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Impact of environmental factors on the health of children and older adults

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Impact of environmental factors on the health of children and older adults

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Editorial: Impact of environmental factors on the health of children and older adults

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Editorial on the Research Topic
Impact of environmental factors on the health of children and older adults

Environmental exposures are among the most pressing public health challenges today. Vulnerable groups, particularly children and older adults, bear a disproportionate burden of these exposures. This Research Topic, "*Impact of environmental factors on the health of children and older adults*," brought together 14 original studies to address the multifaceted health effects of air pollution, toxic exposures, and related environmental risks on these sensitive populations.

Scope and relevance

Air pollution and environmental pollutants have been implicated in a broad range of health conditions including asthma, developmental disorders, cardiovascular disease, and premature mortality. As climate change accelerates, these risks are likely to increase, exacerbating health disparities. This Topic focused on quantifying these effects, developing exposure models, and advancing tools to support public health interventions, particularly in the context of children's development and older adults' chronic conditions.

Article highlights

This Research Topic presents a collection of studies that explore the impact of environmental factors on children's health. Li et al. conducted a nationwide study involving 32,000 children in China and found that 4.1% had elevated blood lead levels. Risk was significantly higher among children exposed to poor air quality and secondhand smoke (Li et al.). Bao et al. analyzed time-series data on pediatric asthma hospitalizations in Eastern China. Although seasonal trends were evident, no consistent association was found with air pollution, suggesting other mediating factors may influence hospitalization risk (Bao et al.).

In Qatar, Husein et al. assessed how meteorological conditions affect the transmission of viral respiratory infections. They identified school-aged children as key drivers of seasonal outbreaks, with temperature and humidity significantly shaping transmission patterns (Husein et al.).

In relation to older adults, Zhang et al. shows that long-term exposure to $PM_{2.5}$ chemical components significantly increases the risk of metabolic syndrome and its components—particularly central obesity, high blood pressure, high fasting glucose, and low HDL—with stronger effects observed among single, divorced, or widowed individuals. In relation to older adults, He et al. estimated the global ischemic heart disease (IHD) burden attributable to particulate matter (PM) pollution in populations aged 70 and above. While global age-standardized DALY rates have declined, total DALYs are projected to rise through 2044 due to aging populations, particularly in low- and middle-income countries (He et al.).

The Topic also includes several studies on environmental risk modeling and assessment. Yang et al. used machine learning to predict outpatient visits for respiratory illness, identifying ozone concentration and temperature as the most influential predictors. Kobza et al. analyzed ozone levels in Upper Silesia, Poland, finding a complex dual effect where low NOx concentrations led to increased ozone formation.

Behavioral and community health dimensions are also addressed. Kaplan et al. developed and validated a scale to measure public awareness of BPA (bisphenol A) exposure, offering a practical tool for future behavioral research. Cervantes et al. reviewed that fungal contamination in schools poses a serious threat to indoor air quality and student health, is influenced by geographic location and season, and requires targeted monitoring and control supported by diverse sampling methods, molecular analysis, and standardized data.

Regarding regional and dietary exposures, Wu et al. demonstrates that pulmonary embolism patients at extremely high altitudes exhibit distinct hematological abnormalities, faster thrombus resolution, and heightened susceptibility among younger individuals, with abnormal uric acid metabolism emerging as a potential risk factor (Wu et al.).

Finally, studies also examined household, occupational and urban environmental risks. Tan et al. finds that household use of solid fuels for cooking or heating significantly increases the risk of cognitive frailty, while switching to clean fuels may reduce this risk. Toure et al. shows that while communities in Siguiri's artisanal mining areas demonstrate moderate knowledge, positive attitudes, and largely adequate practices regarding water pollution, critical gaps in risk awareness highlight the need for integrated education, awareness, and technical support to foster sustainable behaviors. Zhang et al. suggests that insecticide exposure is associated with cognitive impairment in older adults, particularly affecting memory and delayed recall, though further longitudinal research is needed to confirm causality.

Conclusion

Collectively, the 14 articles in this Research Topic offer a rich and multidisciplinary perspective on how environmental exposures affect the health of children and older adults. From novel exposure assessment tools and AI models to global burden estimates and local risk perception studies, this Research Topic underscores the urgency of tailored environmental health policies for vulnerable populations.

We extend our gratitude to the authors, reviewers, and editorial staff for contributing to this important endeavor. We hope the findings here inform future environmental health governance, supporting healthier environments across all stages of life.

Author contributions

YW: Writing – original draft, Writing – review & editing. JL: Writing – review & editing. XL: Writing – review & editing. ZL: Writing – review & editing. JW: Writing – review & editing.

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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Association between long-term exposure to $PM_{2.5}$ chemical components and metabolic syndrome in middle-aged and older adults

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Background: Previous studies indicated that exposure to ambient fine particulate matter ($PM_{2.5}$) could increase the risk of metabolic syndrome (MetS). However, the specific impact of $PM_{2.5}$ chemical components remains uncertain.

Methods: A national cross-sectional study of 12,846 Chinese middle-aged and older adults was conducted. Satellite-based spatiotemporal models were employed to determine the 3-year average $PM_{2.5}$ components exposure, including sulfates (SO_4^{2-}), nitrates (NO_3^-), ammonia (NH_4^+), black carbon (BC), and organic matter (OM). Generalized linear models were used to investigate the associations of $PM_{2.5}$ components with MetS and the components of MetS, and restricted cubic splines curves were used to establish the exposure-response relationships between $PM_{2.5}$ components with MetS, as well as the components of MetS.

Results: MetS risk increased by 35.1, 33.5, 33.6, 31.2, 32.4, and 31.4% for every inter-quartile range rise in $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+, OM and BC, respectively. For MetS components, $PM_{2.5}$ chemical components were associated with evaluated risks of central obesity, high blood pressure (high-BP), high fasting glucose (high-FBG), and low high-density lipoprotein cholesterol (low-HDL).

Conclusion: This study indicated that exposure to $PM_{2.5}$ components is related to increased risk of MetS and its components, including central obesity, high-BP, high-FBG, and low-HDL. Moreover, we found that the adverse effect of $PM_{2.5}$ chemical components on MetS was more sensitive to people who were single, divorced, or widowed than married people.

KEYWORDS

air pollution, particulate matter, metabolic dysfunction, middle-aged and older adults, marital status

1 Introduction

Metabolic syndrome (MetS) is characterized by a group of metabolic-related disorders, which encompass central obesity, elevated blood pressure (high-BP), increased fasting glucose levels (high-FBG), elevated triglyceride levels (high-TG), and reduced high-density lipoprotein levels (low-HDL) (1, 2). Recent studies have shown that about 20 to 30% of adults worldwide have MetS and the number of MetS patients has continued to rise (3, 4). Compared with non-MetS individuals, the prevalence of cardiovascular diseases (5, 6), respiratory diseases (7), diabetes (8, 9), and cancers are significantly elevated among MetS patients (10, 11). Genetic factors, unhealthy lifestyles, and inadequate physical activity have been reported as potential risk factors for MetS (12, 13). However, these characteristics may not fully explain the high MetS prevalence. The negative effects of a hazardous environment, especially air pollution, cannot be ignored (9).

Accumulating epidemiological studies indicated that exposure to air pollution was linked to an increased risk of MetS (4, 5, 8, 10, 12). Among these studies, the impact of fine particulate matter ($PM_{2.5}$) has garnered significant attention from epidemiologists. However, consistent conclusions have not been reached (9). For instance, a cross-sectional study revealed that $PM_{2.5}$ exposure was linked to an increased risk of MetS (12). However, a recent meta-analysis reported no statistically significant relationship of $PM_{2.5}$ with the risk of MetS (9). In addition to inconsistent results, the existing studies focused solely on examining the relationship between $PM_{2.5}$ mass concentration and MetS risk, without assessing $PM_{2.5}$ chemical components, such as sulfates (SO_4^{2-}), nitrates (NO_3^-), ammonia (NH_4^+), organic matter (OM) and black carbon (BC). Only one cross-sectional study has investigated the impact of $PM_{2.5}$ chemical components on MetS risk (14). This study indicated that exposure to SO_4^{2-} was linked to a higher prevalence of MetS, but no significant relationship was discovered between NO_3^-, NH_4^+, and OM (14). However, only a small number of participants ($n = 2045$) were included, and the study was conducted in the Beijing, Tianjin, and Hebei regions. Therefore, further research in larger geographical areas and with more participants to identify the key $PM_{2.5}$ components that cause MetS.

In addition to the limited studies of $PM_{2.5}$ components and MetS, it is important to investigate the connections between various MetS components and $PM_{2.5}$ components to clarify the adverse impacts of $PM_{2.5}$ on the metabolic system. To our knowledge, only 3 previous studies investigated the relationships between $PM_{2.5}$ components and different components of MetS, however, a consistent conclusion has still not been obtained (5, 12, 15). For instance, a cross-sectional study involving 6,628 Chinese adults, found positive correlations between $PM_{2.5}$ exposure and increased risks of high TG and high FBG. However, no significant results were observed for central obesity, low HDL, and high BP (12). A cross-sectional investigation of adolescents and children observed positive links between $PM_{2.5}$ and elevated risks of central obesity. However, they found no significant results for high-FBG, high-BP, low-HDL, and high-TG (15). Based on the limited studies and inconsistent results, further studies are warranted to explore which components of MetS are linked to long-term $PM_{2.5}$ components exposure.

In this nationwide study in China, our objective was to examine the relationships of exposure to $PM_{2.5}$ components (SO_4^{2-}, NO_3^-, NH_4^+, BC, and OM) with MetS and the components of MetS.

2 Methods

2.1 Study population

The participants of this study were from a national cohort study of middle-aged and older Chinese individuals called the China Health and Retirement Longitudinal Study (CHARLS) (16). In brief, approximately 21,000 adults who were at least 45 years old were chosen from 150 cities, in 28 provinces in China. Five waves of the CHARLS were completed in 2011, 2013, 2015, 2018, and 2020. Diagnostic indicators of MetS were only measured in the first wave (2011) and third wave (2015), including waist circumference (WC), BP (systolic BP, SBP; and diastolic BP, DBP), blood lipid (TG, HDL) and FBG. Similar to a previous study of CHARLS (17), we found that only one-fourth of participants could be included in a longitudinal study after matching the data of those two surveys. Therefore, we included participants from CHARLS 2015 in the study. A total of 16,406 adults had a physical examination, 3,560 adults were excluded for the reasons of missing WC, BP, TG, HDL, and FBG data. Finally, 12,846 participants were included (Supplementary Figure S1).

2.2 Diagnosis of MetS

WC, BP, FBG, TG, and HDL of individuals were examined in physical examination. Specifically, a soft measuring tape was wrapped around each participant's waist while they were standing to determine their WC. An electronic blood pressure monitor was worn on the left arm to measure SBP and DBP. The average of the three readings was computed. Fasting venous blood samples were obtained from every individual to determine FBG, TG, and HDL levels.

The Joint Interim Societies' criteria were used in this study's diagnosis of MetS (2). In brief, patients with MetS were defined as those who met two or more of the following criteria in addition to having central obesity (WC ≥ 90 cm for men and 80 cm for women): (1) high BP (SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, clinically confirmed hypertension or taking anti-hypertension medicine); (2) high FBG (FBG ≥ 100 mg/dL, clinically confirmed diabetes history, taking anti-diabetes medicine or insulin injections); (3) elevated TG (>150 mg/dL); (4) low-HDL (< 40 mg/dL for men; <50 mg/dL for women).

2.3 Assessments of $PM_{2.5}$ chemical components

Full-coverage near-real-time $PM_{2.5}$ and its 5 major chemical components (SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC) were assessed at 10 km spatial resolution. Briefly, multi-source fusion $PM_{2.5}$ data, ground observations, and machine learning algorithms were used to predict daily PM2.5 concentrations and components. Previous research provided a more complete description of the $PM_{2.5}$ measurement methodologies and their chemical components (18–20). The three-year average concentration of $PM_{2.5}$ concentrations and components for individuals was used to determine long-term exposure, which was in line with most research on the l long-term effects of air pollutants on health (5, 21, 22).

2.4 Covariates

Directed acyclic graph analysis and literature review were conducted to identify the potential confounders (Supplementary Figure S2). These covariates included: (1) meteorological factors: relative humidity, and air temperature; (2) demographic characteristics: age, and sex; (3) socioeconomic characteristics: residence, marital status, and educational attainment; (4) healthy lifestyles and behaviors: smoking, drinking, physical activity, and cooking fuel use. Detailed description of covariates was clarified in our previous studies (4, 21, 23, 24).

