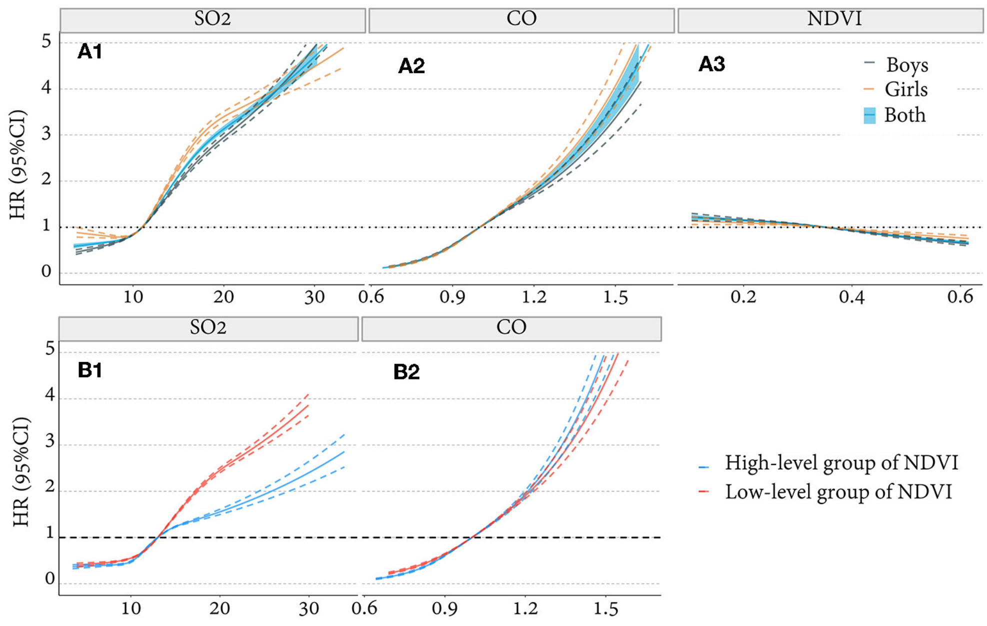

FIGURE 2
The non-linear correlation between SO_2/CO/NDVI and HBP (binary outcome variable). **(A1, A2)** Association of SO_2/CO with HBP adjusted for age, BMI, greenness, and city and stratified by sex. **(A3)** Association between NDVI and HBP adjusted for age, BMI, pollution, and city and stratified by sex. **(B1, B2)** Association of SO_2/CO with HBP adjusted for age, sex, BMI, and city and stratified by greenness level. HR, hazard ratio.

3. Results

There were 219,956 children and adolescents without HBP at the baseline included in the analysis, 46,652 in Beijing and 173,304 in Zhongshan. The characteristic of the study subjects is displayed in Table 1. The mean age was 12.9 (SD: 2.89), and the mean NDVI was 0.30 (SD: 0.08). The average time of follow-up was 3.09 years. Mean SO_2 and CO concentrations were 12.27 (SD: 3.93) $\mu g/m^3$ and 0.97 (SD: 0.14) mg/m^3. Among the participants without HBP at baseline, 52,515 were identified with new HBP during the follow-up, the cumulative incidence was 23.88%, and an incidence density was 7.72 per 100 person-year. The levels of NDVI exposure, BMI, and SO_2 and CO concentrations were higher, but the average age, height, and weight were lower in the HBP group than in the non-HBP group ($p < 0.001$). The location of survey schools in Beijing and Zhongshan, their SO_2 and CO concentration distribution and the NDVI levels in 2014 are shown in Figure 1.

We analyzed the non-linear correlation of SO_2 and CO with the risk of HBP after adjusting age, sex, BMI, greenness, and city. We found that the risk of HBP in children and adolescents increases with the concentration of SO_2 and CO (Figures 2A1, A2), Cox model with RCS. Meanwhile, the association of HBP risk with SO_2 exposure was lower in high-greenery areas than in low-greenery areas, but this was not observed for CO exposure (Figures 2B1, B2), Cox model with RCS. We also explored a relationship between greenness and HBP, that risk of HBP decreases with the increase of NDVI (Figure 2A3).

Based on the above preliminary results, we further analyzed the quantitative association of SO_2, CO, and NDVI with BP levels and HBP risks, as illustrated in Figure 3. We found that the concentration of SO_2 and CO positively correlated with SBP and DBP levels and HBP risks. It also had a higher effect on SBP: increased SO_2 and CO exposure were significantly associated with SBP levels [$\beta = 1.30$ and 0.78, 95% CI: (1.26, 1.34) and (0.75, 0.81)] and were less associated with DBP levels [$\beta = 0.81$ and 0.46, 95% CI: (0.79, 0.84) and (0.44, 0.48)]. The HR of HBP was 1.58 and 1.42 respectively [95%CI: (1.57, 1.60) and (1.41, 1.43)]. NDVI was negatively correlated with SBP and DBP. Therefore, it could protect HBP: an increase in NDVI was significantly associated with SBP [$\beta = -0.53$, 95% CI: (-0.56, -0.49)] and DBP levels [$\beta = -0.65$, 95% CI: (-0.67, -0.63)], and the HR of HBP was 0.90 [95% CI: (0.89, 0.91)].

AF values were used to evaluate the theoretical benefits of HBP reduction through improving SO_2 and CO among children and adolescents. The results showed that eliminating SO_2 and CO exposure around schools could get a considerable theoretical benefit, but the benefit could vary by the levels of greenness. Improvement of SO_2 and CO exposure benefits more in the low-level group of NDVI than in a high-level group of NDVI. The lower greenness group had a higher risk of HBP induced by SO_2 and CO pollution. Figure 4 shows that AF values of HBP risks attributable to SO_2 and CO in the low NDVI group of areas were 26.31% and 20.04% respectively, which were higher than those in a high NDVI group of areas (13.90% and 17.81%).

We also did a stratified analysis by BMI. Those who live in low-level green areas with normal nutritional status obtain great theoretical benefits. For obese participants, there was no significant difference between low and high-level greenness in the AFs of SO_2 and CO. As shown in Figure 4, SO_2 and CO-induced HBP risk was higher for normal-weight children and adolescents with a low-level greenness, the AFs of which were 30.90% and 22.64%, while only 14.41% and 18.65% for those living with a high-level greenness. However, the risk of HBP attributable to SO_2 and CO was not as high as expected for obese children in a low-level greenness (AFs = 10.64% and 8.61%), nor was it significantly lower in the high-level greenness (AFs = 9.60% and 10.72%).

4. Discussion

Previous studies indicated that HBP in childhood or adolescence was a significant predictor for adult HBP and cardiovascular diseases (40, 41). However, the association of greenness and long-term SO_2/CO exposure with childhood BP has yet to be studied in depth, particularly in a longitudinal study with potential causal inference. As far as we know, this was the first study that used a longitudinal, two-center, dynamic cohort in China to confirm that greenness can alleviate the damage effects of SO_2/CO exposure on the risks of HBP among children and adolescents. The study also approved that improving individual exposure to SO_2/CO can significantly benefit those with low-level greenness and normal weight. Our findings supported the reduction of the HBP risks among children and adolescents by improving greenness and reducing gaseous pollution around schools by a variety of measures.

Our findings were consistent with most previous relevant studies (6, 27, 39). For instance, a cross-sectional study of around 10,000 children from seven northeastern cities in China found that higher greenness levels around schools significantly lower the risk of childhood HBP (42). Another cross-sectional study found that high levels of SO_2 and CO increased arterial blood pressure and HBP among children aged 5–17 in northeastern China (16). In addition, a two-decade population-based study in Tehran revealed that diastolic blood pressure was more sensitive to CO while SBP was more sensitive to SO_2. They found that adults exposed to higher SO_2 pollution had a significantly higher risk of HBP than those exposed to CO (14). Combined with our study, we suggested that children might be more sensitive to CO air pollution than adults. Another study on the interaction between obesity and air pollution on BP in Chinese children confirmed that children's obesity amplified the effects of long-term air pollution on BP (15). The result suggested that the BP effects of air pollution might be harder to eliminate in obese children than in normal-weight children. This further confirmed the plausibility of our findings. However, several other findings are inconsistent with ours. A nationwide cross-sectional investigation in China found that increases in greenness were associated with reductions in SBP and DBP (39), but not in our study. The reasons for that might be due to the sample distribution, and greenness measurement differences. Our study filled a gap in the pre-cardiovascular hazard caused by specific gaseous pollutants in cohort studies of 7–17 years-old children and adolescents compared to previous studies. We further found that improving air pollution according to greenness level is a

TABLE 1 Characteristics of children and adolescents across the follow-up analysis.

Characteristics	All† *n* = 219,956	Non-HBP† *n* = 167,441	HBP† *n* = 52,515	*P* value
Sample, *n* (%)				
Girls	96,225 (43.75)	73,426 (43.85)	22,799 (43.41)	0.079#
Boys	123,731 (56.25)	94,015 (56.15)	29,716 (56.59)	
Age (years); mean (SD)	12.9 (2.89)	13.19 (2.90)	11.96 (2.66)	<0.001*
Years of follow-up; mean (SD)	3.09 (1.98)	3.25 (2.01)	2.57 (1.75)	<0.001*
Height (cm); mean (SD)	153.54 (15.46)	154.93 (15.28)	149.11 (15.19)	<0.001*
Weight (kg); mean (SD)	45.65 (15.68)	46.28 (15.39)	43.65 (16.43)	<0.001*
BMI (kg/m^2); mean (SD)	18.80 (3.82)	18.75 (3.69)	18.98 (4.19)	<0.001*
NDVI*100; mean (SD)	30.05 (8.49)	30.10 (8.57)	29.90 (8.23)	<0.001*
SO_2 ($\mu g/m^3$); mean (SD)	12.27 (3.93)	11.88 (3.66)	13.53 (4.48)	<0.001*
CO (mg/m^3); mean (SD)	0.97 (0.14)	0.97 (0.14)	0.99 (0.12)	<0.001*

BMI, body mass index; NDVI, Normalized difference vegetation index. NDVI*100 (mean, SD), SO_2 (mean, SD), and CO (mean, SD) represent the 1-year concentrations of NDVI, SO_2, and CO (1 year before the endpoint of each participant), respectively. #Chi-Square test; *t-test. †There were 219,956 children and adolescents without HBP at the baseline included in the analysis, and 167,441 and 52,515 children and adolescents were identified with non-HBP and new HBP during the follow-up period.