2.5 Statistical analysis

A four-stage investigation was utilized to investigate the relationships between $PM_{2.5}$ chemical components and MetS. First, generalized linear models (GLMs) were used to investigate the links between $PM_{2.5}$ components and the risk of MetS. Second, we applied a restricted cubic spline to investigate the E-R relationships of $PM_{2.5}$ components with MetS risk. Third, we used GLMs and RCS analysis to investigate the association of $PM_{2.5}$ components with the components of MetS and establish the E-R relationships. Finally, subgroup analysis was carried out to determine whether the impact of air pollution on MetS would be modified by participant characteristics. In this stage, we categorized participants into two categories ("<65 years," and "≥65 years") using the cut-off of older adult adults. Physical activity was divided into two categories: "sufficient physical activity" and "insufficient physical activity," according to the World Health Organization's recommendations (8).

Variety sensitivity assessments were also performed. Firstly, we used two-year mean levels of $PM_{2.5}$ components to re-examine the relationships of $PM_{2.5}$ components with MetS and its components (5). Secondly, log-binomial Poisson regressions were conducted to assess the robustness of the positive links of $PM_{2.5}$ components with MetS and its components (4, 25). Thirdly, individuals who had changed their residential address after the CHARLS 2013 and determine whether those results were altered by address change (21). Finally, taking medications for hypertension, and diabetes could potentially introduce confounding effects on the study results, we excluded those taking medication for hypertension to re-examine the association between $PM_{2.5}$ components and MetS and high BP. Similarly, individuals taking antidiabetic medication were excluded to re-evaluate the association between PM2.5 components and MetS and high FBG.

Statistical analyses were carried out using R 4.3.1. The "mice" R package was used to impute the missing covariate data (4), and a two-tailed *p*-value of less than 0.05 was utilized to determine statistical significance.

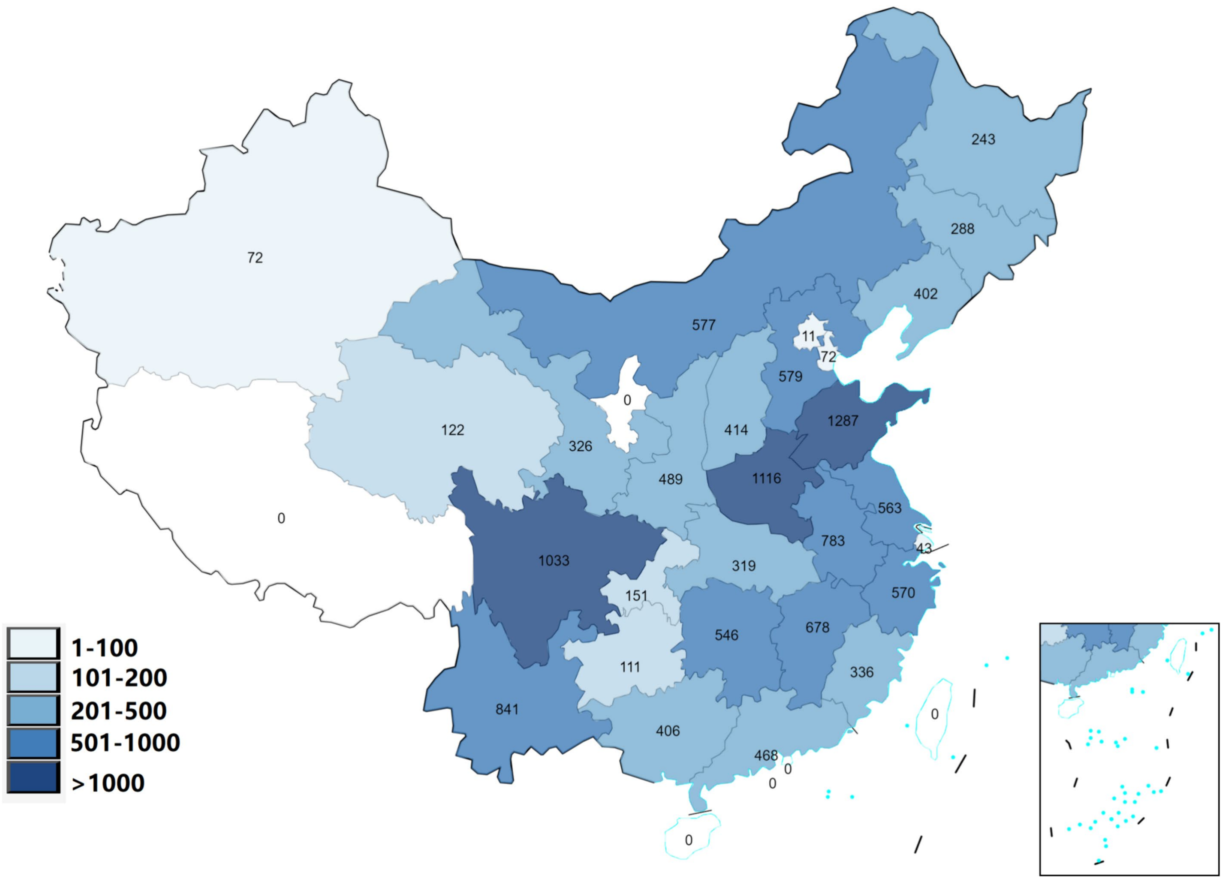

FIGURE 1
The geographical distribution of the participants in the 28 Chinese provinces.

3 Results

3.1 Descriptive statistics

The study included 12,846 adult participants who were selected from 125 cities located in 28 different Chinese provinces. Figure 1 shows the geographical distribution of participants in 28 provinces and Table 1 presents the basic characteristics. There were 4,357 individuals (33.9%) were diagnosed with MetS. For the indicators of MetS, the mean WC, SBP, DBP, FBG, TG, and HDL were 85.34 ± 13.11 cm, 128.31 ± 19.69 mmHg, 75.46 ± 11.20 mmHg, 103.36 ± 35.19 mg/dL, 142.59 ± 90.92 mg/dL, and 51.16 ± 11.46 mg/dL, respectively.

The descriptive characteristics of $PM_{2.5}$ chemical components, temperature, and relative humidity are shown in Supplementary Table S1. The three-year mean levels of $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+, OM and BC exposure were 52.84 ± 22.70 μg/m³, 10.01 ± 3.94 μg/m³, 11.49 ± 5.85 μg/m³, 8.01 ± 3.59 μg/m³, 12.78 ± 4.85 μg/m³, 2.55 ± 0.82 μg/m³, respectively. Pearson correlation analysis showed high collinearity of $PM_{2.5}$ chemical components, with the coefficients of correlation varying from 0.901 to 0.995 (Supplementary Table S2).

3.2 Associations between $PM_{2.5}$ components with MetS risk

In the crude and adjusted models, positive relationships between MetS risk and $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC were observed (Figure 2). In the adjusted model 3, the OR values of MetS were 1.351

TABLE 1 Basic characteristics of participants.

Characteristics[a]	Total (*n* = 12,846)	Non-MetS (*n* = 8,489)	MetS (*n* = 4,357)	*P*-value[c]
Age, years	58.73 ± 13.09	58.65 ± 13.06	58.90 ± 13.14	0.289
Sex				<0.001***
Male	5,907 (46.0)	4,537 (52.4)	1,370 (31.4)	
Female	6,939 (54.0)	3,952 (47.6)	2,987 (68.6)	
Residence				<0.001***
Rural	7,984 (62.2)	5,615 (66.1)	2,369 (54.4)	
Urban	4,862 (37.8)	2,874 (33.9)	1988 (45.6)	
Marital status				<0.001***
Married	11,183 (87.1)	7,340 (87.5)	3,753 (86.2)	
Single, divorced, and widowed	1,663 (12.9)	1,059 (12.5)	604 (13.9)	
Education status[b]				
Elementary school or blow	7,244 (56.4)	4,757 (56.0)	2,487 (57.1)	0.672
Middle school or above	3,203 (24.9)	2,117 (24.9)	1,086 (24.9)	
Smoking status				<0.001***
Non-smoker	7,408 (57.7)	4,416 (52.0)	2,992 (68.7)	
Smoker	5,438 (42.3)	4,073 (48.0)	1,365 (31.3)	
Drinking status[b]				
Non-drinker	3,330 (25.9)	2,471 (29.1)	859 (19.7)	<0.001***
Drinker	9,506 (74.9)	6,011 (70.8)	3,495 (80.2)	
Cooking fuel use[b]				<0.001***
Clean fuel	4,549 (35.4)	2,876 (33.9)	1,673 (38.4)	
Non-clean fuel	3,296 (25.7)	2,331 (27.5)	965 (22.1)	
Physical activity[b]	125.77 ± 108.88	8,117 ± 6,665	6,434 ± 6,028	<0.001***
Waist circumference (WC), cm	85.34 ± 13.11	80.75 ± 12.88	94.22 ± 7.99	
Triglycerides (TG), mg/dL	142.59 ± 90.92	113.25 ± 65.24	199.75 ± 105.52	<0.001***
High-density lipoprotein (HDL), mg/dL	51.16 ± 11.46	53.82 ± 11.65	45.96 ± 9.07	<0.001***
Fasting blood glucose (FBG), mg/dL	103.36 ± 35.19	96.60 ± 26.67	116.52 ± 44.76	<0.001***
Systolic blood pressure (SBP), mmHg	128.31 ± 19.69	124.82 ± 19.12	135.12 ± 18.99	<0.001***
Diastolic blood pressure (DBP), mmHg	75.46 ± 11.20	73.72 ± 10.85	78.84 ± 11.11	<0.001***

[a]Data was shown as mean ± standard deviation (SD) for continuous variables, and count (percentage, %) for categorical variables. [b]Missing values existed. Specifically, education status had 18.7% (2399) missing values, drinking status had 0.08% (10) missing values, cooking fuel use had 38.9% (5001) missing values and physical activity had 36.1% (4645) missing values. [c]*P*-value for significance test between MetS and non-MetS groups. **P*-value < 0.05, ***P*-value < 0.01, ****P*-value < 0.001.

(95%CI, 1.261, 1.445), 1.335 (95%CI, 1.242, 1.434), 1.336 (95%CI, 1.245, 1.434), 1.312 (95%CI,1.222, 1.409), 1.324 (95%CI,1.238, 1.415), and 1.314 (95%CI, 1.229, 1.406) for every IQR increase in $PM_{2.5}$ (33.35 μg/m^3), SO_4^{2-} (6.30 μg/m^3), NO_3^- (9.01 μg/m^3), NH_4^+ (5.60 μg/m^3), OM (7.21 μg/m^3), and BC (1.25 μg/m^3), respectively. Figure 3 presents the E-R relationships of $PM_{2.5}$ components with MetS risk. We discovered that, with increases in $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC, the OR of MetS increased progressively.

3.3 Associations between $PM_{2.5}$ components with the components of MetS

Figure 4 and Supplementary Table S3 present the GLM analysis of the relationships of $PM_{2.5}$ components with the risks of MetS components. We discovered that exposure to the chemical components of $PM_{2.5}$ was linked to a higher risk of central adiposity, high blood pressure, elevated FBG, and low HDL. As for high TG risk, NO_3^- and NH_4^+ showed negative relationships, whereas $PM_{2.5}$, SO_4^{2-}, OM, and BC showed no significant associations.

The E-R relationships between $PM_{2.5}$ chemical components and the components of MetS are displayed in Figure 5. Except for high TG, we found that the risks for central obesity, high BP, high FBG, and low HDL increased gradually with rising levels of $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC (p-value < 0.05).

3.4 Subgroup analysis

The findings of the subgroup analysis by participant character are displayed in Table 2. We discovered that older adult adults (≥65 years), females, participants with higher education levels, non-smokers, drinkers, and solid fuel users were more susceptible to $PM_{2.5}$ components, even if the P-interaction showed no statistical

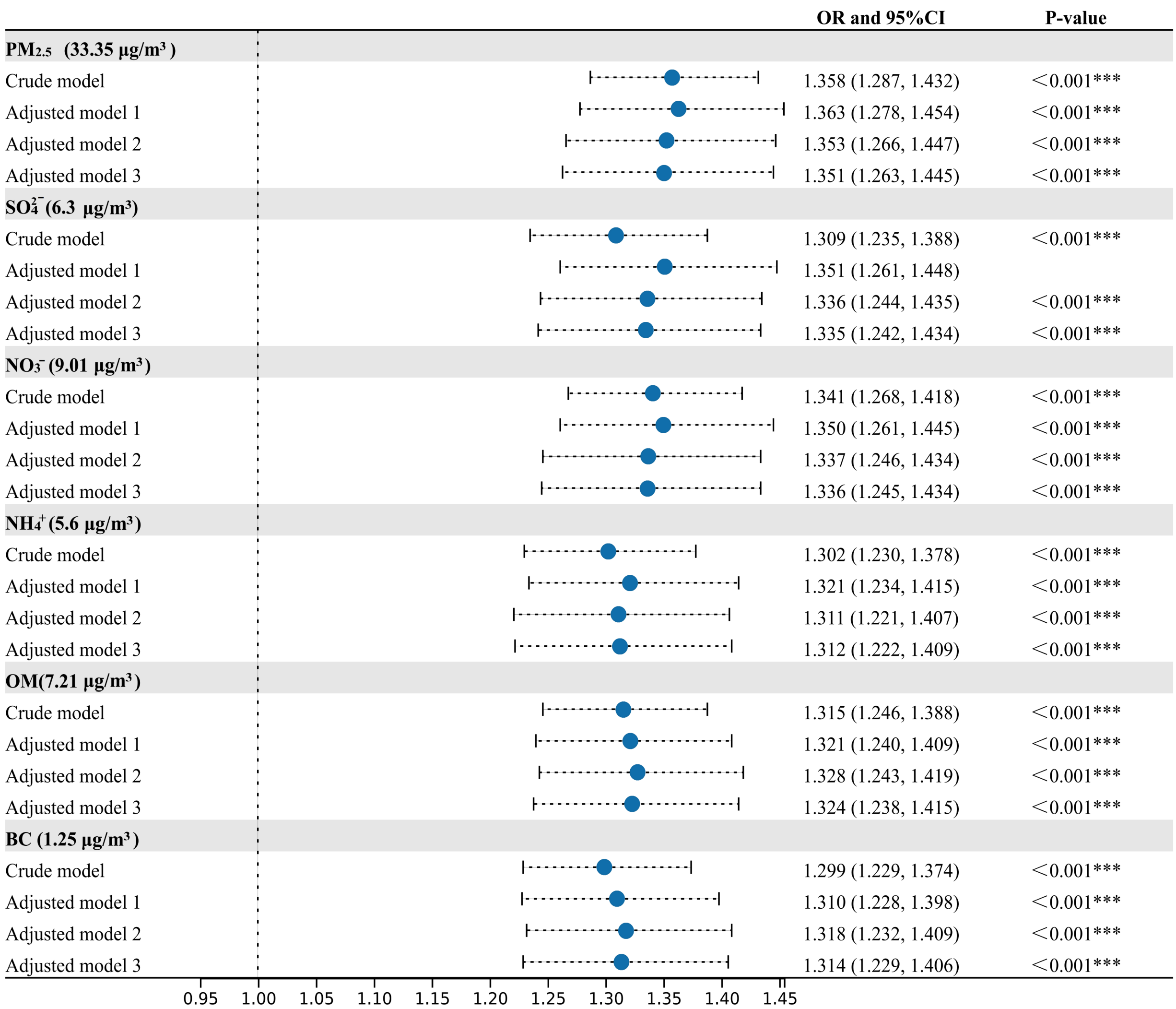

FIGURE 2
Associations of $PM_{2.5}$ and its compositions with the prevalence of metabolic syndrome (MetS). Crude model, without adjustment; Adjusted model 1, adjusted for temperate and relative humidity; Adjusted model 2, adjusted for temperate, relative humidity, age, sex, residence, marital status, education status; Adjusted Model 3, adjusted for temperate, relative humidity, age, sex, residence, marital status, education status, smoking status, drinking status, physical activity and cooking fuel use. *p-value < 0.05, **p-value < 0.01, ***p-value < 0.001.

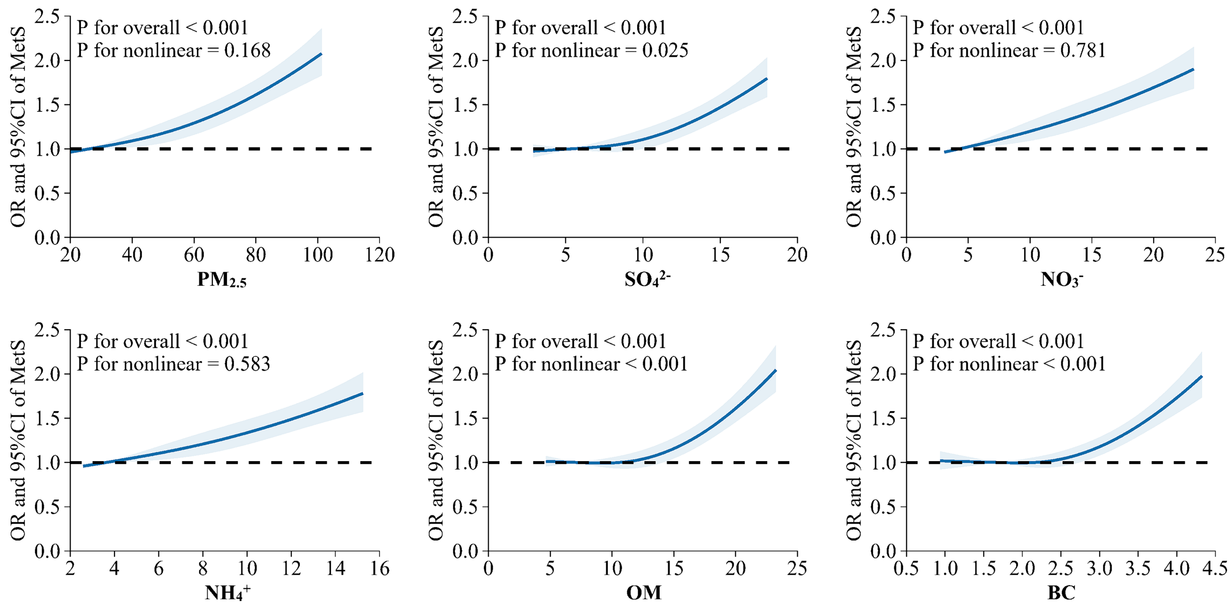

FIGURE 3
Exposure-response relationship between long-term exposure to $PM_{2.5}$ and its chemical components with metabolic syndrome (MetS) risk.

significance. Moreover, people who were single, divorced, or widowed were more vulnerable to $PM_{2.5}$ components than married people, according to subgroup analysis by marital status (P-interaction < 0.05).

3.5 Sensitivity analysis

The sensitivity analysis results are shown in Supplementary Tables S4–S8. For the relationships of $PM_{2.5}$ components with MetS risk, all sensitivity analyses showed positive and significant results for $PM_{2.5}$ concentration and components, which were all consistent with the main effects models. As for the components of MetS, consistent results and positive associations were also observed in all sensitivity analyses. Except for the relationships of SO_4^{2-} with high TG after excluding individuals who had altered their residential address, insignificant associations were shown for $PM_{2.5}$, SO_4^{2-}, OM, BC, and negative associations were found for NO_3^-, NH_4^+ in all sensitivity analyses, which were consistent with the main effects models. The sensitivity analysis excluding users of anti-hypertensive or anti-diabetic medication yielded consistent and robust results.

4 Discussion

This nationwide cross-sectional investigation in China discovered that exposure to $PM_{2.5}$ chemical components (SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC) was significantly linked to an elevated risk of MetS and its components, except for high TG. To our knowledge, the current study may be the first nationwide study examining the long-term impact of $PM_{2.5}$ components on MetS and its components. Furthermore, we discovered that single, divorced, or widowed persons were more vulnerable to the harmful effects of $PM_{2.5}$ components exposure on MetS than those married adults.

Our research revealed a positive association between $PM_{2.5}$ and MetS risk. Previous studies also have reported similar findings (5, 12, 14, 15, 22, 26, 27). For instance, a meta-analysis revealed that for every 5 μg/m³ increase in $PM_{2.5}$, the risk of MetS increased by 14% (RR = 1.14, 95%CI: 1.03, 1.25) (10). According to the KORA F4/FF4 cohort study, there was a 14% (OR = 1.14, 95%CI: 1.02, 1.28) increase in MetS risk for every 1.4 μg/m³ rise in $PM_{2.5}$ (27). The China Multi-Ethnic Cohort research showed that with every 29.55 μg/m³ increase in $PM_{2.5}$, the OR value of MetS was 1.38 (95%CI, 1.23, 1.55) (22). Our research's effect estimations were comparable to those of Feng et al.'s (22) study but lower than those of Voss et al.' s study and Ning et al.'s study, which might be ascribed to differences in study subjects, chemical components of $PM_{2.5}$, study areas, and sample size (5).

As a mixture of primary and secondary pollutants, the harmful impacts of $PM_{2.5}$ components also should be noticed. Our study indicated that exposure to SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC were related to elevated MetS risk. Several investigations examined the relationship of $PM_{2.5}$ components with MetS risk (14, 28), and most of the findings supported the findings of this investigation. A cross-sectional study involving 10,066 Chinese adolescents indicated that the OR values of MetS were1.14 (95%CI: 1.04, 1.24), 1.09 (95%CI: 1.04, 1.13), 1.07 (95%CI: 1.04, 1.11) and 1.24 (95%CI, 1.14, 1.35), for every 1 μg/m³ rise in SO_4^{2-}, NO_3^-, OM, BC, respectively. The SCOPA-China Cohort study found that each 3.76 μg/m³ rise in SO_4^{2-} was linked with a 13.3% (OR = 1.133, 95%CI: 1.053, 1.220) rise in MetS risk. However, no significant results were found for NO_3^-, NH_4^+. The in-significant results might be explained by the limited sample size (n = 2045) and region (Beijing-Tianjin-Hebei region). Compared with Yi et al.'s study, our study provided new evidence that exposure to OM and BC would increase MetS risk. In addition to the few investigations on $PM_{2.5}$ components and MetS, several published research have found that exposure to $PM_{2.5}$ components was related to an elevated risk of MetS-related disorders such as hypertension

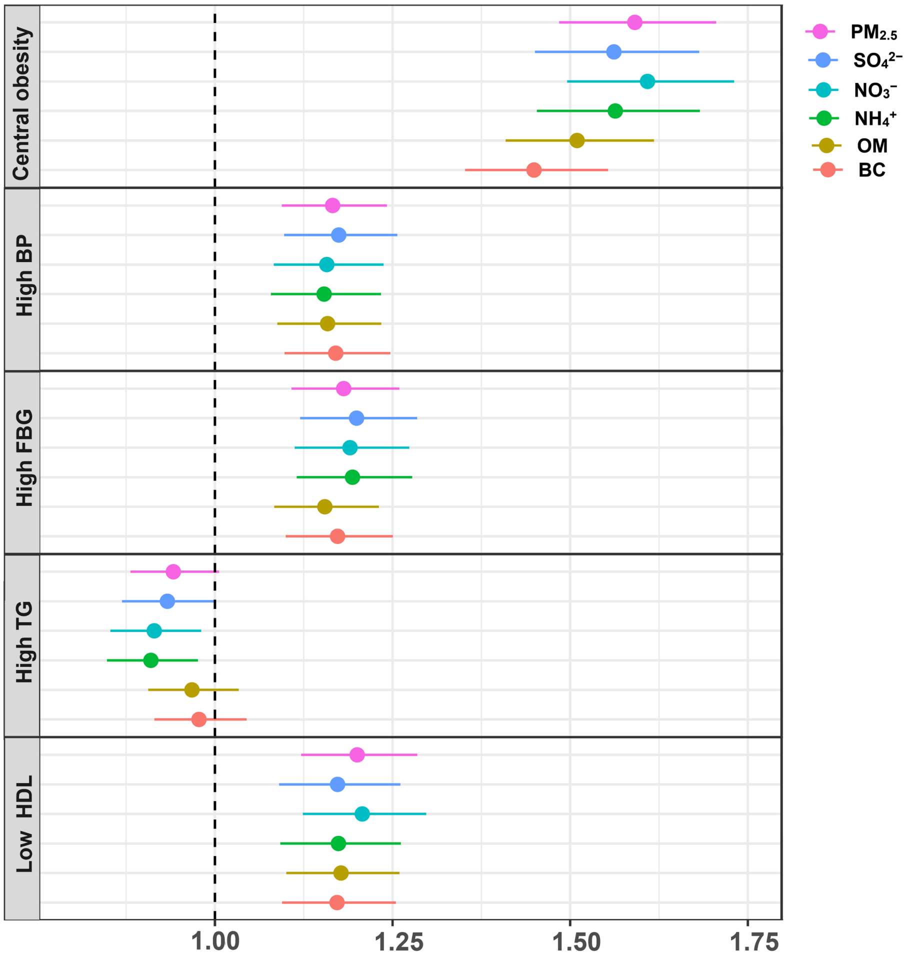

FIGURE 4
Associations between $PM_{2.5}$ and its chemical components with the components of MetS. Adjusted for temperate, relative humidity, age, sex, residence, marital status, education status, smoking status, drinking status, physical activity and cooking fuel use.