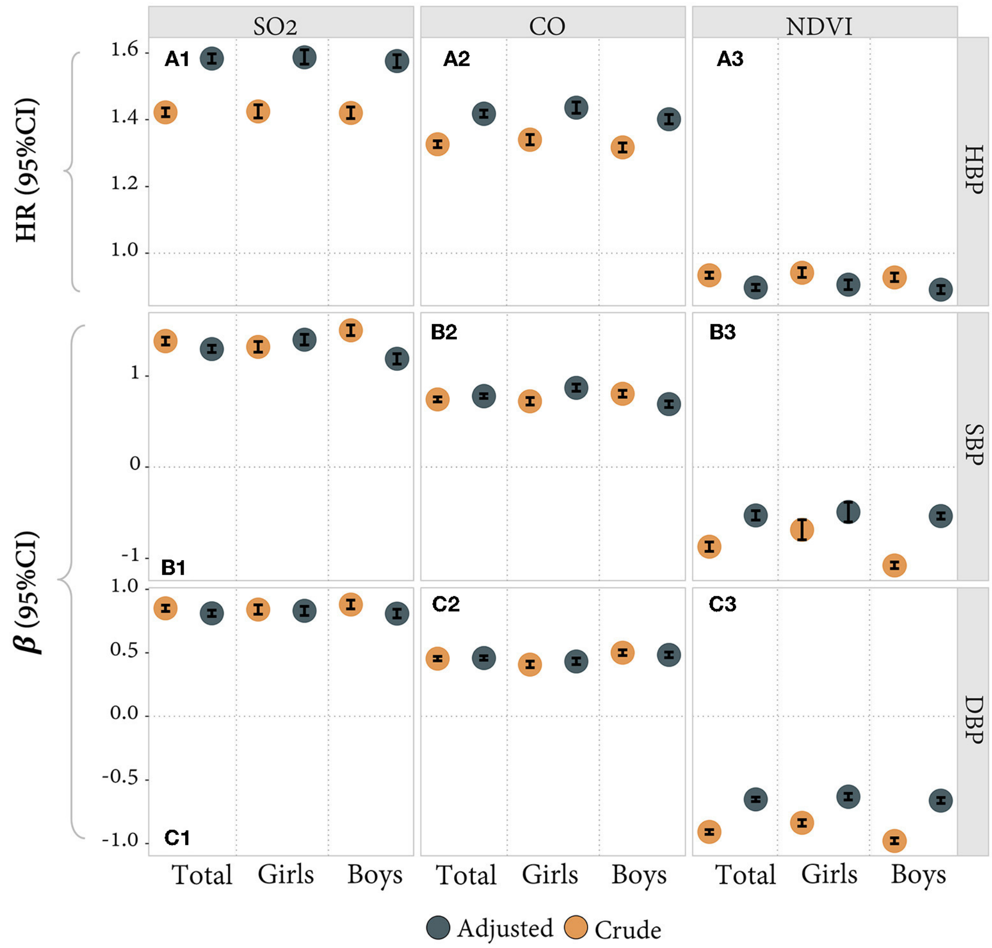

FIGURE 3
(A1–A3) The quantitative correlation between SO_2/CO/NDVI and HBP (binary outcome variable and Cox model). **(B1–B3, C1–C3)** The quantitative association between SO_2/CO/NDVI and SBP/DBP (continuous outcome variable and GEE model). Estimates adjusted for age, BMI, and city and stratified for sex (total estimates also adjusted for sex). β = estimated coefficient. HR, hazard ratio.

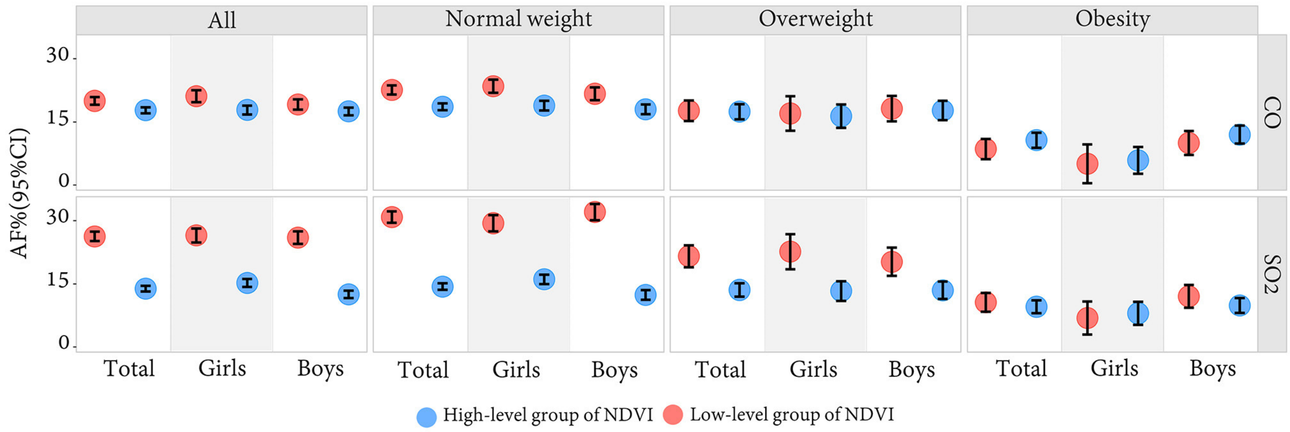

FIGURE 4
The attributable fraction of SO_2 and CO on HBP in the low-level group and the high-level group of greenness by sex and BMI.

specific healthy measure, and theoretical benefits vary with children of different body sizes.

Viewpoints vary on the mechanism underlying HBP or BP affected by gaseous pollutants. One theory posited that gaseous (NO_x, SO_2, CO, and O_3) and particle (PM_{10} and $PM_{2.5}$) pollution triggers pulmonary oxidative injury and systemic inflammation, leading to oxidative stress, with consequences of endothelial injury, vasoconstriction, thrombosis, and changes in blood pressure (43). Another study suggested that pollutants activate respiratory sensory nerves, affecting airway receptors, baroreceptors, and chemoreceptors, thereby modifying the autonomic nervous system control of BP (44). There were also several perspectives on the effect mechanisms of greenness on BP, such as reducing stress, improving physical activity, and reducing respiratory diseases (45–48). We hypothesized that greenness could also control BP by changing pollution levels. Through analyzing individual air quality components or different geographical regions in China, we discovered that greenness had a prominent role in improving urban air quality, especially in northern China. Its contribution can reach 16.2% (49). Studies demonstrated that trees could direct filter air pollutants, such as SO_2, which are absorbed mainly through stomata. Absorption is not the only way in which plants improve air quality. The higher the tree canopy cover, the better the barrier effect, and the more pollutant mixtures from high in the air can be limited. Tree species, plants cover rate, length of the leaf season, pollution concentration, and precipitation in different cities will all affect the air purification of greenness, thus bringing about different levels of health benefits (49–53). However, for obese children, the function of greenness is very limited in eliminating the pollutants-related HBP risk attributed to pollutants. These findings and mechanisms indicated that targeted measures should control the individual pollutants in different areas and for children with different BMIs.

In addition to the above findings, secondary results are shown in the above figures and Supplementary Appendix. We found that greenness had a protective effect on participants' blood pressure. The mechanism follows: green plants absorb SO_2 and CO primarily *via* leaf stomata and reduce air temperatures by transpiration, influencing microclimate, which can then promote physical activity and social engagement, and link to mental health benefits (50, 54, 55), thus bringing physical health benefits. Our study also investigated the differences in results between boys and girls, in different ages, as shown in Figures 2–4 and Supplementary Figure A2. There was an obvious difference between boys and girls on the nonlinear associations of SO_2, CO, and greenness with the risk of HBP, indicating that girls are more subjected to pollutants and greenness differences than boys. The participants were grouped into four age groups every 3 years as an interval and analyzed in subgroups. The group of 7–9 years old was more sensitive than the other groups. The association between CO and HBP outcomes was weaker in the 13–15 years old group, their association of NDVI with HBP was even the opposite. The result might be because of the indoor and outdoor activity time among children with academic pressure. However, no detailed age sensitivity to gaseous pollutants has been reported in previous studies. In addition, two typical northern and southern cities were included in our study to reflect China's overall situation in and to improve the result scalability. Considering the differences between cities, we also tested the data for both cities separately. Although the two cities may have some differences in detail, the overall results appear to be consistent with the combined results after we adjusted for the city in our main results, as shown in Supplementary Figures A7, A8. The blood pressure hazards caused by SO_2, and CO pollution were similar in Zhongshan. Still, the greenery protective effects were more stable across genders in Zhongshan than in Beijing, probably due to pollutant proportions and the plant species in the two cities. Therefore, we also did some sensitivity analysis, as shown in Supplementary Figures A3–A8.

This study has the following strengths: first, we used a dynamic longitudinal cohort covering almost all school-age students for 12 years. Second, this study focused on northern and southern cities in China, making the results more representative and balanced. Third, we used the restricted cubic spline analyses to explore the non-linear association between exposure and ending, which might be more relevant to reality. At last, in addition to exploring the independent association between gaseous pollutants and green space with BP separately. We also assessed the benefits of improving a single pollutant under different greenness conditions to provide theoretical ideas for policy development.

There were still some limitations: firstly and most importantly, we used a convenient sample to develop a cohort study and only collected physical examination and environmental data. No family background or lifestyle habits were included. As a result, our study did not investigate some confounders, like salt intake, parents' education level, temperature, and traffic noise, which might lead to fluctuation in the theoretical benefits of greenness (42, 56, 57). Secondly, we adopted annual mean air pollutants concentrations and NDVI at the school level. The inherent limitations of NDVI did not allow us to distinguish between plant types, which might also affect health differently. And the home addresses collected in our study were imprecise, but the school addresses were accurate to latitude and longitude coordinates. Although students may spend even time at school and home, the local climatic and geographic conditions were similar. As a result, we used the school environment as individual exposure. Thirdly, we assumed that students included in our study did not change schools. Individuals may still develop HBP after exposure, but we did not follow up on this situation, so we might underestimate the incidence of HBP in our study. In addition, a one-time BP value is not sufficient to confirm the HBP, three repeated visits on different occasions would be more accurate. Fourth, our study did not consider children who dropped out of school; therefore, it could not represent the entire children and adolescent population. As our study was based on a dynamic open cohort of a natural population, selection bias still exists. It excluded more obese children and included children with lower BMI and weaker effects on HBP, while the effect of SO_2 and CO on blood pressure was still observed.

5. Conclusions

In summary, our study supported a positive correlation between air pollution and HBP risks among children and adolescents, and a negative correlation between greenness and HBP risks. Meanwhile, the greenness reduces the risks of HBP attributed to SO_2 and CO exposure among students, but its benefit was more effective for normal-weight participants than those obese. It was suggested that some targeted measures should be taken to reduce the specific gaseous pollutants. According to the characteristic of various districts, improving green space construction and preventing childhood obesity could reduce the burden of childhood HBP and subsequent cardiovascular disease risks.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Biomedical Ethics Committee of Peking University Health Science Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YZ and SC conceived the study design, performed the analysis, interpreted the findings, and wrote the manuscript. LC, YW, and JW prepared, analyzed, cleaned the data, interpreted the findings, and helped with manuscript preparation. TM, MC, and QM cleaned the data, interpreted the findings, and helped with manuscript preparation. JL, LW, WL, XL, JZ, and XW helped with manuscript preparation. JM and XG contributed to the conception of the work. YX and JZ worked on study design and data collection and helped with manuscript preparation. YD contributed to the conception of the work and helped with manuscript preparation. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1097510/full#supplementary-material

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Fine particulate matter air pollution and the mortality of children under five: a multilevel analysis of the Ethiopian Demographic and Health Survey of 2016

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Background: Every year, polluted air is costing the globe 543,000 deaths of children under five. The particulate matter below 2.5 μm diameter ($PM_{2.5}$) is a part of air pollution that has adverse effects on children's health. In Ethiopia, the effect of ambient $PM_{2.5}$ is least explored. This study aimed to assess the association between $PM_{2.5}$ and under-five mortality in Ethiopia.