(29), and diabetes (30, 31), which could also support our findings. Overall, the positive relationships between MetS risk and $PM_{2.5}$ chemical components were validated by this nationwide cross-sectional investigation.

This study showed positive links between the chemical components of $PM_{2.5}$ and the risks of central obesity, high BP, high FBG, and low HDL. A Chinese cross-sectional study of adolescents found similar positive relationships (28). They found that exposure to SO_4^{2-}, NO_3^-, BC, and OM were related to elevated central obesity risk, and exposure to NO_3^-, OM, and BC were linked with elevated high BP risk (28). Several studies focused on a specific component of MetS could also support our findings (32, 33). For example, a Chinese cross-sectional study reported the positive relationships of SO_4^{2-}, NO_3^-, NH_4^+, OM, BC with FBG levels, NO_3^- and BC with SBP levels, and NO_3^-, NH_4^+, OM with DBP levels (32). However, no significant relationships between SO_4^{2-}, OM, and BC and high TG risk were found in this investigation, which could be attributed to the various health of PM2.5 chemical components, sample size, and techniques of air pollutants measurement.

In subgroup analysis, we found that marital status could modify the impact of $PM_{2.5}$ chemical components on MetS risk. When comparing the OR values of MetS in different marital status groups, we found that people who were single, divorced, or widowed had a higher risk of MetS than married individuals, with significant *P-interaction* values for $PM_{2.5}$, SO_4^{2-}, NO_3^-, NH_4^+, OM, and BC. The modification effect of marital status could be explained by lower socioeconomic status among single, divorced, or divorced adults than that of married adults (34). Firstly, individuals who were single, divorced, or divorced might have a significantly increased chance of exposure to severe $PM_{2.5}$ pollution (35). Secondly, individuals who were single, divorced, or divorced may tend to have less access to social and healthcare support, resulting in poorer health outcomes and less engagement in measures to reduce exposure to air pollution (36–39).

Although the biological mechanisms of $PM_{2.5}$ components on MetS were still unknown (10), several possible biological mechanisms focusing on $PM_{2.5}$ mass have been proposed. Firstly, $PM_{2.5}$ can get into the circulatory systems through the respiratory tract, causing oxidative stress and systematic inflammation and, leading to body weight increase (40), blood pressure rises (41), glucose metabolism disorder (42), and lipid metabolism disorders (4, 28, 43, 44). Secondly, $PM_{2.5}$ could lead to autonomic nervous system dysfunction by activating

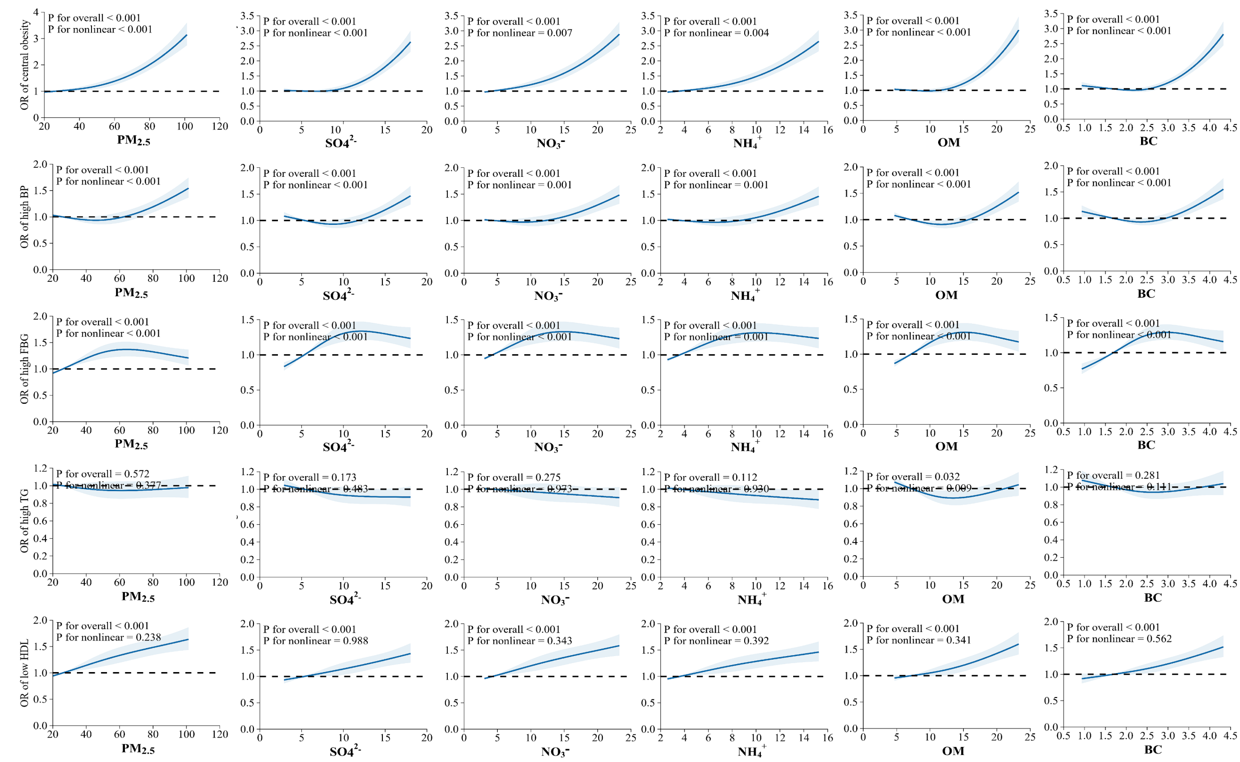

FIGURE 5
Exposure-response relationship between exposure to $PM_{2.5}$ chemical components with the components of metabolic syndrome (MetS).

pulmonary autonomic reflections (45, 46), causing elevated blood pressure (43), insulin resistance (47), and lipid metabolism disorders (48). Thirdly, epigenetic changes, such as aberrant methylation of DNA, have been recognized as critical biological mechanisms of exposure to $PM_{2.5}$-induced metabolism (49). Additionally, $PM_{2.5}$ may cause renin-angiotensin-aldosterone pathway dysfunction (4), leading to structural and functional kidney changes (50) and resulting in higher BP and elevated hypertension risks (51).

Some limitations need to be recognized. Firstly, due to the cross-sectional design of this study, the cause-and-effect cannot be concluded. Longitudinal studies should be conducted to strengthen our findings. Secondly, since the high co-linearity between $PM_{2.5}$ chemical components was observed, a multi-pollutants model could not be performed. Thirdly, the collection of hypertension, diabetes, and most covariate data relied on self-report questionnaires, which introduces the possibility of reporting bias and recall bias. Fourthly, although missing values for covariates such as education status, cooking fuel use, and physical activity were imputed using the Monte Carlo method in this study, it should be acknowledged that there may still be some degree of error concerning the actual values. Fifthly, some participants are currently taking medications for hypertension, diabetes, and lipid-lowering, which could potentially introduce confounding effects on the study results. However, the sensitivity analysis excluding users of anti-hypertensive or anti-diabetic medication yielded consistent and robust results. The use of lipid-lowering medications was not investigated in CHARLS. Confounding factors related to the use of these medications should be considered in future studies. Finally, it should be noted that due to the lack of data on dietary factors and other lifestyle variables in the CHARLS survey, potential confounders may still exist. However, meteorological factors, demographic characteristics, socioeconomic characteristics, health lifestyles, and behaviors have been adjusted in our study, and consistent outcomes from crude and adjusted models served as evidence of the robustness of our findings. Further studies incorporating control for the confounding effects of dietary factors are necessary to validate our findings.

5 Conclusion

The present research found that long-term exposure to $PM_{2.5}$ components was related to an elevated risk of MetS and its components, including central obesity, high FBG, high BP, and low HDL. The adverse effect of $PM_{2.5}$ chemical components on MetS was more sensitive to people who were single, divorced, or widowed than married people. Our study provides new epidemiological insights into the potential adverse impacts of $PM_{2.5}$ components on the metabolic system, and the modification effect of marital status. Further longitudinal studies should be carried out to confirm our findings.

Data availability statement

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

TABLE 2 Subgroup analysis for the associations of long-term exposure to $PM_{2.5}$ chemical components with MetS.

Subgroup	$PM_{2.5}$		SO_4^{2-}		NO_3^-		NH_4^+		OM		BC	
	OR and 95%CI	*P*-inter	OR and 95%CI	*P*-inter	OR and 95%CI	*P*-inter	OR and 95%CI	*P*-inter	OR and 95%CI	*P*-inter	OR and 95%CI	*P*-inter
Age		0.206		0.112		0.113		0.097		0.143		0.094
≥65 years	1.385 (1.283, 1.495)		1.381 (1.272, 1.499)		1.380 (1.273, 1.496)		1.358 (1.252, 1.473)		1.362 (1.262, 1.470)		1.360 (1.258, 1.470)	
<65 years	1.281 (1.149, 1.427)		1.241 (1.105, 1.394)		1.246 (1.112, 1.395)		1.218 (1.087, 1.365)		1.243 (1.116, 1.385)		1.221 (1.094, 1.364)	
Sex		0.132		0.155		0.106		0.120		0.456		0.585
Female	1.424 (1.294, 1.567)		1.409 (1.271, 1.563)		1.418 (1.282, 1.569)		1.390 (1.255, 1.539)		1.359 (1.235, 1.496)		1.341 (1.215, 1.479)	
Male	1.306 (1.205, 1.415)		1.289 (1.183, 1.405)		1.286 (1.181, 1.399)		1.264 (1.160, 1.376)		1.301 (1.201, 1.410)		1.298 (1.197, 1.408)	
Residence		0.975		0.943		0.923		0.714		0.714		0.759
Rural	1.353 (1.228, 1.490)		1.331 (1.200, 1.476)		1.331 (1.203, 1.473)		1.306 (1.186, 1.439)		1.306 (1.186, 1.439)		1.299 (1.177, 1.435)	
Urban	1.350 (1.246, 1.463)		1.337 (1.226, 1.458)		1.339 (1.230, 1.458)		1.335 (1.232, 1.446)		1.335 (1.232, 1.446)		1.324 (1.221, 1.436)	
Marital status		0.010**		0.015*		0.005**		0.008**		0.028*		0.034*
Married	1.125 (0.963, 1.315)		1.108 (0.936, 1.311)		1.087 (0.923, 1.280)		1.073 (0.909, 1.266)		1.132 (0.969, 1.323)		1.127 (0.961, 1.321)	
Single, divorced, and widowed	1.394 (1.299, 1.496)		1.378 (1.278, 1.487)		1.383 (1.283, 1.490)		1.357 (1.258, 1.463)		1.360 (1.268, 1.460)		1.351 (1.258, 1.451)	
Education status		0.490		0.658		0.449		0.567		0.473		0.628
Elementary school or blow	1.316 (1.187, 1.459)		1.311 (1.172, 1.466)		1.295 (1.160, 1.445)		1.281 (1.147, 1.431)		1.289 (1.163, 1.428)		1.290 (1.162, 1.433)	
Middle school or above	1.371 (1.269, 1.482)		1.349 (1.242, 1.466)		1.358 (1.252, 1.473)		1.329 (1.224, 1.442)		1.345 (1.245, 1.454)		1.329 (1.229, 1.438)	
Smoking status		0.143		0.173		0.098		0.114		0.428		0.575
Smoking	1.310 (1.210, 1.418)		1.294 (1.189, 1.408)		1.288 (1.186, 1.400)		1.267 (1.165, 1.377)		1.301 (1.203, 1.408)		1.298 (1.199, 1.406)	
Non-smoking	1.426 (1.292, 1.574)		1.411 (1.267, 1.570)		1.426 (1.284, 1.583)		1.397 (1.257, 1.552)		1.363 (1.235, 1.505)		1.343 (1.214, 1.486)	
Drinking status		0.796		0.687		0.817		0.821		0.938		0.851
Drinker	1.371 (1.215, 1.547)		1.367 (1.199, 1.559)		1.354 (1.193, 1.538)		1.329 (1.169, 1.511)		1.331 (1.178, 1.504)		1.330 (1.174, 1.507)	
Non-drinker	1.348 (1.252, 1.451)		1.328 (1.227, 1.437)		1.332 (1.233, 1.440)		1.308 (1.210, 1.415)		1.324 (1.231, 1.424)		1.313 (1.219, 1.414)	
Cooking fuel use		0.175		0.359		0.254		0.321		0.079		0.190
Clean fuel	1.308 (1.205, 1.420)		1.302 (1.192, 1.423)		1.297 (1.189, 1.415)		1.278 (1.171, 1.395)		1.270 (1.171, 1.377)		1.273 (1.172, 1.383)	
Solid fuel	1.414 (1.287,1.553)		1.379 (1.248, 1.523)		1.389 (1.260, 1.532)		1.357 (1.230, 1.497)		1.406 (1.279, 1.546)		1.376 (1.250, 1.514)	
Physical activity		0.976		0.928		0.898		0.918		0.726		0.766
Insufficient physical activity	1.358 (1.253, 1.471)		1.345 (1.234, 1.466)		1.348 (1.238, 1.467)		1.322 (1.214, 1.439)		1.341 (1.238, 1.453)		1.330 (1.227, 1.443)	
Sufficient physical activity	1.360 (1.235, 1.497)		1.337 (1.206, 1.483)		1.337 (1.209, 1.479)		1.314 (1.186, 1.455)		1.314 (1.193, 1.448)		1.307 (1.183, 1.443)	

*P-value < 0.05, **P-value < 0.01, ***P-value < 0.001.