Methods: The study used the data from the Ethiopian Demographic Health Surveys conducted in 2016, collected between January 18 and June 27. All children under five who had data on child mortality and location coordinates were included in the study. Exposure to ambient $PM_{2.5}$ concentration was a satellite-based estimate by the Atmospheric Composition Analysis Group at Washington and Dalhousie University, in the United States and Canada, respectively. Annual mean pollution levels and mortality datasets were matched by children's geographical location and dates of birth, death, and interview. The relationship between ambient $PM_{2.5}$ and under-five mortality was determined by a multilevel multivariable logistic regression on R software. The statistical analyses were two-sided at a 95% confidence interval.

Results: The study addressed 10,452 children with the proportion of under-five mortality being 5.4% (95% CI 5.0–6.8%). The estimated lifetime annual mean exposure of ambient total $PM_{2.5}$ was 20.1 ± 3.3 μgm^{-3}. A 10-unit increase in the lifetime annual mean ambient total $PM_{2.5}$ was associated with 2.29 [95% CI 1.44, 3.65] times more odds of under-five mortality after adjusting for other variables.

Conclusion: Children under five are exposed to higher levels of ambient $PM_{2.5}$ concentration, exceeding the limit set by the World Health Organization. Ambient $PM_{2.5}$ is significantly associated with under-five mortality, adjusting for other variables. Strong measures need to be taken to reduce air pollution.

KEYWORDS

particulate matter <2.5μm (PM) 2.5, under-five children, air pollution, sub-Sharan Africa, Ethiopia, outdoor air pollution, Demographic Health Survey (DHS), Atmospheric Composition Analysis Group (ACAG)

Introduction

Every year, ambient air pollution is costing the globe around 3 million premature deaths while contributing to climate change and adverse economic impacts. The magnitude of pollution and its impact is higher in low- and middle-income countries (LMICs) (1). Ambient air pollution affects the entire population and all age groups, with children and the older adult being more susceptible (2).

Globally, among children under five, 543,000 deaths are attributed to both polluted indoor and outdoor air (3). Low nasal filtration, high ventilation rates, and higher metabolic rates in children might have contributed to a higher tendency of these pollutants to be deposited in them, consequently, affecting the lungs, renal and hepatic functions (4), and growth of the lungs (5). The burden is higher in Africa due to the higher consumption of polluting fuels, mainly biomass fuels (3).

Fine particulate matter of 2.5 µm diameter ($PM_{2.5}$) is one of the indicators of ambient air quality that is monitored (6, 7). Particulate matter (PM) is suspended particles in the ambient and indoor air that constitute both solid and liquid particles of any kind (8). Among children, short-term $PM_{2.5}$ exposure has been associated with pneumonia (9, 10) and upper and lower respiratory tract infection (ULRI) (10). $PM_{2.5}$ is also associated with an increase in viral and bacterial load (11), cough, wheezing, and lower respiratory infection in children (12). Pneumonia (3, 13–15) and acute respiratory illness are the leading causes of under-five mortality in the world (3). A longer time of exposure was associated with symptoms of cough, convulsion, or fever (16) and higher rates of all-cause under-five mortality in Nairobi (16) and western and central Africa (17) and infant mortality in sub-Saharan Africa (18). Most air pollution-related health impact assessments are based on long-term exposures including annual mean concentrations (19–21).

However, previous studies showing the strong relationship between ambient $PM_{2.5}$ and its detrimental human health effect have largely been conducted in developed nations; most are in North America and Europe. In developed nations, there is a relatively low air pollution status (22, 23) which might contribute to the small amount of mortality compared to developing countries. Hence, pooled estimates on the impact magnitude of ambient $PM_{2.5}$ from major studies conducted in the global north might be underestimated (18, 24, 25). This was apparent in the pooled estimates from a meta-analysis of studies from five WHO regions—estimates of $PM_{2.5}$ and all-cause mortality association showed 0.25 to 2.08% variations across the regions (22), China (23), and at the global level (25). In Africa, only a few studies have investigated and found that long-term exposure to ambient $PM_{2.5}$ was associated with child mortality (16–18, 26). Thus, further study helps to better understand the degree of the effect of ambient $PM_{2.5}$ in Africa.

Abbreviations: ACAG, Atmospheric Composition Analysis Group; AOD, Aerosol optical depth; AOR, Adjusted odds ratio; ARI, Acute respiratory illness; CI, Confidence interval; CRS, Coordinate Reference System; DHS, Demographic Health Survey; EA, Enumeration Area; EDHS, Ethiopian Demographic Health Survey; EEA, European Environment Agency; EU, European Union; GPS, Global Positioning System; ICC, Interclass correlation; LMICs, Low- and middle-income countries; PM, Particulate matter; $PM_{2.5}$, Particulate matter mass concentration size below 2.5µm diameter; SD, Standard deviation; ULRI, Upper and lower respiratory tract infection among children; US, United States; VIF, Variance inflation factor; WHO, World Health Organization.

Secondly, though under-five mortality has largely reduced since 2000 in sub-Saharan Africa, it remains the highest in need of urgent attention—75.8 deaths per 1,000 live births in 2019 (27, 28). Ethiopia is among the sub-Saharan African countries where the under-five mortality rate declined to 59 deaths per 1,000 live births in 2019 (29) from 116 deaths per 1,000 live births in 2006 (30, 31). The reduction was achieved due to improvements in sanitation, nutrition, and access to maternal and child health services. The 59 deaths per 1,000 live births is much higher than the aim or goal intended to be achieved, which is 25 deaths per 1,000 live births (32). The role of $PM_{2.5}$ in the death toll of under-five mortality is still a subject of debate. Thus, further studies will help to better explain the role of $PM_{2.5}$ on under-five mortality and reduce deaths (18).

Thirdly, due to the country's insubstantial monitoring stations, apparatus, and competency of technicians, there are minimal inquiries into ambient $PM_{2.5}$ and its adverse impact on health. Hence, there is a clear knowledge gap about ambient $PM_{2.5}$ and its relationship with under-five mortality in Ethiopia. To the best of our knowledge, this paper is the first in Ethiopia to investigate ambient $PM_{2.5}$ and its association with under-five mortality by controlling for individual characteristics.

Materials and methods

Study area and study design

Ethiopia is the largest landlocked country, with an estimated population of 110 million in the horn of Africa, located between 3°24' and 14°15' North and 33°00' and 48°00' East. It has nine regions and two cities divided for administrative purposes (33). The Ethiopian Demographic Health Survey (EDHS) followed a two-stage community-based cross-sectional study design. EDHS 2016 was collected from January 18 to June 27, 2016 (30).

Source and study population

The source population of the study was all children under five born 5 years before the survey period (January 2011 to June 2016) in Ethiopia. While all children under five born 5 years before the survey period in the selected Enumeration Areas (EAs) were the study population.

The inclusion criteria

All children under five born 5 years before the survey period in the selected households whose mortality data and cluster's Global Positioning System (GPS) coordinates were recorded in the EDHS dataset were included in this study. Children without mortality and geographical location coordinates information were excluded.

Sample size

The EDHS 2016 selected 645 EAs (202 urban and 443 rural EAs). Information was collected for 10,641 (11,022 weighted) children

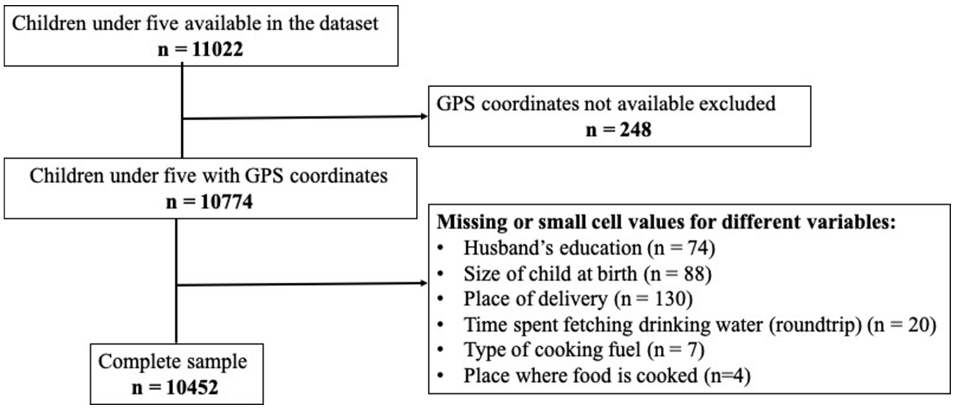

FIGURE 1
Flow chart of the inclusion of observations in the dataset for each step of this study sample analysis.

under five (30). After removing clusters with no location coordinates and data cleaning, a total of 9,856 (10,452 weighted) children under five were included in this study (Figure 1).

Ambient $PM_{2.5}$ concentration data derived from satellites were available across all geographical spaces in the study area.

Sampling procedures

The EDHS collects samples that are representative of both the regional and national levels as well as urban and rural areas. Its data is also to be comparable across different nations through standardized questionnaires. Households were selected after a list of first-level administrative units and their list of enumeration areas (EAs) was provided. We selected an equal number of households (28 households from each EA) from the registered list of households in the EAs using the systematic probability method. Information from all women aged 15–49 years (reproductive-aged women) was collected in all selected households. The women provided information about their children who were under five if they had any. The sampling, methodology, and procedure details have been found published elsewhere (30).

Data collection tools and procedures

The data of children under five needed for this study were retrieved from the Demographic Health Survey (DHS) website.[1] The dataset with filenames starting with ETBR (birth record), ETHR (a household record), ETPR (an individual record), and ETGE (geographical location) was downloaded. The EDHS 2016 interviewers used tablets (personal digital assistants) to enter the responses of study participants. The 2016 EDHS also used a standardized questionnaire by translating the questions into local languages and back to the original language. Interviewers were also calibrated by providing training and frequent supervision before and during data collection, respectively (30).

Dependent variable

Under-five mortality also known as death before the age of 60 months was the dependent variable, with dichotomous values of "dead" or "alive."

Exposure variable

Exposure to lifetime annual mean total $PM_{2.5}$ in μgm^{-3} (microgram per cubic meter) atmospheric air is the main independent variable. In this study, "$PM_{2.5}$ is a mixture of solid and liquid particles suspended in the ambient air" and its "mass concentration of particles diameter is less than 2.5 μm."

Controlled variables

The socio-demographic (mother's educational status, age of the mother, household wealth index, mother's employment status, mother's marital status, husband's occupational status, husband's educational level, and family size), individual/child-related (sex of the child, birth order, child age, size of the child at birth, plurality of a child, and place of birth), environmental-related [source of drinking water (categorized into "improved" and "unimproved"), type of toilet/latrine facility ("improved" and "unimproved")—categorized according to the updated joint monitoring program (JMP),[2] presence of any kind of drinking water treatment in the household ("Yes" or "No"), type of cooking fuel (recorded as "clean fuels" if the fuel is liquefied petroleum gas (LPG), natural gas, biogas, or electricity; other kinds of cooking fuel are in the category

1 https://dhsprogram.com/Data

2 https://washdata.org/monitoring/drinking-water

of "solid fuels"), and place where food is cooked ("not inside the house," "inside the house in a separate room," or "inside the house not in a separate room")], and community-level (region and residence) variables were controlled.