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Ethics statement

The CHARLS study received approval from the Institutional Review Board of Peking University (Code: IRB00001052-11015). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JJZ: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. JLZ: Conceptualization, Data curation, Formal analysis, Software, Writing – original draft. ZD: Conceptualization, Data curation, Visualization, Writing – original draft. JN: Methodology, Software, Visualization, Writing – original draft. XL: Methodology, Software, Visualization, Writing – review & editing. WY: Visualization, Writing – original draft. ZN: Conceptualization, Methodology, Software, Writing – review & editing. YY: Conceptualization, Methodology, Software, Writing – review & editing.

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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.2024.1462548/full#supplementary-material

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Daily diurnal temperature range associated with emergency ambulance calls: a nine-year time-series study

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Background: Diurnal temperature range (DTR) is associated with the increased risk of morbidity and mortality. However, the relationship between DTR and emergency ambulance calls (EACs), which more accurately and immediately reflect the health impacts of temperature changes, remains underexplored in China.

Methods: We collected daily data on EACs and meteorological factors from 2009 to 2017 in Guangzhou, China. DTR, representing the temperature range within a day, was calculated by subtracting the minimum temperature from the maximum temperature for each day. Generalized additive models were used to estimate the association between DTR and EACs for all-cause, cardiovascular diseases, and respiratory diseases. Additionally, subgroup and sensitivity analyses were conducted in our study.

Results: We found significant associations between daily DTR and EACs. The excess risks (ERs) were 0.47% (95% CI: 0.14, 0.81%) for all-cause EACs, 0.94% (95% CI: 0.46, 1.43%) for cardiovascular-related EACs, and 1.31% (95% CI: 0.76, 1.86%) for respiratory -related EACs at lag01, respectively. Subgroup analyses indicated that these associations were notably stronger among the older, males, and during the warm season. Specifically, there was an increase of 1.16% (95% CI: 0.59, 1.74%) in cardiovascular-related EACs among the older adult, compared to 0.45% (95% CI: −0.21, 1.12%) among those younger than 65 years. Among males, the increase was 1.39% (95% CI: 0.79, 1.99%), compared to 0.13% (95% CI: −0.53, 0.79%) among females. During the warm season, the increase was 1.53% (95% CI: 0.74, 2.34%), compared to 0.75% (95% CI: 0.14, 1.37%) during the cold season.

Conclusion: DTR might increase the risk of daily all-cause, cardiovascular-related, and respiratory-related EACs in Guangzhou, China. The associations were particularly strong among older adults, males, and during the warm season. Implementing public health policies is essential to mitigate the adverse health effects of DTR.

KEYWORDS

emergency ambulance calls, China, diurnal temperature range, time-series analysis, generalized additive models (GAMs)

Introduction

Climate change, driven primarily by human activities, is exerting growing adverse effects on human health (1). Numerous studies over the past decade have highlighted these impacts, suggesting an increased burden of disease and mortality associated with climate change (2, 3). Elevated temperatures can cause heat stress, dehydration, and cardiovascular issues (4). Conversely, cold spells have been closely associated with higher mortality rates (5). These contrasting effects illustrate the intricate and diverse ways in which climate change influences human health.

The diurnal temperature range (DTR), quantified as the variance between daily maximum and minimum temperatures over 24-h periods, serves as a novel metric of climate change and a significant risk factor for human health (6, 7). For example, one study in a Mediterranean region reported that the incidence rate ratio was 1.03 (95% CI: 1.01, 1.06) for extreme high DTR (8). Aghababaeian et al. (9) found that the DTR was associated with the hospital admission on respiratory disease and cardiovascular disease in Dezful, Iran. Besides, one time-series study in Bangkok observed that short-term DTR exposure have impact on elevated risk of hospital admissions due to cardiovascular disease (10).

Previous studies have primarily examined on the relationship between DTR and hospital admissions, morbidity, and mortality (8, 11–13). However, emergency ambulance calls (EACs) might be more sensitive to the acute human health effects, making them a more suitable indicator for reflecting the immediate impacts of short-term exposure to DTR (14). For instance, a multi-city study in Japan indicated that EACs might provide a more appropriate endpoint for observing the acute health effects of climate change (15). Nevertheless, few studies have estimated the association between DTR and EACs for all-cause, cardiovascular, and respiratory diseases.

We thus conducted this time-series study aiming to assess the association between DTR and EACs in Guangzhou, China. We hypothesize that DTR can elevate the EACs.

Methods

Study area

Guangzhou, nestled in Southern China, boasts a subtropical humid-monsoon climate, characterized by an annual average temperature of 22°C, rainfall of 1800 millimeters, and a relative humidity of 80%. Guangzhou, as the capital city of Guangdong Province, had a population of 18.6 million in 2020. The large number of people provided sufficient statistical power of observation, resulting in higher quality health outcome data (16).

Outcome data

The data about all-cause, cardiovascular-related, and respiratory-related EACs were obtained from the Guangzhou Emergency Center spanning the period from January 2009 to December 2017. As the primary emergency dispatch agency in Guangzhou, this center coordinates approximately 200 ambulances and ensures emergency responses within half an hour after receiving an emergency call, serving over 10,000,000 residents, regardless of the time of day (17).

After each emergency call, trained medical personnel completed a standardized data entry form, including demographic information, clinical diagnoses, and main symptoms. The disease outcomes were diagnosed by physicians according to patients' symptoms, medical inquiries, and examinations, adhering to standardized procedures with rigorous quality assurance and control protocols. Significantly, EACs resulting from suicides, traumatic accidents, and events related to pregnancy or childbirth were excluded from our analysis. Experienced emergency physicians diagnosed cardiovascular and respiratory events based on observed symptoms and signs, maintaining a low rate of misclassification (18).

Meteorological factor

Meteorological factors, including daily maximum, mean, and minimum temperatures, as well as relative humidity and wind speed, were obtained from the National Weather Data Sharing System. Data from the Guangzhou weather station was utilized to represent the daily exposure of the general population. Following definitions from prior studies (19, 20), the DTR was calculated by subtracting the minimum temperature from the maximum temperature on the same day.

Statistical models

The short-term association between DTR and daily EACs due to all-cause, cardiovascular diseases, and respiratory diseases was assessed using generalized additive models (GAM) (21). We controlled for potential confounders such as temporal trends, day of the week (DOW), public holidays (PH), daily mean temperature, relative humidity, and wind speed. Temporal trends were adjusted using natural cubic splines with 6 degrees of freedom (df) per year, while daily mean temperature and relative humidity were controlled with 3 df each (22). The model was defined as below:

$$\begin{aligned}\log\left[\mathrm{E}\left(Y_t\right)\right] &= \beta * DTR + \mathrm{s}\left(\mathrm{t,df} = 6 / \mathit{year}\right)\\ &+\mathrm{s}\left(\mathit{Temp}03\mathrm{,df} = 3\right) + \mathit{as.factor}\left(\mathit{DOW}\right)\\ &+\mathrm{s}\left(\mathrm{RH,df} = 3\right) + \mathrm{s}\left(\mathrm{WD,df} = 3\right) + \mathit{as.factor}\left(\mathit{PH}\right)\end{aligned}$$

In the core model, $E(Y_t)$ represents the expected number of EACs on day t. The coefficient of the DTR is denoted by β. The functions () is a smoothing function, and *t* accounts for long-term and seasonal trends. Temp03 is the moving average of the temperature over the previous 3 days. DOW indicates the day of the week. RH and WD represent the relative humidity and wind speed, respectively. PH is a binary variable indicating the public holiday.

We assessed the possible adverse effects of DTR using different lag structures. Single-lag day models considered lag effects from the same day (lag0) up to 5 days lag (lag5). Multi-day lag models evaluated accumulated effects using moving averages for the current day and the previous 1–5 days (lag01, lag02, lag03, lag04, and lag05).

Subgroup analyses

To check whether the effects of DTR on EACs varied by age group (age < 65 vs. age ≥ 65), sex (male vs. female), and season (cold vs. warm), we conducted analyses stratified by these strata. Based on previous studies (17, 21), the warm seasons defined as April to September, and the cold seasons as the period from October to March of the following year. We determined groups differences by calculating the 95% confidence intervals (CI) as described below:

$$D_1 - D_2 \pm 1.96\sqrt{(SE_1)^2 + (SE_2)^2}$$

where D_1 and D_2 are the estimates for the two strata, and SE_1 and SE_2 represent their corresponding standard errors (18).

We performed two sensitivity analyses to ensure the robustness of our main findings. First, we altered the df for temporal trends and meteorological factors, ranging from 5 to 8 and from 4 to 6, respectively. To address the interactions between ambient air pollutants and temperature on EACs (23), we have further adjusted air pollutants, including $PM_{2.5}$, PM_{10}, O_3, NO_2, and SO_2, in our main models.

We reported results as excess relative risk (ER) with 95% CI, the ER was calculated as (relative risk [RR] − 1) * 100%. Statistical analyses were performed using R version 4.3.1. Statistical significance was defined as a p-value less than 0.05.

Results

Table 1 displays the means, standard deviations (SDs), percentiles of daily EAC counts, and meteorological factors in our study. During the study period, a total of 914,304 EACs from all causes were recorded, including 85,484 EACs from cardiovascular diseases and 61,034 EACs from respiratory diseases. The daily mean counts of EACs due to all causes, cardiovascular diseases, and respiratory diseases were 320.8, 30.0, and 21.4, respectively. The mean DTR during the study period was 7.7°C (SD: 3.0), with a median DTR of 7.7°C (interquartile range: 5.6–9.6°C). The daily averages for temperature, relative humidity, and wind speed were 22.6°C, 78.1%, and 2.1 m/s, respectively.

Figure 1 illustrates the estimates and 95% CI of EACs due to all-cause, cardiovascular diseases, and respiratory diseases for each 1°C increment in DTR. This is presented across different lag days (lag0 to lag5) and moving averages (lag01 to lag05). In general, we observed a largest and robust effect on lag01, so in the subsequent analyses, we mainly reported the effects of lag01. We observed significant effects of DTR on all-cause, cardiovascular-related, and respiratory-related EACs in Guangzhou. Specifically, for each 1°C increase in DTR at lag01, there was a 0.47% (95% CI: 0.14, 0.81%) increase in all-cause EACs, a 0.94% (95% CI: 0.46, 1.43%) increase in cardiovascular-related EACs, and a 1.31% (95% CI: 0.76, 1.86%) increase in respiratory-related EACs. Similar lagged effect patterns were observed for DTR with all-cause and cause-specific EACs. In the single-day lag structures, nearly all DTR-EAC associations decreased from lag0 to lag5. In the moving average lags pattern, the effects decreased gradually from lag01 to lag05, with the largest effects observed at lag01.

To further investigate potential non-linear associations between DTR and the risk of EACs from all-cause, cardiovascular diseases, and respiratory diseases, we employed non-linear spline models to estimate the dose–response curves for DTR-EAC associations. Figure 2 reveals nearly linear relationships between DTR and the log-relative risks of EACs due to all causes, cardiovascular diseases, and respiratory diseases.

We further examined the associations between DTR and the risk of EACs due to all causes, cardiovascular diseases, and respiratory diseases, stratified by age, sex, and seasons to estimate potential effect modification. Table 2 indicates significant effect modification by age, sex, and seasons. The effects of DTR on EACs due to all causes, cardiovascular diseases, and respiratory diseases were significantly higher among males, the older adult, and during warm seasons. Specifically, we observed an increase of 1.16% (95% CI: 0.59, 1.74%) in cardiovascular-related EACs for each 1°C increase in DTR among the older adult, compared to 0.45% (95% CI: −0.21, 1.12%) among residents younger than 65 years. Additionally, we found an increase of 1.39% (95% CI: 0.79, 1.99%) in cardiovascular-related EACs among males, compared to 0.13% (95% CI: −0.53, 0.79%) among females. Moreover, there was a 1.53% (95% CI: 0.74, 2.34%) increase in cardiovascular-related EACs during warm seasons, compared to 0.75% (95% CI: 0.14, 1.37%) during cold seasons.

TABLE 1 Summary statistics of daily emergency ambulance calls and meteorological variables in Guangzhou, China, from 2009 to 2017.

	Mean	SD	Percentile				
			Min	25th	50th	75th	Max
No. of daily EACs							
All-cause	320.8	80.5	2.0	283.0	330.0	372.0	553.0
Cardiovascular	30.0	10.3	0.0	24.0	30.0	37.0	68.0
Respiratory	21.4	8.0	0.0	16.0	21.0	26.0	52.0
Meteorological variables							
Temperature, °C	22.6	6.2	3.4	18.2	24.4	27.7	32.3
DTR, °C	7.7	3.0	1.0	5.6	7.7	9.6	18.6
Relative humidity, %	78.1	11.6	27.0	72.0	80.0	86.0	100.0
Wind Speed, m/s	2.1	1.0	0.1	1.4	1.9	2.6	8.1

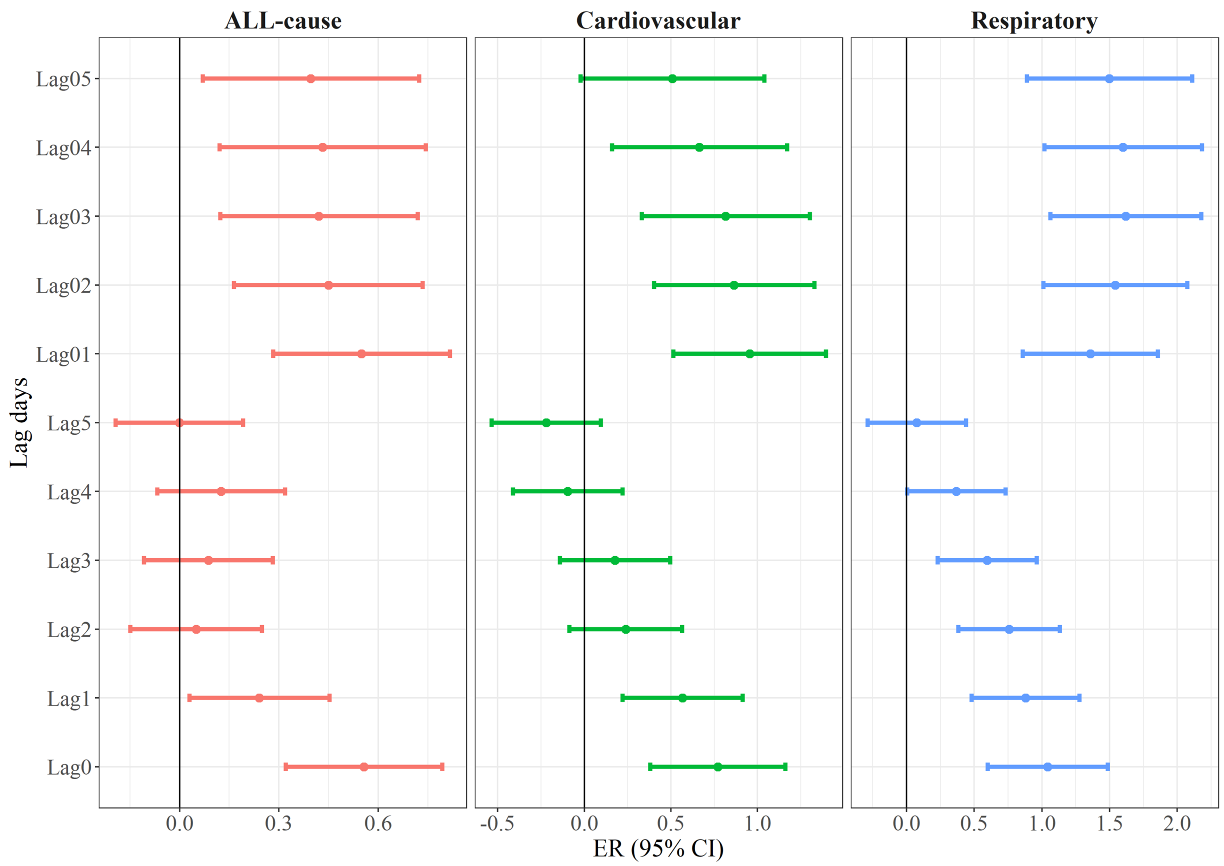

FIGURE 1
Excess risk (and 95% confidence interval) of emergency ambulance calls per 1°C increment in diurnal temperature range at different lag days.

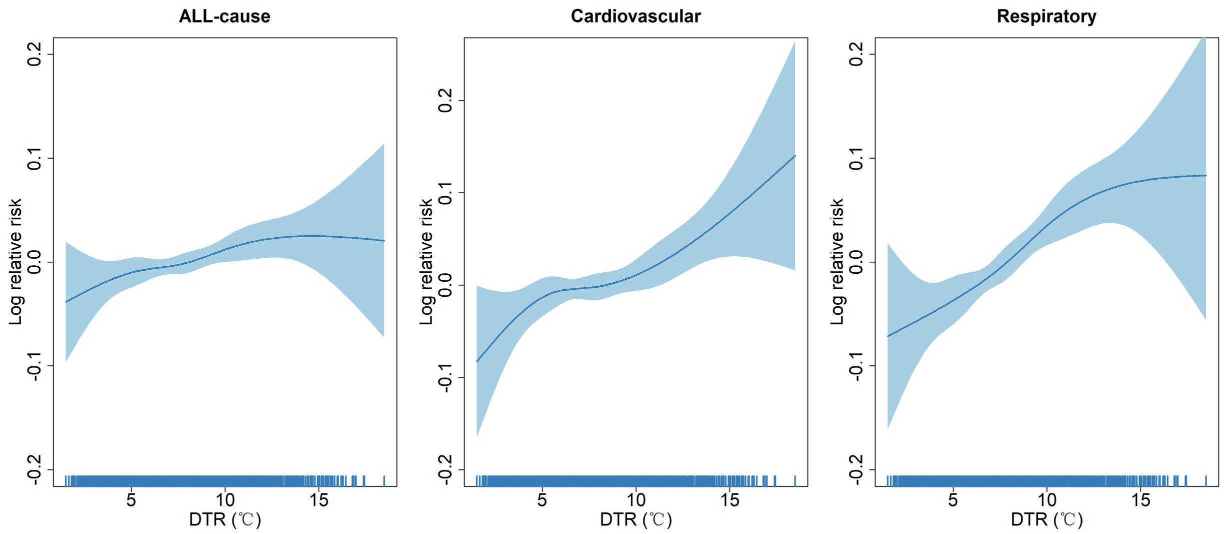

FIGURE 2
Concentration-response curves showing the non-linear association between diurnal temperature range and log relative risks of emergency ambulance calls.

TABLE 2 Excess risk and 95% confidence intervals of emergency ambulance calls due to all-cause, cardiovascular diseases, and respiratory diseases for each 1°C increment in DTR stratified by age group, sex, and season.

Stratum	All-cause		Cardiovascular		Respiratory	
	ER (95% CI)	$P_{interaction}$	ER (95% CI)	$P_{interaction}$	ER (95% CI)	$P_{interaction}$
Age		0.25		**<0.01**		**<0.01**
<65	0.29 (−0.10, 0.68)		**0.45 (−0.21, 1.12)**		**0.37 (−0.45, 1.20)**	
≥65	0.68 (0.28, 1.07)		**1.16 (0.59, 1.74)**		**1.66 (1.02, 2.30)**	
Sex		0.45		**<0.01**		0.76
Male	0.54 (0.17, 0.92)		**1.39 (0.79, 1.99)**		1.36 (0.68, 2.04)	
Female	0.32 (−0.07, 0.71)		**0.13 (−0.53, 0.79)**		1.28 (0.50, 2.07)	
Season		0.88		**<0.01**		0.68
Warm	0.50 (0.22, 0.78)		**1.53 (0.74, 2.34)**		1.35 (0.69, 2.01)	
Cold	0.50 (0.04, 0.96)		**0.75 (0.14, 1.37)**		1.24 (0.52, 1.98)	

The bold texts represent the statistically significant differences ($p < 0.05$).

Our sensitivity analyses, which altered the dfs for temporal trend and meteorological factors, yielded minimal alterations to the effect estimations (Supplementary Table S1), indicating the robustness of our main results. Secondly, we reconstructed our models by adjusting air pollutants and the results agreed with the main findings (Supplementary Table S2).

Discussion

This time-series study, conducted over 9 years in Guangzhou, China, included 914,304 emergency ambulance calls (EACs). We found that a higher DTR was significantly associated with increased risks of EACs for all-cause, cardiovascular diseases, and respiratory diseases. Subsequent dose–response analyses revealed nearly linear relationships between DTR and all-cause, cardiovascular-related, and respiratory-related EACs. Additionally, we identified notable association modifications by age, sex, and season, with elevated ERs observed among the older adult, male individuals, and during warm seasons compared to those under 65 years of age, female individuals, and cold seasons, respectively. These findings persisted when alternative dfs were applied to temporal trend and meteorological variables.

Our findings align with multiple studies investigating the associations of DTR and human health (24–26). For example, a time-series study in Hong Kong, China has reported that a 1.70% (95% CI: 0.30, 3.10%) increase in daily cardiovascular mortality each 1°C increment in DTR at lag03 (24). Another study across several cities found that increased DTR at a lag of 6 days was associated with a higher risk of hospitalization for chronic respiratory diseases (RR = 1.09, 95% CI: 1.08, 1.11) (25). However, these epidemiologic studies mainly focused on mortality or hospital admissions. Few have examined on EACs, which are more suitable indicator for assessing the immediate health effects of short-term DTR exposure. Our study partly addresses the knowledge gap between DTR and EACs and reconfirms that positive associations exist in accordance with previous studies.

Several underlying biological mechanisms may illustrate the associations between DTR and EACs. First, short-term fluctuations in DTR can induce oxidative stress and inflammation, which are known to exacerbate both cardiovascular and respiratory events (27–30). Second, the cardiovascular system must constantly adjust to these temperature changes, which can increase heart rate and blood pressure, potentially triggering cardiovascular events in vulnerable populations (31). Third, sudden temperature shifts can impair respiratory function by causing bronchoconstriction and increasing the susceptibility to respiratory infections, thus heightening the risk of respiratory diseases (6).

We found that DTR had a larger effect on cardiovascular-related EACs among the older residents compared to younger residents, which consistent with previous studies (19, 26). For instance, Amoatey et al. (26) observed a higher impact of DTR among the older population in Victoria state of Australia. It was possible that older individuals have a reduced ability to regulate their core body temperature in response to fluctuating temperatures. Additionally, the higher prevalence of chronic diseases in this age group means that rapid daily temperature changes can place extra stress on their cardiovascular systems, potentially triggering cardiovascular events (32).

We observed that male residents were vulnerable to DTR, which has been widely reported in previous studies (33, 34). For example, a time-series study conducted in China, showed that the greatest effect values were observed in males (ER = 1.35, 95% CI: 0.33, 2.39%) at lag06, compared to females (0.86, 95% CI: 0.24, 1.49%) at lag 01 (33). One possible explanation is the difference in thermoregulation between different gender. Males typically have a higher metabolic rate, which can lead to greater heat production and increased susceptibility to temperature changes (35). Additionally, hormonal differences, such as higher testosterone levels in males, might affect the cardiovascular system, making it more reactive to temperature fluctuations (36). Furthermore, studies suggest that males may have less subcutaneous fat than female, reducing their insulation against temperature extremes and increasing their vulnerability to climate changes (37).

Consistent with previous study (11, 12, 38), our findings indicate that DTR had a more detrimental health effect during warm seasons. Several underlying mechanisms may explain these observed associations. A plausible explanation involves the influence of temperature on the body's thermoregulatory capabilities. High temperature can disrupt sweat evaporation, resulting in diminished cooling efficiency and heightened thermal stress on the body. This heightened stress can raise heart rate and blood pressure, thereby increasing the risk of cardiovascular events (39, 40). Additionally, higher temperatures may enhance oxidative stress in the body, leading to cellular damage and inflammation, which are risk factors for cardiovascular diseases (41, 42).