Data on children's ambient total $PM_{2.5}$ exposure

In Ethiopia, there is a limited air quality monitoring system (22, 34). Accordingly, in the absence of air quality monitoring systems (ground-based $PM_{2.5}$ concentration data), satellite-based $PM_{2.5}$ concentration estimates across the globe surface have been employed (22, 35). This study, therefore, used satellite-based $PM_{2.5}$ concentration estimated by the Washington and Dalhousie Universities, Atmospheric Composition Analysis Group (ACAG). The ACAG at the universities produces estimates of $PM_{2.5}$ across the globe, including Ethiopia, at 0.01° × 0.01° spatial resolution. The group estimates the ground-level $PM_{2.5}$ from the year 1998 to 2019 using satellite remote sensing (NASA's MODIS, MISR, and SeaWiFS) AOD retrievals and combining it with the chemical transport model (from GEOS-Chem). They also validate their estimate with land-based $PM_{2.5}$ monitoring systems by employing Geographically Weighted Regression (GWR). The detailed estimation technique is published elsewhere (35). The V4.GL.02 version dataset was used, and it is available publicly for free and can be downloaded from https://sites.wustl.edu/acag/datasets/surface-pm2-5/. The annual mean $PM_{2.5}$ concentration for the years from 2011 to 2016 was extracted from the downloaded ArcGIS-compatible raster datasets.

The lifetime annual mean total $PM_{2.5}$ concentration exposure for each child was determined. For dead children, the lifetime annual mean total $PM_{2.5}$ concentration was the exposure period of all the months up until death; for alive children, the lifetime annual mean total $PM_{2.5}$ concentration was the exposure period up until the month EDHS 2016 data was collected.

The geographical coordinates of EAs' were matched with the average annual total $PM_{2.5}$ concentration data. The DHS randomly displaced the EA's geographical coordinates up to 2 km in urban and 5–10 km in rural areas to protect the respondents' privacy. As a result, the average annual total $PM_{2.5}$ within a circular radius of 3.3 km in urban areas and 6.7 km in rural areas was taken for each cluster. The month and year of the child's date of death, birth, and interview were matched with the EA's average annual total $PM_{2.5}$ concentration. A weighted total $PM_{2.5}$ exposure was taken if the exposure period falls within two or more different years—the weighting procedure has been described in detail in previous studies (18, 26).

Data management procedures

The DHS datasets were merged using common/identifier variables (identification (ID), cluster, household, line, and birth number). R software version 3.6.3 was used to merge, recode, clean, and run descriptive and multilevel regression models while matching the geographical locations, raster clip, raster residual analysis, and sample raster values were performed using ArcGIS software version 10.7.

Data analysis

Before any analysis, the sample was weighted for the complex survey design (36), the variables were described, and sensitivity analysis was done. Sensitivity analysis is a method used to check the influence of the changes in the values of the independent variables (i.e., of missing values) on the bivariate relationship of the independent and dependent variables (37). Proportions across sub-groups and mean and standard deviations (SD) for continuous variables were used to summarize the variables.

A separate bivariate logistic regression model was built for each controlled variable and the lifetime annual mean $PM_{2.5}$ exposure to assess their association with under-five mortality. Variables that showed a significance level of 15% were considered for the multilevel multivariate model. The degree of variation of under-five mortality among clusters was determined using two methods; the first method used was to compare the statistically significant difference between a null logistic regression and a null multilevel logistic regression model using EAs as random effect intercept. The second method used was to describe the heterogeneity of under-five mortality among clusters using interclass correlation (ICC). The ICC is "*a measure of the proportion of variation in the outcome or under-five mortality that occurs between groups or clusters* versus *the total variation present*" (38). In the multilevel multivariate logistic regression model, controlled variables have been added to the model step by step. Socio-demographic, child-related, environmental-related, and community-level variables were added to the model, respectively. Model assumptions were checked if they were met. The final model was selected by a backward stepwise variable selection technique. At each step, variables with a significance level of 15% and variance inflation factor (VIF) > 3 (39) were removed from the model. The selected final model had the highest log-likelihood. All statistical tests computed were two-sided tests at a 95% confidence interval.

Data quality and processing

The EDHS used re-interviewing households, checking one to two interviewers' questionnaires per data collector, reviewing periodical field control table tools, dual entry of information by two different persons, and cleaning of missed values to ensure the quality of data (30). In this study, a careful dataset merging using dataset "identifier" or common variables, data quality parameters (36), and defensive codding while cleaning the data was done. Care was also taken in the choice of the coordinate reference system (CRS) and statistical packages (40).

Ethics approval and consent to participate

Permission was gotten from the DHS archive and geographic database to use the DHS data. The global estimate of annual mean PM2.5 concentration was made accessible to the public by the ACAG and was used for free. Furthermore, the study was approved by the College of Health Sciences of Addis Ababa University Ethical Review Committee with a reference number SPH/1119/13.

TABLE 1 Socio-demographic factors of the study participants EDHS 2016, *n*=10,452.

	Total population		Under-five mortality		
	n	%	Dead (%)	Alive (%)	*P***
Socio-demographic factors					
Age of the mother					0.31
15–24	2,271	21.7	5.9	94.1	
25–29	3,192	30.5	5.8	94.2	
30–34	2,372	22.7	5.1	94.9	
≥35	2,617	25.0	6.4	93.6	
Mother's education					<0.001*
No education	6,858	65.6	6.5	93.5	
Primary	2,823	27.0	5.0	95.0	
Secondary and above	771	7.4	3.8	96.2	
Mother's current marital status					0.88
Not in a union/not living with a partner	535	5.1	6.0	94.0	
In a union/living with a partner	9,917	94.9	5.8	94.2	
Mother's employment status					0.36
Not working	5,806	55.5	6.0	94.0	
Working	4,646	44.5	5.6	94.4	
Wealth index					<0.001*
Poorest	2,428	23.2	7.2	92.8	
Poorer	2,373	22.7	6.1	93.9	
Middle	2,173	20.8	5.3	94.7	
Richer	1926	18.4	6.1	93.9	
Richest	1,552	14.9	3.3	96.7	
Husband's education					0.003*
No education	4,739	47.8	6.6	93.4	
Primary	3,945	39.8	5.5	94.5	
Secondary and above	1,233	12.4	4.4	95.6	
Husband's employment status					0.15
Not working	737	7.4	6.9	93.1	
Working	9,180	92.6	5.7	94.7	
Family size					<0.001*
≤three	5,078	48.6	6.9	93.1	
Above three	5,374	51.4	4.7	95.3	
Sex of household head					0.47
Female	1,434	13.7	5.5	94.5	
Male	9,018	86.3	5.9	94.1	

**A bivariate logistic regression. *Used in the multilevel multivariate analysis.

Results

Characteristics of respondents

The size of the sample included in this study analysis was 10,452. The overall children's mothers' age mean (SD) was 29.6 ± 6.6. Children's mothers between 25 and 29 years old constituted the majority, 29.9%. Most of the children's mothers were married or living with a partner (94.9%), not working (55.5%), with no education status (65.6%), and had the poorest wealth index (23.2%). The study participants with a man as the head of the household (86.3%), a family size above three (51.4%), a husband with no education (47.8%), and a working husband (92.6%) were also the majority (Table 1).

The total sample size proportion of under-five mortality was 5.4% (95% CI 5.0–5.8%). According to respondents, 52% of the children under five were boys, 41.6% had average birth weight, 2.5% were twins, and 26.7% were born in institutions. Children's age mean ± SD in months was 27.8 ± 18.7, the category ≥24 months constitutes 54.5% (Table 2).

TABLE 2 Child-related factors of the study participants EDHS 2016, n=10,452.

	Total population		Under-five mortality		
	n	%	Dead (%)	Alive (%)	*P***
Child/individual factors					
Sex of the child					<0.001*
Female	5,018	48.0	4.9	95.1	
Male	5,434	52.0	6.7	93.3	
Size of the child at birth					<0.001*
Very large	1891	18.1	6.8	93.2	
Large	1,466	14.0	4.8	95.2	
Average	4,351	41.6	5.0	95.0	
Small	1,059	10.1	5.9	94.1	
Very small	1,685	16.1	7.8	92.2	
Child age (in months)					<0.001*
≤12	2,823	27.0	18.3	81.7	
12–24	1934	18.5	3.6	96.4	
>24	5,695	54.5	0.5	99.5	
Birth order					0.06*
Third and below	5,121	49.0	5.4	94.6	
Fourth and above	5,331	51.0	6.3	93.7	
The plurality of a child					<0.001*
Yes	265	2.5	20.4	79.6	
No	10,187	97.5	5.4	94.6	
Place of delivery					<0.001*
Home	7,662	73.3	6.7	93.3	
Institution	2,790	26.7	4.0	96.0	

**A bivariate logistic regression. *Used in the multilevel multivariate analysis.

The lifetime annual mean satellite-based ambient $PM_{2.5}$ exposure among children under five was 20.1 ± 3.3 μg m^{-3}. The majority (67.2%) of households collect their drinking water within ≤30 min roundtrip distance. The proportion of households with improved drinking water sources, improved toilet facilities, and clean fuel was 56.8, 5.1, and 3.4%, respectively. Most (80.9%) of the respondents were residing in rural areas (Table 3).

Determining the association between ambient $PM_{2.5}$ concentration and under-five mortality in Ethiopia

In the bivariate logistic model of lifetime annual mean $PM_{2.5}$ and under-five mortality, the lifetime annual mean $PM_{2.5}$ showed a significant association with under-five mortality ($p = 0.001$) (Table 3).

Fitting multilevel multivariate logistic regression model

There was a significant difference between the null multilevel logistic regression model, EAs being the random effect intercept, and the empty logistic regression model (value of p <0.001). The ICC and the random effect intercept variance of the null model were 10.0% and 0.34, respectively.

The final model selected based on the criteria set prior to analysis was Model 4, as seen in Table 4. In the final model, a 10-unit increase in lifetime annual mean exposure to ambient $PM_{2.5}$ was associated with 2.29 [95%CI 1.44–3.65] times more odds of being dead, adjusting for all other variables (Table 4).

Moreover, in the final model (Model 4), children under five with mothers without formal education ($p = 0.02$), very large birth size ($p = 0.04$), those who were twins ($p < 0.001$), those born at home ($p < 0.001$), those whose food was cooked inside a house without a separate room ($p = 0.001$), and residing in the Somali ($p = 0.002$), Harari ($p = 0.02$), and Dire Dawa ($p = 0.02$) regions were more likely to die, compared with those whose mothers had a secondary and above education, a large birth size, singletons, delivered in an institution, whose food was cooked outside of the house, and resided in the Tigray region, respectively; the results were statistically significant. In contrast, children under five with a family size above three ($p < 0.001$), were between 12 and 24 months ($p < 0.001$), age ≥ 24 months ($p < 0.001$), and were girls ($p < 0.001$) were less likely to die, compared with a family size ≤3, age ≤12, and being a boy under five, respectively; the results were statistically significant (Table 4).

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TABLE 3 Environmental-related and community-level factors of the study participants EDHS 2016, *n*=10,452.

	Total population		Under-five mortality		
	n	%	Dead (%)	Alive (%)	*P***
Environmental factors					
Ambient $PM_{2.5}$ (mean ± SD)	20.1 ± 3.3	21.7 ± 5.2	20.0 ± 3.3	*0.001*	20.1 ± 3.3
Source of drinking water					0.009*
Improved	5,940	56.8	5.3	94.7	
Unimproved	4,512	43.2	6.6	93.4	
Time to fetch (roundtrip in minutes)					0.02*
≤30	7,018	67.2	5.4	94.6	
>30	3,434	32.8	6.6	93.4	
Any kind of household water treatment					0.31
Yes	881	8.4	5.1	94.9	
No	9,571	91.6	5.9	94.1	
Type of toilet facility					<0.01
Improved	533	5.1	3.1	96.9	
Unimproved	9,919	94.9	6.1	93.9	
Type of cooking fuel					<0.001*
Clean fuel	352	3.4	2.3	97.7	
Solid fuel	10,100	96.6	6.0	94.0	
The place where food is cooked					<0.001*
Outside the house	5,978	57.2	5.1	94.9	
Inside but in a separate room	711	6.8	5.0	95.0	
Inside but not in a separate room	3,763	36.0	7.6	92.4	
Community-level variables					
Type of place of residence					<0.001*
Urban	1,179	11.3	3.1	96.9	
Rural	9,273	88.7	6.5	93.5	
Region					<0.001*
Tigray	679	6.5	3.8	96.2	
Afar	112	1.1	8.7	91.3	
Amhara	2009	19.2	4.8	95.2	
Oromia	4,628	44.3	5.5	94.5	
Somali	351	3.4	6.4	93.6	
Benishangul	115	1.1	7.4	92.6	
SNNPR	2,227	21.3	5.4	94.6	
Gambela	25	0.2	6.1	93.9	
Harari	25	0.2	6.9	93.1	
Addis Ababa	238	2.3	2.7	97.3	
Dire Dawa	43	0.4	5.5	94.5	

**A bivariate logistic regression. *Used in the multilevel multivariate analysis.

Discussion

This study assessed the relationship between long-term exposure to ambient fine particulate concentration levels and the mortality of children under five in Ethiopia. The study used a community-based two-stage survey design and satellite-based ambient $PM_{2.5}$ exposure level. Total $PM_{2.5}$ is significantly and positively associated with under-five mortality. It found that the annual mean ambient total $PM_{2.5}$ children are exposed to is higher than the health-recommended concentration level. These findings revealed $PM_{2.5}$ plays a significant role in the burden of under-five mortality. The results also provide insights for the government on the importance of increasing its effort

TABLE 4 Multivariable multilevel logistic regression analysis of $PM_{2.5}$ and other factors associated with under-five mortality, EDHS 2016, *n*=10,452.

		AOR** 95% CI	AOR*** 95% CI	AOR**** 95% CI
	Under-five mortality (%)	Model 2	Model 3	Model 4
$PM_{2.5}$ ($\mu g\,m^{-3}$) (mean ± SD)[a]*	21.7 ± 5.2	1.34 (1.07, 1.66)*	1.33 (1.07, 1.66)*	2.29 (1.44, 3.65)*
Mother's education				
No education	6.5	1.58 (1.08, 2.31)*	1.74 (1.15, 2.62)*	1.65 (1.08, 2.54)*
Primary	5.0	1.15 (0.78, 1.69)	1.15 (0.78, 1.73)	1.10 (0.72, 1.67)
Secondary and above	3.8	(Reference)		
Wealth index				
Poorest	7.2	2.08 (1.49, 2.89)*	1.24 (0.85, 1.80)	0.80 (0.48, 1.33)
Poorer	6.1	1.84 (1.29, 2.63)*	1.18 (0.79, 1.74)	0.88 (0.53, 1.45)
Middle	5.3	1.59 (1.09, 2.32)*	1.10 (0.73, 1.66)	0.86 (0.52, 1.44)
Richer	6.1	1.95 (1.35, 2.82)*	1.29 (0.86, 1.93)	1.12 (0.68, 1.85)
Richest	3.3	(Reference)	(Reference)	(Reference)
Family size				
≤three	6.9	(Reference)	(Reference)	(Reference)
Above three	4.7	0.55 (0.46, 0.66)*	0.57 (0.47, 0.70)*	0.58 (0.47, 0.71)*
Sex of the child				
Female	4.9		0.67 (0.55, 0.81)*	0.66 (0.55, 0.80)*
Male	6.7		(Reference)	(Reference)
Size of the child at birth				
Very large	6.8		1.43 (1.01, 2.04)*	1.46 (1.03, 2.09)*
Large	4.8		(Reference)	(Reference)
Average	5.0		0.88 (0.64, 1.20)	0.92 (0.67, 1.26)
Small	5.9		0.94 (0.62, 1.42)	1.01 (0.66, 1.53)
Very small	7.8		0.94 (0.66, 1.33)	0.99 (0.70, 1.41)
Child age (in months)				
≤12	18.3		(Reference)	(Reference)
12–24	3.6		0.16 (0.12, 0.21)*	0.16 (0.12, 0.21)*
>24	0.5		0.02 (0.01, 0.03)*	0.02 (0.01, 0.03)*
The plurality of a child				
Yes	20.4		5.57 (3.71, 8.36)*	5.41 (3.59, 8.16)*
No	5.4		(Reference)	(Reference)
Place of delivery				
Home	6.7		2.35 (1.81, 3.05)*	2.21 (1.69, 2.90)*
Institution	4.0			(Reference)
The place where food is cooked				
Outside the house	5.1			(Reference)
Inside but in a separate room	5.0			1.17 (0.72, 1.86)
Inside but not in a separate room	7.6			1.49 (1.17, 1.90)*
Type of residence				
Urban	3.1			(Reference)
Rural	6.5			1.64 (0.99, 2.72)
Region				
Tigray	3.8			(Reference)
Afar	8.7			0.78 (0.43, 1.43)

(Continued)

TABLE 4 (Continued)

		AOR** 95% CI	AOR*** 95% CI	AOR**** 95% CI
	Under-five mortality (%)	Model 2	Model 3	Model 4
Amhara	4.8			0.79 (0.46, 1.34)
Oromia	5.5			1.11 (0.67, 1.84)
Somali	6.4			2.89 (1.48, 5.65)*
Benishangul	7.4			1.55 (0.92, 2.59)
SNNPR	5.4			1.22 (0.72, 2.06)
Gambela	6.1			1.36 (0.77, 2.38)
Harari	6.9			2.08 (1.12, 3.86)*
Addis Ababa	2.7			0.99 (0.44, 2.21)
Dire Dawa	5.5			2.21 (1.17, 4.18)*
Random effects				
ICC in %		**7.6**	**5.9**	**5.6**
Model comparison				
Log-likelihood		**−2130.6**	**−1581.8**	**−1566.2**

[a]*Ten-unit increase. Statistically significant at $p < 0.05$. **Adjusted for socio-demographic variables. ***Adjusted for socio-demographic and child-related variables. ****Adjusted for socio-demographic, child-related, environmental-related, and community level variable. Model 1 was built previously separately for each controlled variable.

in monitoring air quality to reduce its pollution level and negative effect on health.

The lifetime annual mean satellite-based ambient $PM_{2.5}$ children are exposed to in their lifetime was 20.1 ± 3.3 μgm^{-3}. This is beyond the World Health Organization (WHO) 2021 guideline—which updated the 2005 global air quality guideline—annual exposure limit of 5 μgm^{-3} (20). The result is consistent with evidence from LMICs such as China, India, Pakistan, Bangladesh (19), Africa, and Eastern Mediterranean (3) where almost no population, including children under five, breathe air below 10 μgm^{-3} $PM_{2.5}$ concentration. Higher levels of $PM_{2.5}$ is still a problem in European Member (EU) states too. According to the European Environment Agency (EEA), 97% of European urban residents are exposed to $PM_{2.5}$ higher than 5 μgm^{-3}. The road transport, energy, industry, and agriculture sectors are the sources of $PM_{2.5}$ in Europe (41). In China and India, however, coal, construction dust, and burning solid fuels are the major emitters of $PM_{2.5}$ (19, 23). In Ethiopia, most households—almost 70% in urban and 99% in rural areas—depend on solid fuels, mainly woody biomass, animal dung, and crop stalks (29). A study conducted on source apportionment of $PM_{2.5}$ in Addis Ababa found that traffic flow, biomass, and dust sources are the major constituents (42).

Adjusting for other variables, a 10 μgm^{-3} increase in ambient $PM_{2.5}$ was significantly associated with more odds of death. Furthermore, children in households whose food was cooked outside of the house, with mothers without formal education, who had a very large birth size, who were twins, and who were born at home were found to be significantly and positively associated with under-five mortality. On the contrary, children with a family size above three, between 12 and 24 months, age ≥24 months, and who were girls were significantly and negatively associated with under-five mortality.

A significant association between a 10 μgm^{-3} increase in ambient $PM_{2.5}$ and under-five mortality that was found in this study is consistent with previous studies in India (43), Asia (44, 45), and sub-Saharan Africa (26). However, there is a difference between previous studies and this study's estimated effect sizes; there was an increase in odds of under-five mortality with a 10-unit increase in lifetime annual mean $PM_{2.5}$ concentration, adjusting for other variables (17, 46). This might be attributed to the use of different definitions—death per 1,000 live births—, separate estimations for the different types of $PM_{2.5}$ (total $PM_{2.5}$ versus salt and dust removed $PM_{2.5}$), and differences in adjusted variables. It may also be because the estimate by Karimi and Shokrinezhad (46) was a pooled estimate, and the majority of studies included were from developed nations. The magnitude of the effect of $PM_{2.5}$ on under-five mortality is higher among developing and least developed countries compared to developed countries (47). Fine particulate matter, as a result of its smaller mass concentration diameter size, can penetrate the blood-gas barrier. This allows the different chemical constituents of $PM_{2.5}$ to circulate in the blood system and reach the different human organs (48). Especially, $PM_{2.5}$ deposition in children is higher due to their fast breathing, lower nasal filtration, higher metabolic rate, and limited ability to metabolize toxic pollutants (4). Different substances, i.e., organic matter, elemental carbon, soil dust, sulfate, nitrate, and ammonium ions, form $PM_{2.5}$ although it varies from place to place (49). Nephrotoxic heavy metals—chromium and cadmium—components of $PM_{2.5}$ can also reach the kidney to affect its function (50), which might lead to death. $PM_{2.5}$ is also associated with notable under-five mortality killer diseases pneumonia (3, 9, 14) and ARI (14, 15, 51).

Environmental-related variables—the type of drinking water source, toilet facility, and cooking fuel—were not significant in the final model. The following reasons could be the important factors that come into play. First, not all sources labeled as improved drinking water are free of fecal or disease-causing organisms (52). Second, there is a reintroduction of microbes into drinking water during collection by contaminated hands, containers, utensils, and/or insects (53, 54). Finally, households with improved drinking water may not necessarily have improved toilet facilities or vice versa (55). Even after access to improved facilities, the quality is influenced by human behavior, i.e., hand washing, personal hygiene, and consistent use of improved facilities (53, 54). Similarly, the use of clean fuel does not mean households are well-ventilated and the indoor air is relatively acceptable (56). This study supports the statement. Cooking food inside a house with no separate room, a proxy to ventilation, was associated with higher odds of under-five mortality.

Strengths and limitation

The study provides insights into the relationship between ambient $PM_{2.5}$ concentration level and under-five mortality at the individual level for the first time, and to the best of our knowledge, at the national level in Ethiopia. The study overcame the absence of ground-level ambient $PM_{2.5}$ concentration data by using a freely available satellite-based estimate of ACAG.

The study is limited in accounting for indoor stay ($PM_{2.5}$ exposure from indoor air was not quantified) and the movement of children from place to place in determining exposure to ambient $PM_{2.5}$. It is also limited in not using ground-based $PM_{2.5}$ nor making adjustments to the retrieved satellite-based $PM_{2.5}$ as it is subject to measurement error. Currently, ground-based data is assumed to be a gold standard relative to satellite-based data. The authors compared the annual mean $PM_{2.5}$ from satellite-based measurements and the three land-stationed BAM $PM_{2.5}$ monitors in Addis Ababa (57) for similar geographical points. A large concentration difference was noticed at Tikur Anbessa Specialized Hospital and International Community School. However, a similar concentration level was observed at the United States (US) Embassy in Addis Ababa. A difference is expected considering that validated satellite-based $PM_{2.5}$ has used a small number of land stations in Africa, including Ethiopia (58, 59). As a result, caution should be taken in interpreting the results of this study.