There are several limitations to this study. First, as a time-series analysis of daily EACs, the results are susceptible to potential ecological fallacy bias (43). Second, some important covariates, including socioeconomic status, living environment, and lifestyle, were unavailable in our study. Third, our study was performed in a single city in China due to data accessibility, limiting the generalizability of the findings.

Conclusion

Our study indicates that DTR could elevate the risk of the EACs due to all-cause, cardiovascular diseases, and respiratory diseases. The impact of DTR may be pronounced among the older adult individuals, male residents, and during warm seasons. It underscores the necessity for pertinent public health policies, encompassing educational initiatives and health promotion efforts, to alleviate the adverse health repercussions result from higher DTR.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: please contact author for data requests. Requests to access these datasets should be directed to huangxqgd2h@163.com.

Author contributions

CG: Writing – review & editing, Supervision, Formal analysis, Investigation, Visualization. KC: Writing – original draft, Writing – review & editing. GC: Writing – original draft, Writing – review & editing. JW: Writing – original draft, Writing – review & editing. JZ: Formal analysis, Methodology, Writing – review & editing. XH: Supervision, Visualization, Writing – review & editing. MD: Writing – review & editing, Formal analysis, Funding acquisition.

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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.2024.1454097/full#supplementary-material

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Development of the Bisphenol A exposure scale in adults

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Objective: This study was conducted to develop a scale for assessing the attitudes of adults regarding the determination of Bisphenol A exposure.

Methods: The study sample comprised of 370 individuals who volunteered to participate. According to the Explanatory Factor Analysis (EFA) results of the investigation, a scale structure consisting of a total of 3 sub-dimensions was obtained. In the Confirmatory Factor Analysis, the scale item factor loading values were acceptable.

Results: The fit indices for the scale were CMIN/df = 1,618, RMSEA = 0.058, NFI = 0.914, CFI = 0.965, and IFI = 0.790, indicating a satisfactory level of agreement. The scale was determined to have a Cronbach value of 0.79 and a high degree of reliability. The item-total score correlation coefficients of the scale ranged from 0.327 to 0.534 and exhibited a high degree of discrimination, as determined.

Conclusion: Based on the analyses conducted, it was determined that the Adult Bisphenol A Exposure Scale is a valid and reliable instrument for determining the attitudes of adults toward contact with and use of Bisphenol A-containing products.

KEYWORDS

Bisphenol-A, scale, Bisphenol-A exposure, good health and well-being, responsible consumption and production

1 Introduction

Environmental pollutants are a significant problem in the globe. Bisphenol A (BPA), one of these substances, is a chemical found in plastics, storage containers, packaging, and a variety of other everyday items. It has been suggested that this substance may have a negative effect on the hormonal system and lead to early puberty, obesity, behavioral issues, and fetal sex difficulties. Although BPA has an estrogenic effect as one of the endocrine disrupting chemicals and is reported to have less effect than other endocrine disruptors, its negative effects on human health are significant due to its widespread use in industry and everyday life. Long-term exposure to endocrine-disrupting chemicals (EDC) has been shown to be associated with metabolic dysfunction, reproductive system disorders, endocrine-related malignancies, and neurodevelopmental disorders (1). EDCs are environmental compounds that have the potential to disrupt the endocrine system of humans and wildlife (1). Numerous studies have demonstrated that long-term exposure to these chemicals may be associated with metabolic dysfunction, reproductive system disorders, endocrine-related malignancies, and neurodevelopmental disorders in humans (1–6). Bisphenol-A is the most prevalent EDC due to its ubiquitous utilization. As one of the pollutants that attract the most attention and have the greatest potential to imperil human and environmental health, it is regarded as a significant public health issue of which society should be aware.

BPA was first synthesized by Aleksandr P. Dianin in 1891, and its potential commercial use was investigated during the 1930s search for synthetic estrogen. In the 1940s and 1950s, the plastics industry identified BPA's uses (7). Bisphenol A (BPA) is produced by the condensation of phenol and acetone (8) in the presence of an acid or alkaline compound. BPA is soluble in all organic solvents and partially in water. At ambient temperature, it exists as a white solid particle or crystal (7). It can bind to the estrogen receptor (ER) like estradiol and exert both estrogenic and anti-androgenic properties (9, 10). These properties are related primarily to the 4-hydroxyl group on the N-phenyl ring and the hydrophobic moiety at the 2-position of the propane moiety (9). Since the majority of BPA-containing products come into contact with food, this is crucial for human health and the environment (11).

BPA is used in the production of certain plastics and compounds. It is present in polycarbonate (PC) plastics, which are frequently utilized in food and beverage containers such as water bottles and other consumer goods. Epoxy resin, which is used to coat the interior of metal products such as food cans, also contains BPA (12). Humans can be exposed to BPA through multiple routes, including transdermal, oral, and inhalation. Major sources of BPA exposure include packaged foods, thermal paper, infant items, pollution, medical equipment, and dental materials, among others (13). Humans are most frequently exposed to BPA through tinned foods and beverages. BPA leaches from canned foods and beverages. Environmental conditions, such as high temperature, sunlight, and acidic tinned foods such as tomatoes, exacerbate this absorption to the point where it seeps into the food through the can linings. Everyday activities, such as using plastic implements to microwave food and storing plastic beverage bottles in heated vehicles, also increase BPA leaching from plastics into food (14, 15). Scientists and the general public have begun to express concern due to the expanding use of Bisphenol A (BPA) in a variety of applications and the mounting evidence of its endocrine-disrupting effects (16).

People are primarily exposed to BPA through food (17). However, given that natural foods that are expected to be BPA-free, as well as edible animals and animal products, are grown in a polluted and hazardous environment, it can be predicted that the problem will not be limited to plastic, tinned, or ready-to-eat foods. Tons of BPA are used annually in numerous industrial sectors, and it disperses into the environment and atmosphere. In groundwater near waste sites contaminated with BPA-containing substances, a higher concentration of BPA and accumulation of plastic detritus have been discovered (18).

The majority of people today are employed and consume ready-made goods. Even though people have the ability to protect themselves from BPA, they continue to unknowingly use products containing BPA. However, no scale evaluating the use of plastic packaged products by adults and Bisphenol A exposure information has been identified in the literature. In order to eliminate this deficiency in the scientific field, it is believed that the construction of a scale that evaluates the use of plastic packaged products and Bisphenol A exposure information will contribute to the literature.

2 Methods

This is a methodological study conducted to ascertain the exposure status of adults to Bisphenol A. The design of the scale consisted of four stages: scale development, factor structure, reliability and validity assessment.

2.1 Phase 1. Scale's development

Following an exhaustive literature evaluation, a pool of questions containing suggestions regarding the use of plastic packaged products was compiled. After constructing the pool of scale items, expert opinions on content validity were obtained. The received expert opinions were evaluated using the Lawshe method (19). After the survey was completed, its language was evaluated, and any necessary adjustments were made. In accordance with expert opinions, the number of items in the scale was reduced to 37. The invariance of the scale over time was evaluated by administering it a second time to 50 academicians and administrative personnel who were not included in the study group 4 weeks after the initial administration, and calculating the correlation between the scores obtained in the two administrations. In addition to the "Adult Bisphenol A Exposure Scale," the study's questionnaire included inquiries about the sociodemographic characteristics (age, gender, occupation) of the participants.

2.2 Phase 2. Factorial structure

Using Exploratory Factor Analysis (EFA), the purpose of this phase is to evaluate the factor structure. Additionally, the internal consistency of the factors was analyzed using Reliability Analysis.

2.2.1 Participants

In this study, there was no sample selection to determine the sample size; instead, the sample size was determined by the requirement that the number of samples be five to 10 times the average number of items on the scale in scale development studies (20). It was 35.38 ± 10.03 years. 34.6% of the participants were between the ages of 29 and 34, 51.6% were male, and 55.1% were administrative staff. In addition, researchers were given an informed consent form prior to the study. Volunteer researchers participated in the study, while participants with insufficient data were excluded.

2.2.2 Data analysis

In our research, the elements were initially constructed by the researcher based on a review of the relevant literature. Then, the scale was constructed, factors were extracted utilizing Exploratory Factor Analysis, and the consistency of the factors was examined utilizing Reliability Analysis. The research data was analyzed using the IBM SPSS 25 bundle program and AMOS 24 software. Participants' data were summarized using mean, standard deviation, percentage, and frequency distributions. The initial stage involved the calculation of the correlation matrix. The Bartlett and Kaiser Meyer Olkin (KMO) tests were then computed to determine if the data were suitable for factor analysis and if each item contained the necessary assumptions for this analysis and subsequent tests (21, 22). Then, to construct a conceptual model, "Principal Axis Factoring" was selected as the method, and "promax" was used to conduct factor analysis. After this step, the internal consistency (Cronbach's alpha) of each factor's items was determined.

2.3 Phase 3: Reliability, validation of the Bisphenol A exposure scale in adults

Confirmatory Factor Analysis (CFA) is a statistical method used to evaluate the fit between theoretical constructs and measurement models and to verify their validity. Model fit indices derived from the CFA method are used to assess the accuracy of the EFA results on a comparable sample data set collected by the researcher and to evaluate the scale's validity (Figure 1). As the estimation point for CFA, the Maximum Likelihood method was used. This technique is often used to enhance the normal distribution assumption, parameter estimation, and fit indices. Diverse methodologies were used to evaluate the scale's reliability: The item-total score correlation, internal consistency (Cronbach), test–retest, and upper-lower 27% discrimination procedures were utilized. Intraclass correlation and Pearson correlation analysis were applied to the test–retest procedure. Construct validity was determined using Exploratory and Confirmatory Factor Analysis (EFA and CFA, respectively). Principal axis factorization and promax rotation were favored throughout the EFA phase. In determining the number of factors, only those variables with eigenvalues of one or greater were considered. By using the method of determining the variance according to the explanation (contribution) rate, a variance rate between 40 and 60% was considered sufficient. The chi-square value $p > 0.05$ was used as a criterion for assessing the CFA model's quality of fit. In addition, NNFI (Non-normed Fit Index), NFI (Normed-Fit Index), CFI (Comparative Fit Index), and RMSEA (Root Mean Square Error of Approximation) fit indices were determined. As criteria for acceptable levels of fit indices, NNFI and CFI > 0.95, NFI > 0.90, and RMSEA<0.05 were used. At a significance level of $p < 0.05$, the obtained study results were evaluated.

3 Results

Bisphenol A Exposure Scale in Adults; Bartlett's sphericity test was statistically significant ($x^2 = 1197.172$, $p < 0.001$), and Kaiser-Meyer-Olkin (KMO = 0.81) was greater than 0.60. Since the individual KMO values of the 3rd, 11, 28, and 29th items on the scale were less than 0.60, they were excluded from the study to preserve the integrity of the analysis, in accordance with the literature. These two experiments demonstrated that factor analysis is applicable to this scale. As a result of the EFA, "Communality" values were discovered first. Communality is a value that measures the relationship between the items and the factors, and a value below 0.40 is not desirable. Items numbered 2, 4, 6, 7, 9, 10, 12, 15, 16, 20, 22, 30, 31, 32, 33, and 34, as well as items 21 and 27, are also eliminated from the scale because they coincide. Removed. It was observed that there were a total of three factors. Factor 1 is comprised of five items with factor loadings ranging from 0.531 to 0.848, and its contribution to the total variance explained is 29.7%. Factor 2 consists of five items with factor loadings ranging from 0.574 to 0.974; its contribution to the total

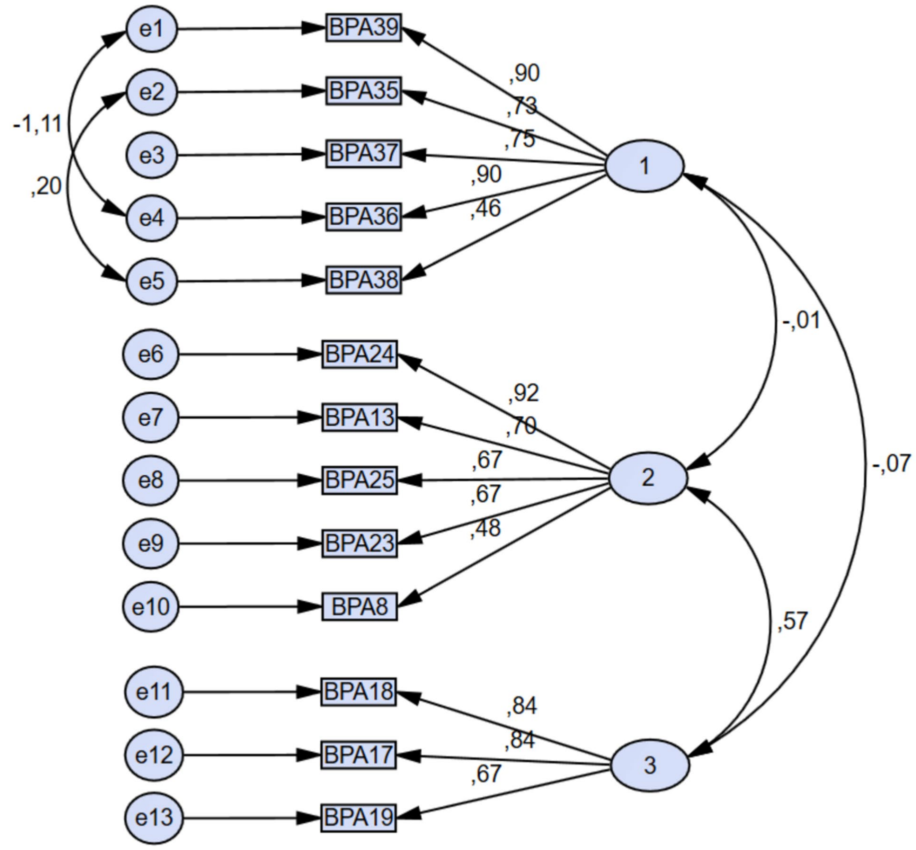

FIGURE 1
Confirmatory factor analysis fit indices and model view.