Conclusion

This study determined the annual mean ambient $PM_{2.5}$ exposure of children under five in their lifetime. Fine particulate matter annual exposure concentration among children under five exceeded the WHO recommended level. Ambient $PM_{2.5}$ was significantly associated with higher odds of under-five mortality, adjusting for other variables. These results support the importance of taking measures to improve ambient air quality. The government should take strong actions to reduce air pollution and help achieve the goal set to decrease under-five mortality. The authors recommend further investigation which considers movement and indoor stay in determining ambient $PM_{2.5}$ exposure in Ethiopia. It is also recommended to identify which constituents of $PM_{2.5}$ are greatly affecting under-five mortality in Ethiopia.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://dhsprogram.com/Data, https://sites.wustl.edu/acag/datasets/surface-pm2-5/.

Ethics statement

The studies involving human participants were reviewed and approved by the College of Health Sciences of Addis Ababa University Ethical Review Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

ABS did the study design, data acquisition, data cleaning, data analysis, and interpretation and contributed to the drafting, revising, and editing of this manuscript. AK and WT participated in the principal supervision, interpretation, and revision of the final manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The influence of neighborhood built environment on school-age children's outdoor leisure activities and obesity: a case study of Shanghai central city in China

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Objective: The aim of this study was to examine the influencing pathways of the neighborhood built environment on children's outdoor leisure activities and obesity.

Methods: A total of 378 elementary school students from 10 schools in central Shanghai were selected by a convenient sampling method for questionnaire survey and accelerometer tracking.

Results: 1) The neighborhood built environment could affect children's obesity not only through direct effect (β =0.15, p <0.05), but also through the mediating effect of outdoor leisure activities (β =0.19, p<0.05). 2) For boys, the neighborhood built environment could affect children's obesity not only through direct effect (β =0.17, p <0.05), but also through the mediating effect of outdoor leisure activities (β =0.26, p <0.05). For girls, the neighborhood built environment could affect children's obesity only through the mediating effect of outdoor leisure activities (β =0.13, p <0.05).

Conclusion: The neighborhood built environment and outdoor leisure activities are important influencing factors in children's obesity. The neighborhood built environment and outdoor leisure activities could have direct and indirect effects on children's obesity, while there are gender differences in the influencing pathways of the neighborhood built environment on children's obesity. This study suggests that improving the neighborhood built environment and promoting outdoor leisure activities in children have important value for influencing children's obesity.

KEYWORDS

social ecology theory, neighborhood built environment, outdoor leisure activities, obesity, school-age children

1. Introduction

The Blue Paper of the China Child and Adolescent Nutrition and Health Report 2016 points out that, from 1985 to 2014, the detected rate of obesity among students in China increased sharply, and the risk of chronic diseases such as cardiovascular and hyperglycemia due to obesity subsequently increased (1). The Healthy China Initiative (2019–2030) also points out that the rate of students' obesity meeting the standard was only 31.8% in 2017, and the obesity problem has become a serious health threat to school-age children and adolescents in China (2). Providing a supportive environment for children and encouraging them to participate in diverse outdoor leisure activities are important means to promote physical activity and reduce their obesity, and are also an important entry point for the construction of child-friendly cities.

Social ecological theory suggests that individual health is influenced by the interaction of multiple factors such as individual factors (cognition, attitude, self-efficacy, etc.), interpersonal factors (peer support, parental support, etc.), environmental factors (parks, green spaces and recreational facilities, etc.), and policy. It has also been confirmed that obesity is closely related to geography, and geographic research on the relationship between human health and geography has gradually turned to the influence of elements of the urban built environment on human health (3–5). According to the spatio-temporal model of children's activity domain proposed by Matthews, children's daily activities are centered on the home and expand outward in a circle-like manner from familiar and habitual areas (6). Studies have shown that 63% of children's physical activities occur within the vicinity of their homes (7); the results of studies on the characteristics of children's outdoor activities in China also show that children's outdoor activities mainly occur in and around residential areas (8). The neighborhood built environment, as a spatial carrier carrying children's life and growth, accommodates most of the daily activities of children and is an important social determinant of children's health.

There is abundant international research on the relationship between the built environment and children and adolescents' outdoor activities and their health, and studies have found that built environment factors such as the commuting distance to and from school, greenery around residential neighborhoods and schools, intersection density, open space distribution, and access to outdoor sports fields and facilities can have significant effects on the outdoor activities of children and adolescents (9–11). In addition, a large number of studies have confirmed that the urban built environment is significantly associated with the healthy development (obesity) of children and adolescents, including factors such as the residential density, road density, neighborhood safety, and recreational facilities; all of these can significantly affect children and adolescents' outdoor activities and obesity (12, 13). At the same time, there are significant gender difference in this correlation (14). Currently, research in the field of the built environment and physical activity in China has mainly focused on the effects of microscopic activity venues, facility configuration, and design on the physical activity and health of elders (15–17), with little attention dedicated to school-age children (18). Accurate identification of the influencing factors of children's obesity and their acting pathways could provide both theoretical support for promoting the healthy development of children and adolescents and guidance for the effective prevention and intervention of obesity in children and adolescents.

Previous studies mostly examined the relationship between two variables in the built environment: physical activity and obesity. This study simultaneously placed three variables in one model, to examine the influencing pathways of the neighborhood built environment on children's outdoor leisure activities and obesity, which is an important supplement to the research in this field. This study used children's obesity as the dependent variable and the neighborhood built environment as the explanatory variable. With children's outdoor leisure activities as the mediating variable, the factors influencing children's obesity were grouped into a hypothetical theoretical model (as in Figure 1). It was hypothesized that the neighborhood built environment is an important factor determining children's outdoor leisure activity, which in turn influences their obesity, and that the neighborhood's built environment can either directly influence children's obesity or indirectly influence children's obesity through outdoor leisure activities; moreover, the influence path may also have gender differences.

2. Materials and methods

2.1. Data collection

There are 10 administrative regions in Shanghai central city, and randomly select a primary school in each administrative region to conduct a meeting on the recruitment of subjects. All primary school students voluntarily participated in the meeting and signed up for this study. A total of 378 ordinary primary school students were recruited from 10 primary schools in Shanghai central city for the survey. The economic level of the central city is higher than that of the non-central city, and this area has the highest house prices in Shanghai, so the family economic statuses of children involved in this study is generally high. All surveys were completed from November 2 to 30, 2020. Before the survey, the school was the unit used to recruit the test subjects and hold a meeting for the subjects. At the meeting, we guided them on how to fill in the questionnaire and wear measuring equipment, as seen in the research flowchart (Figure 2). The questionnaire content includes gender, age, grade, home address, height, weight, waist circumference, etc. This study was approved by the Institutional Review Board of Shanghai University. Written informed consent was obtained from the adolescents involved in the study and their parents or guardians.

2.2. Variables

2.2.1. Neighborhood built environment

The neighborhood built environment variables investigated included density, diversity design, and accessibility. The density involved two variables: population density and building density. The diversity design involved three variables: street connectivity, *per capita* road length, and mixed land utilization rate. The accessibility involved four variables: the number of traffic stations, distance to a traffic

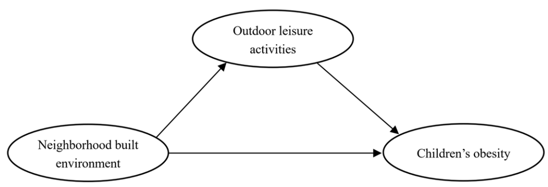

FIGURE 1
Hypothetical path model.

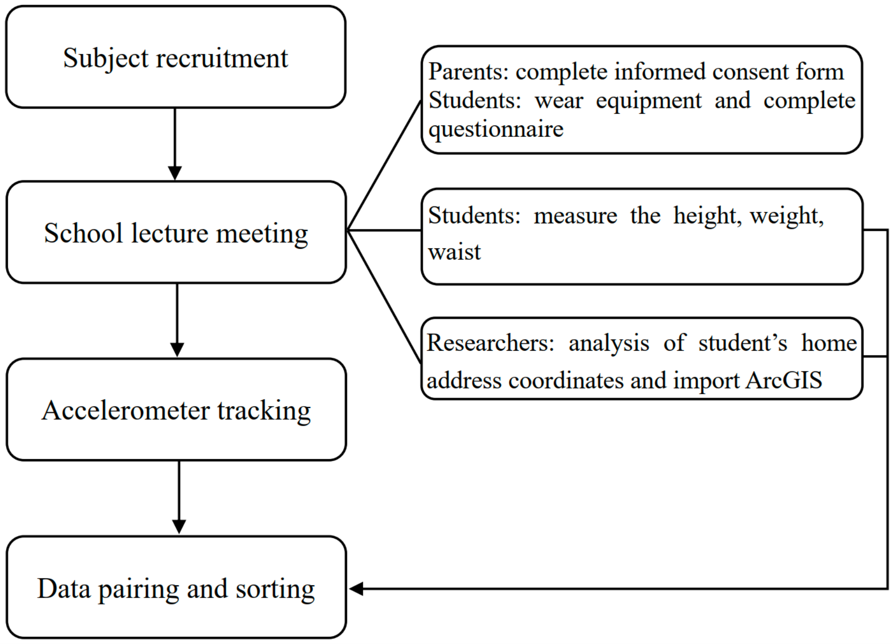

FIGURE 2
Research flowchart.

station, distance to a fitness facility, and distance to a commercial area (19). Geographic information system (GIS; ArcGIS 10.2, Environmental Systems Research Institute, RedLands, America) technology was used to collect the neighborhood built environment variables. The full-element digital map and vector map of the downtown streets of Shanghai were imported into ArcGIS 10.2 to obtain the spatial data. The spatial data included various fitness and leisure facilities, public places, the road network, the rail transit network, etc. Based on the radius of public facilities (such as bus stops and fitness trails) in Shanghai and the division of urban public sports space proposed by Cai et al. (20), the buffer radius was set at 1500 m. A buffer zone with a range of 1,500 m was generated with the participants' residential area as the center. Next, clip processing was performed on the buffer zone to extract the data on the built environment variables.

2.2.2. Outdoor leisure activities

Children's outdoor leisure activities were obtained using an ActiGraphGT3X+ accelerometer. It was found that the built environment is not a significant predictor of children and adolescents' physical activity on weekdays but a significant predictor on weekends (19). Therefore, the variables selected for this study were children's outdoor leisure activity on weekends, specifically the mean value of children's moderate-to-high-intensity outdoor leisure activity on weekends, the amount of outdoor leisure activity of children on weekends, and the duration of adolescents' outdoor leisure activity on weekends. The initialization of the device was completed before the survey, and a briefing session was conducted to instruct the subjects to put on and take off the survey device and confirm the wearing time (Saturday and Sunday, 7:00 ~ 21:00, except for bathing, swimming, and sleeping) and wearing site (right hip). After the survey, the survey devices were returned to the research team for unified retrieval. The ActiGraph GT3X$^+$ parameters are shown in Table 1.

TABLE 1 ActiGraph GT3X$^+$ parameters.

	Parameter	Details
1	Monitor	ActiGraph GT3X$^+$
2	Sampling frequency	30 Hz
3	Sampling interval	5 s
4	Wearing time	≥480 min/24 h
5	Number of days of data collection required for valid data collection	≥3 days on weekdays and one day on weekends
6	Physical activity intensity levels	Low: 100–1,679 counts per minute (CPM)
		Moderate-to-vigorous: 1,680–3,368 CPM
		High: >3,368 CPM

2.2.3. Obesity

Children's obesity was evaluated using a combination of body mass index and waist-to-height ratio. The body mass index is an important standard that is commonly used internationally to measure the degree of obesity and healthiness of the human body; it is also an important indicator in the national obesity standards for students. In addition, the study also chose the index of waist-to-height ratio to jointly evaluate the obesity of adolescents. A study developed by Sun et al. compared the consistency of the body mass index and waist-to-height ratio in judging the obesity of adolescents and found that judging the obesity of adolescents using the waist-to-height ratio combined with body mass index was better than judging it using a single method (21). In our study, trained researchers went to the school and performed all of the measurements on all of the children at the school meeting. Due to the large age span of school-age children, to make the data more comparable, we standardized the BMI and WHR and obtained the new standardized scores: body mass index z-score (zBMI) and waist-to-height ratio z-score (zWHR) (22).

2.3. Statistical analysis

The neighborhood built environment, leisure physical activity, and obesity were obtained by measuring variables, respectively, forming three measurement models. The structural relationship of the three potential variables established by the three measurement models forms a structural model, and the structural factor relationship of the potential variables was discussed with the strategy of path analysis. This study conducted validating factor analysis using SPSS 22.0 software and then constructed structural equation models using AMOS 24.0 software to calculate the relationship of each potential variable and validate the theoretical model proposed by the study. The observed indicators of the neighborhood built environment include 9 items, such as the population density, street connectivity, number of traffic stations, etc.; the observed indicators of children's outdoor leisure activities are the time spent on medium-to-high-intensity outdoor leisure activities on weekends, total count value, and total activity time. A structural equation model was used to verify the relationship between the neighborhood built environment, outdoor leisure activities, and children's obesity. Using mean to fill in missing data during data processing and analysis. Alpha level used $p < 0.05$. The multivariate fit index was used to evaluate the pathway model of the neighborhood built environment affecting children's obesity, and the evaluation indicators were $\chi 2$ /df, RMSEA, RMR, NFI, CFI, GFI, and AGFI (23).

3. Results

A total of 400 questionnaires were distributed for the study; 391 were collected, 380 valid data were recovered by accelerometers, and 378 valid data were obtained by complete matching of questionnaires with accelerometer data. The basic situation of the subjects is shown in Table 2.

As shown in Table 3, the descriptive statistics of the study variables showed that the mean the BMI value was 20.02 for boys and 19.97 for girls, which are normal grades on the scale for each grade in the National Physical Fitness Standards for Students. According to the critical value point of abdominal obesity for boys (0.47) and girls (0.45), which was delineated by Zhou et al. based on the data of 16,914 children and adolescents in six provinces and cities in China (24), it can be found that, in the waist-to-height ratio index, the values of the waist-to-height ratio of boys and girls in this study did not reach the threshold value of abdominal obesity, but boys those of were slightly higher than girls (0.46 > 0.42). Meanwhile, the standard deviation of the waist-to-height ratio for boys and girls was relatively large, indicating that the dispersion degree of children's waist-to-height ratio was relatively large. Among the indicators of outdoor leisure activities, the length of moderate-to-vigorous outdoor leisure activity was 70.21 min/day for boys and 60.92 min/day for girls, which is basically in line with the standard recommended by the Guidelines for Physical Activity for Children and Adolescents in China, which stipulates that children and adolescents should engage in at least a total of 60 min of daily moderate to vigorous physical activity (25).

The modified model fit results in this study were: χ^2/df = 2.05, RMSEA = 0.07, RMR = 0.04, NFI = 0.97, CFI = 0.95, GFI = 0.98, and AGFI = 0.96; All indicators were within the standard range, indicating that the pathway model of the neighborhood built environment affecting children's obesity fits well and that the theoretical model was acceptable. As shown in Figure 3, according to the path model of the neighborhood built environment affecting children's obesity: 1) the neighborhood built environment comprises three dimensions—density, diversity design, and accessibility—among which the density is measured by two observations, diversity design is measured by three observations, and accessibility is measured by four observations; 2) outdoor leisure activity is measured by three observations: the mean value of moderate-to-vigorous outdoor leisure activity, amount of outdoor leisure activity, and duration of outdoor leisure activity; 3) children's obesity is measured by two variables: body mass index z-score and waist-to-height ratio z-score. The relationship between the potential variables reflected in the path model shows the following: 1) The direct effect of the neighborhood built environment on children's obesity is 0.15 (CI [0.08, 0.27]), the indirect effect of the neighborhood built environment on children's obesity through outdoor leisure activities is 0.38 × 0.49 = 0.19 (CI [0.01, 0.10]), and the overall effect of the neighborhood built environment on children's obesity is 0.15 + 0.19 = 0.34 (CI [0.13, 0.32]). The direct and indirect effects of the neighborhood built environment on children's obesity are statistically significant at the 0.05 level, indicating that neighborhood built environment could direct affect children's obesity and also indirect affect it through outdoor leisure activities. The indirect effect of the neighborhood built environment on children's obesity is greater than the direct effect, indicating that the effect of the neighborhood built environment on children's obesity was mainly achieved through the indirect effect of outdoor leisure activities.

To examine the gender differences in the influence of the neighborhood built environment on children's obesity, this study constructed pathway models to determine the influence of the neighborhood built environment on boys' obesity (Figure 4) and girls' (Figure 5) obesity. As above, multivariate fit indicators were also used to evaluate the pathway models of the urban built environment affecting boys' and girls' obesity, respectively. The results demonstrated that: 1) the fitting indicators for the pathway model of the neighborhood built environment affecting boys' obesity were: χ^2/df = 2.50, RMSEA = 0.06, RMR = 0.04, NFI = 0.96, CFI = 0.95, GFI = 0.97, and AGFI = 0.95; All indicators are within the standard range, indicating that the pathway model of the neighborhood built environment affecting the boys' obesity fits well and the model is acceptable; 2) The fitting indicators for the

TABLE 2 Basic information about the subjects.

Categories		Number (%)	Age (M±SD)
Gender	Boys	195 (51.59)	9.11 ± 1.20
	Girls	183 (48.41)	9.32 ± 1.09
Grade	Grade one	72 (18.78)	6.58 ± 1.21
	Grade two	74 (19.58)	7.44 ± 0.98
	Grade three	79 (20.90)	8.63 ± 1.31
	Grade four	77 (20.63)	9.27 ± 0.98
	Grade five	76 (20.11)	10.48 ± 1.11

TABLE 3 Descriptive analysis of variables.

Variables			Boys (M±SD)	Girls (M±SD)	Total (M±SD)
Obesity		Body mass index	20.02 ± 2.83	19.97 ± 2.34	20.00 ± 2.66
		Waist-to-height ratio	0.46 ± 0.45	0.42 ± 0.54	0.45 ± 0.50
Neighborhood built environment	Density	Population density (number/km^2)	56,174 ± 20,865	55,234 ± 21,174	55,801 ± 20,977
		Building density (%)	0.53 ± 0.18	0.55 ± 0.20	0.54 ± 0.19
	Diversity design	Street connectivity (number/km^2)	23.24 ± 7.15	23.18 ± 6.98	23.20 ± 7.11
		Per capita road length (m)	0.26 ± 0.47	0.27 ± 0.46	0.26 ± 0.46
		Mixed land utilization rate	14 ± 2	15 ± 3	14 ± 3
	Accessibility	Number of traffic stations	7 ± 3	8 ± 2	8 ± 2
		Distance to traffic station (m)	211.34 ± 100.98	208 ± 102.45	210.61 ± 101.24
		Distance to fitness facility (m)	135.23 ± 121.62	130.99 ± 109.87	133.67 ± 110.78
		Distance to commercial area (m)	350.11 ± 221.54	361.05 ± 210.55	355.52 ± 215.84
Outdoor leisure activities		Moderate-to-vigorous physical activity (min/day)	70.21 ± 20.45	60.92 ± 17.78	64.43 ± 20.07
		Total count	278,476.24 ± 32,562.47	193,447.81 ± 56,432.52	240,811.63 ± 45,747.48
		Total activity time (min)	285.52 ± 100.44	254.17 ± 101.35	265.28 ± 100.24

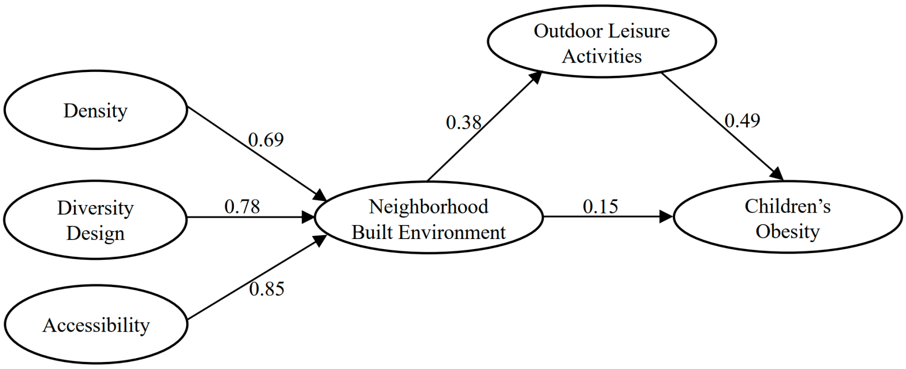

FIGURE 3
A pathway model of neighborhood built environment influencing children's obesity. This is a simplified model, where the solid lines represent significance and the normalized path coefficients are labeled.

pathway model of the neighborhood built environment affecting girls' obesity were: χ^2/df = 2.48, RMSEA = 0.07, RMR = 0.03, NFI = 0.95, CFI = 0.96, GFI = 0.94, and AGFI = 0.97; All indicators were within the standard range, indicating that the pathway model of the neighborhood built environment affecting girls' obesity also fits well and the model is acceptable.

As shown in Figure 4, using the path model of the neighborhood built environment affecting boys' obesity, we can find that the direct effect of the neighborhood built environment on boys' obesity is 0.17 (CI [0.21, 0.35]), the indirect effect of the neighborhood built environment on boys' obesity through outdoor leisure activities is $0.46 \times 0.57 = 0.26$ (CI [0.05, 0.14]), and the overall effect of the neighborhood built environment on boys' obesity is $0.17 + 0.26 = 0.43$ (CI [0.30, 0.41]). Both the direct and indirect effects of the neighborhood built environment on boys' obesity were statistically significant at the 0.05 level, indicating that the neighborhood built environment could direct affect children's obesity and through outdoor leisure activities indirect affect children's obesity. As shown in Figure 5, the path model of the neighborhood built environment affecting girls' obesity revealed that the direct effect of the neighborhood built environment on girls' obesity is 0.07 (CI [−0.13, 0.02]) but is not statistically significant at the 0.05 level, meanwhile the indirect effect of the neighborhood built environment on girls' obesity through outdoor leisure activities is $0.32 \times 0.41 = 0.13$ (CI [0.21, 0.34]) and is significant at the 0.05 level, indicating that the neighborhood built environment could only affect girls' obesity through the indirect effect of outdoor leisure activities. It was found that there are gender differences in the pathways by which the neighborhood built environment affects children's obesity; for boys, the neighborhood built environment could direct affect their obesity and through outdoor leisure activities indirect affect their obesity, while for girls, the neighborhood built environment could only indirect affect their obesity through outdoor leisure activities.

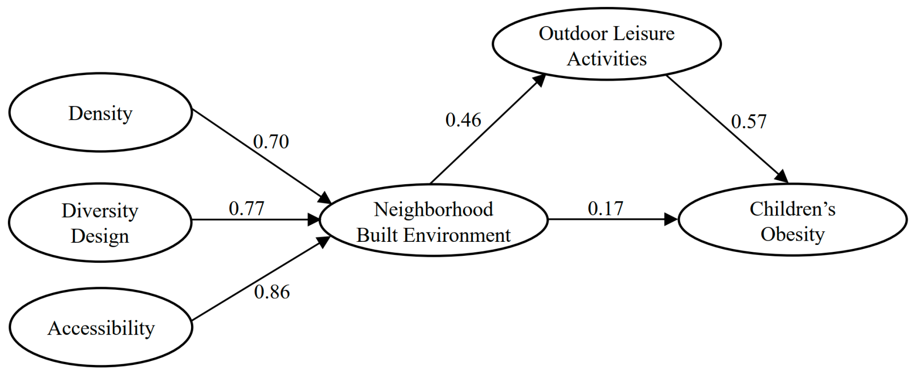

FIGURE 4
The pathway model of the neighborhood built environment affecting boys' obesity. This is a simplified model, where the solid lines represent significance and the standardized path coefficients are labeled.

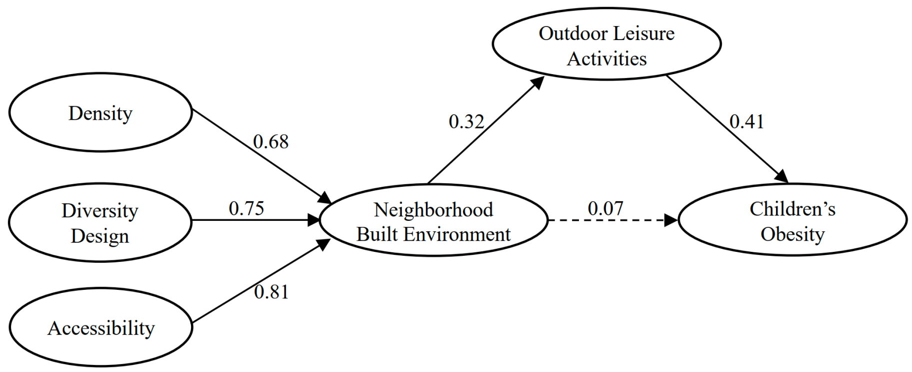

FIGURE 5
The pathway model of the neighborhood built environment affecting the girls' obesity. This is a simplified model, where the solid line represents significance, the dashed line represents insignificance, and the standardized path coefficients are labeled.

4. Discussion

This study found that the neighborhood built environment plays an important role in reducing children's obesity and that it can directly affect children's obesity. Density, diversity design, and accessibility are important factors of the neighborhood built environment that affect children's obesity. Many domestic and international studies have shown that the correlation between the urban built environment and children and adolescents' obesity is significant. Studies from the United States have shown that the neighborhood environment is the second most important factor affecting the obesity of residents after individual characteristics (26). Based on survey data of 1,265 Chinese students, Wong et al. found that the neighborhood environment has a significant correlation with student obesity, and this is especially evident because students who lived in neighborhoods far from parks were more likely to be obese, i.e., the likelihood of school-age children being obese was positively correlated with their closest distance to nearby parks (27). Moreover, the scholar De-Bont also suggested that destination accessibility could effectively prevent the prevalence of obesity (28). In the current state of research, the results of domestic and international studies involving built environment accessibility elements have achieved consensus that the accessibility of surrounding facilities in a community neighborhoods could prevent adolescent obesity. In terms of street facility configuration, An et al. used a systematic literature review and found that the built environment has a significant impact on childhood and adolescent obesity in China, as well as that residential and surrounding sidewalks and parks are all relevant to the healthy development of children and adolescents (29).

This study found that the neighborhood built environment can also indirectly influence children's obesity through the mediating role of outdoor leisure activities. The indirect effect accounted for 55.56% of the total effect, indicating that the neighborhood built environment plays a positive antecedent role in reducing children's obesity and the mediating role through outdoor leisure activities is the main pathway through which the neighborhood built environment influences children's obesity. At present, the academic community has basically reached a consensus on the relationship between physical activity and obesity, especially on the important role of physical activity in suppressing childhood and adolescent obesity; Moreover, domestic and foreign scholars have reached a high degree of agreement on physical activity's ability to suppress adolescent obesity. Thus, how to promote and increase the physical activity level of children and adolescents is the main direction to curb childhood and adolescent obesity. In terms of accessibility, it has been found that accessibility to public facilities is positively associated with physical inactivity among children and adolescents and that accessibility to sports venues has a positive effect on physical activity levels (2, 30). In addition, the accessibility and availability of parks and green spaces have a significant positive impact on residents' physical activity satisfaction; specifically, the shorter the distance and time to parks and green spaces, the higher the residents' physical activity satisfaction. Further, the more availability of parks and green spaces, the higher the residents' physical activity satisfaction, and the quality of residences and surrounding vegetation are also closely related to residents' physical activity satisfaction (31). In terms of design diversity, children and adolescents without sidewalks near their residences are more likely to be physically inactive, and student physical activity levels are positively correlated with the availability of multiple alternative trails near their residences, whether in central urban or suburban areas; building more recreational fitness facilities in the community can also help children and adolescents maintain or increase their recreational physical activities (18). Overall, based on the general context of urban planning, through the rational layout of urban space, improving the accessibility and diversity of facility design and actively planning or renovating the community fitness environment to achieve neighborhood-built-environment-based physical activity interventions for children and adolescents are not only effective in promoting children and adolescents' physical activity but also have far-reaching effects, and the neighborhood built environment plays an important role in children and adolescent health promotion.

In addition, gender differences in the pathways of the neighborhood built environment on children's obesity were found. For boys, the neighborhood built environment not only directly influences their obesity but also indirectly influences their obesity through the mediating effect of outdoor leisure activities; however, for girls, the neighborhood built environment does not directly influence their obesity but only indirectly influences their obesity through the mediating effect of outdoor leisure activities. Thus, the analysis of variance revealed that boys' obesity could be directly influenced by the urban built environment compared to girls, i.e., the neighborhood built environment is more likely to influence boys' obesity. This is generally consistent with the results of existing studies. Hu et al. found that boys without open space near their homes are more likely to be physically inactive, and boys without walking paths near their homes are more likely to be overweight and obese (32). Huang et al. (33) also found that for boys, higher residential density results in longer screen time and is also positively associated with the amount of time boys spent online and playing video games; They also posited that increased screen time/sedentary time is also a major potential contributor to adolescent obesity. Based on a study of the relationship between BMI and walking and environmental factors around the residences of school-age children in Macau, Ho et al. found that walking convenience around the residence and community could significantly influence obesity in male school-age children, and in addition, accessibility to facilities around the residence and community of male school-age children could also promote walking and reduce the prevalence of obesity (14). In this study, the direct effect of the neighborhood built environment on girls' obesity is insignificant. However, this does not mean that the neighborhood built environment has no effect on girls' obesity; the reason for this may be caused by the inconsistency in the observed variables of the built environment selected by different authors and is related to the observed variables of the built environment selected in this study.

There are limitations and challenges to the present study. First, this study adopted a cross-sectional study design, which cannot accurately reflect the causal relationship between variables. In the future, follow-up investigation could be continued, and the causal relationship between variables could be further verified through longitudinal follow-up research. Second, many factors affect children's obesity, and more research variables could be included in the future, such as the family economic level, parents' education, etc., and more in-depth multivariate analyzes are also very necessary.

5. Conclusion

The neighborhood built environment could affect children's obesity not only through direct effect, but also through the mediating effect of outdoor leisure activities. Among them, the mediating role of outdoor leisure activities is the main pathway through which the neighborhood built environment influences children's obesity. In addition, there are gender differences in the pathways through which the neighborhood built environment influences children's obesity. For boys, the neighborhood built environment could affect children's obesity not only through direct effect, but also through the mediating effect of outdoor leisure activities, while for girls, the neighborhood built environment could affect children's obesity only through the mediating effect of outdoor leisure activities. Overall, the neighborhood built environment is more likely to affect the obesity of boys.

Research suggests that the neighborhood built environment plays an important role in the healthy development of adolescents during the critical period of growth and development, as typified by the ancient Chinese expression that "Mencius' Mother Moved Three Times." Therefore, reducing children's obesity can be achieved from the perspective of urban planning by improving the built environment of neighborhoods and promoting children's participation in active outdoor leisure activities. The World Health Organization released the "Healthy Cities: Effective Approach to a Rapidly Changing World" in 2020, which explicitly proposes the promotion of healthy urban planning and design. This aligns with the viewpoint of this study that actively improves the built environment of cities to promote the healthy development of school-age children. In terms of density, it was appropriate to increase population density and building density, which could increase children's social interaction and be beneficial to their physical and mental health. In terms of diversity design, increasing street connectivity, *per capita* road length, and mixed land utilization rate could have a beneficial impact on children's health. In terms of Accessibility, the physical activity level of children could be improved and their health can be promoted by increasing traffic stops around residential areas, shortening the distance to traffic stations, fitness facilities and business districts. In addition, the relevant government departments should also pay attention to the different needs of different genders and different groups of people in urban planning and construction to consider all factors and conduct coordinated development.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Shanghai University. The participants legal guardian/next of kin provided their written informed consent to participate in this study.

Author contributions

WT and XL: conceptualization. WT: methodology, formal analysis, investigation, writing—original draft preparation, resources, supervision, and project administration. TX: validation. WT, XL, and TX: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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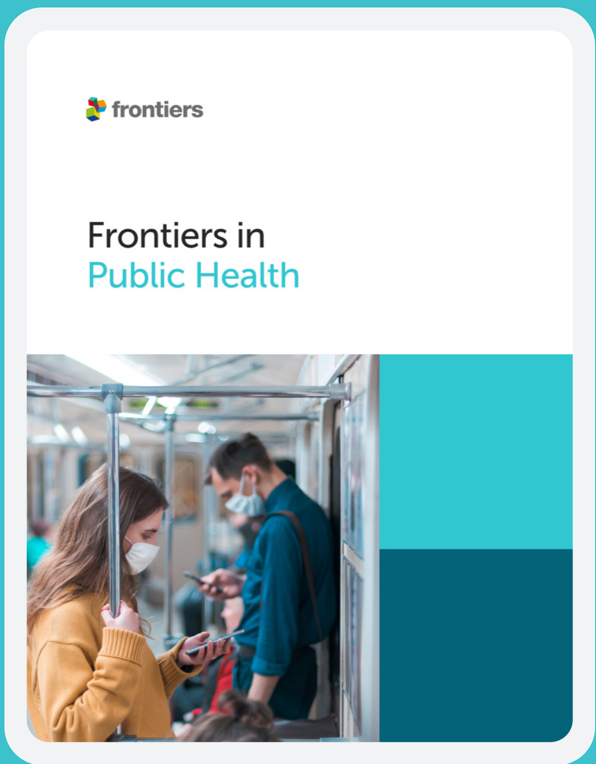

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