TABLE 1 Bisphenol A exposure scale explanatory factor loadings for adults.

Item no	Items	Factors and factor loadings		
		1	2	3
39	Do you use cosmetic products such as lipstick, blush, foundation?	0.848		
35	Do you use sun protection cream?	0.800		
37	Do you use hair dye, hair styler, conditioner for cosmetic purposes?	0.793		
36	Would you use a face mask for cosmetic purposes?	0.774		
38	Do you use perfume, deodorant, roll-on for cosmetic purposes?	0.531		
24	Do you consume soft drinks such as soda, fizzy drinks, and fruit juice in plastic packages?		0.974	
13	Do you consume canned drinks at home or outside?		0.771	
25	Do you consume drinks with plastic straws?		0.667	
23	Do you consume products such as milk, cream and kefir in plastic packages?		0.584	
8	Do you drink hot liquid foods in plastic cups?		0.574	
18	Can you use vinegar in plastic containers?			1.011
17	Do you use oils in plastic containers?			0.670
19	Would you consume pickles in plastic containers?			0.549
Eigenvalues		4.243	3.234	1.244
Total variance explained (%)		29.681	21.968	7.246
Cumulative variance explained (%)		29.681	51.649	58.895
Kaiser Meyer Olkin (KMO) and Bartlett Test Results				
Bartlett test		KMO	0.815	
		χ^2	1197.172	
		sd	78	
		p	<0.001	

Extraction method: Principal axis factoring, Rotation method: Promax.

variance explained is 21.9%. Factor 3 comprises of three items with factor loadings ranging from 0.549 to 1.011; its contribution to the total variance explained is 7.2%. The calculated total explained variance rate was 58.9% (Table 1).

3.1 Introductory information of the participants

The 370 participants in the study ranged in age from 23 to 73, with an average age of 35.38 ± 10.03 years. 34.6% of the participants were between the ages of 29 and 34, 51.6% were male, and 55.1% were administrative staff (Table 2).

3.2 Validity findings

3.2.1 The validity of scope and content

In order to develop the "Bisphenol A Exposure Scale in Adults," 9 experts with a high level of knowledge and experience in the field (three professors, two associate professors, one lecturer, and one public health nurse) evaluated a pool of 40 questions. The "Expert Evaluation Form" was sent to the experts' email addresses so they could submit their evaluations. Using the Lawshe method, the data from the expert evaluation form were analyzed. While the Content Validity Rate (CVR) was determined for each item, the Content Validity Index (CVI) was determined for the complete scale form.

TABLE 2 Distribution of descriptive characteristics of participants (*n* = 370).

Variables	Mean ± Sd	Min. – Maks.
Age	35.38 ± 10.03	23–73
Variables and Subgroups	**Frequency (n)**	**%**
Age categories		
23 to 28 years	90	24.4
29 to 34 years	128	34.6
35 to 40 years	86	23.2
41 and older	66	17.8
Gender		
Female	179	48.4
Male	191	51.6
Position		
Academician	166	44.9
Administrative personnel	204	55.1
Total	370	100.0

SD, Standard deviation; Min., Minimum; Maks., Maximum.

Each item's CVR rate should ideally be positive (+) and near to 1. If the values derived from expert opinions are 0 or negative (−), the question in query pool should be eliminated.

In a new scale to be developed using the Lawshe method, it is anticipated that the CVR for each item and the CVI for the total number of items will exceed the value calculated based on the number of experts in the Lawshe content validity criterion values Table (23) (19). The value corresponding to nine experts in the Lawshe content validity criterion Table is 0.778 in this instance. In accordance with the advice of experts, items with scores below 0.778 were eliminated from the query pool. In this regard, expert opinions determined that the 5, 14, and 26th items did not meet the content validity criterion. CVR and CVI were recalculated after removing these objects. The entire CVI value was determined to be 0.93 by the Lawshe method.

3.2.2 Construct validity

Statistical analysis techniques including factor analysis, internal consistency analysis, and hypothesis testing are used to examine construct validity (24). EFA and CFA were conducted within the scope of this study to ascertain construct validity. For the construct validity analysis of the Bisphenol A Exposure Scale in Adults, it was first determined whether or not each item was appropriate for Exploratory Factor Analysis (EFA). KMO and Bartlett tests were used in this regard. To evaluate the sample size, a KMO value of 0.815% was calculated. This result suggests the sample size is adequate for EFA. The calculated result of the Bartlett test was $\chi^2 = 1197.172$, p0.001. Therefore, this result indicates whether the correlation coefficients between the items are suitable for EFA.

Prior to examining the results of this analysis, the KMO values of each sample item were evaluated. Since the individual KMO values of the 3rd, 11, 28, and 29th items on the scale were less than 0.60, they were excluded from the study to preserve the integrity of the analysis, in accordance with the literature. The eigenvalue coefficient is utilized when determining or separating factors. In general, factorization occurs when this value is 1 or greater. The number of factors in the scale, eigenvalue coefficients, explained variances, and factor loadings of each item in terms of the factor it is under are enumerated in Table 1.

Figure 1 depicts the use of model fit indices derived from the CFA method to test the accuracy of the EFA results on an identical sample data set collected by the researcher and to assess the validity of the scale. Maximum Likelihood method was used as the estimation point in CFA.

In our research, CMIN/DF ($\chi^2 = 97.069$ / df = 60, $p = 0.002$) = 1.618 (Chi-square / degrees of freedom) value, RMSEA = 0.058 (Root Mean Square Error of Approximation), GFI = 0.930 (Goodness of Fit Index), AGFI = 0.894 (Adjusted Goodness of Fit Index), NFI = 0.914 (Normed Fit Index), NNFI (TLI) = 0.954 (Non- Normed Fit Index), CFI = 0.965 (Comparative Fit Index), IFI = 0.965 (Incremental Fit Index) fit index values show that the model has a good fit. To enhance the AGFI and NFI values, a modification (adjustment) was applied between items 35 and 38 and between items 36 and 39.

The sub-dimension factor loadings ranged from 0.46 to 0.90 for Factor 1, 0.48 to 0.92 for Factor 2, and 0.67 to 0.84 for Factor 3 (Figure 1).

3.3 Reliability results

In order to test the reliability of the scale within the scope of this study, the frequently used item sub-dimension and item total score analyses, Cronbach reliability coefficient, lower-upper 27% comparison (item discrimination), and test–retest methods for invariance over time were selected.

Bisphenol A Exposure Risk Scale sub-dimension item correlation analysis results (Corrected Item-Total Correlation) are given in Table 3.

The Adult Bisphenol A Exposure Scale was created as a 5-point Likert scale. When the distributions of the scale total and sub-dimensions are examined, namely "always = 0," "often = 1," "sometimes = 2," "rarely = 3" and never = 4″, the lowest value that can be derived from the scale is 0, the lowest value that can be obtained from the scale is 0. The highest value found in this study was 52, and the average score was 24.74 ± 9.37. The Cronbach reliability coefficient for the full scale was calculated to be 0.79.

Comparing the difference between the item total score averages for the Lower and Upper 27% groups yields statistically significant information regarding the internal consistency of the scale as well as the item validity. A total of 370 individuals who participated in the study had their average scores ranked from highest to lowest. According to the calculation, there should be 100 individuals in each of the upper and lower 27% sections. According to the results of the independent samples t test conducted between the two groups for the scale total, the upper 27% group's average score was higher than the lower 27% group's average score, and the difference was statistically significant ($t = 36.589$, SD: 198, $p < 0.001$). Similar outcomes were observed for variables 1, 2, and 3. Accordingly, it can be stated that the distinctive characteristics of the items on the total scale and all subfactors, as well as the measurement capability of the measuring instrument in terms of internal consistency, are all high (Table 4).

The analysis determined that the intra-class correlation coefficient is 0.952. This value indicates that the scale's reliability is outstanding (Table 4).

The homogeneity of the participants' responses to the scale elements was evaluated using Hotelling's T2 test. As determined by the analysis, Hotelling's T2 = 727.446; $F(12, 358) = 58.813$, p 0.001. Based on this result, it can be concluded that the scale does not contain any response bias.

Table 5 presents the final version of the Bisphenol A Exposure Scale in Adults, reflecting the comprehensive adjustments and validations made throughout the study.

4 Discussion

In this research, a scale was created to assess adult Bisphenol A exposure. The adult Bisphenol A exposure scale consists of three factors and 15 items. The first factor is "Personal BPA exposure" with 5 items, the second is "BPA exposure related to the home environment" with 5 items, and the third is "BPA exposure related to shopping attitude" with 3 items. Scale items 1 and 15 will not be evaluated. The gauge was constructed using a 5-point Likert scale. Participants' responses were scored as follows: "always = 0″, "often = 1″, "sometimes = 2″, "rarely = 3″, and "never = 4" The scale's minimum value is 0 and its maximum value is 52, while the average score for this study was 24.74 ± 9.37. A high score indicates a minimal exposure to Bisphenol A. The Cronbach reliability coefficient for the full scale was calculated to be 0.79. Test–retest is one of the methods for analyzing the reliability of an instrument. This test provides information regarding the scale's

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TABLE 3 Item-subdimension and total score correlations for the Bisphenol A exposure risk scale for adults (*n* = 370).

All items		Adjusted	
		Sub-dimension item total score correlation	Item total score correlation
		r	r
1.	Have you heard of a chemical called BPA or Bisphenol?	Not included	Not included
Factor 1			
39.	Do you use cosmetic products such as lipstick, blush, foundation?	0.753	0.343
35.	Do you use sun protection cream?	0.724	0.355
37.	Do you use hair dye, hair styler, conditioner for cosmetic purposes?	0.729	0.431
36.	Would you use a face mask for cosmetic purposes?	0.727	0.478
38.	Do you use perfume, deodorant, roll-on for cosmetic purposes?	0.495	0.400
Factor 2			
24.	Do you consume soft drinks such as soda, fizzy drinks, and fruit juice in plastic packages?	0.511	0.534
13.	Do you consume canned drinks at home or outside?	0.678	0.490
25.	Do you consume drinks with plastic straws?	0.587	0.475
23.	Do you consume products such as milk, cream and kefir in plastic packages?	0.812	0.479
8.	Do you drink hot liquid foods in plastic cups?	0.602	0.345
Factor 3			
18.	Can you use vinegar in plastic containers?	0.681	0.430
17.	Do you use oils in plastic containers?	0.752	0.415
19.	Would you consume pickles in plastic containers?	0.577	0.327
40.	Have you had a dental filling?	Not included	Not included

TABLE 4 Test–retest analysis results based on intra-class correlation coefficient concerning the reliability of the Bisphenol A exposure scale in adults.

		%95		F test			
		Confidence interval		Statistics value			
		Lower limit	Upper limit		df1	df2	*p*
Single measurements	0.909	0.843	0.947	21.727	49	49	<0.001
Average measurements	0.952	0.915	0.973	21.727	49	49	<0.001

df, degrees of freedom.

internal consistency (25, 26). As its name suggests, test–retest is founded on measurements taken at specific periods or time intervals. It is suggested that this duration be between 4 and 6 weeks. In test–retest scale investigations, two distinct test results are typically analyzed for reliability (26). Reporting any one of these results is sufficient. The Pearson Product Moment Correlation Coefficient and the Intraclass Correlation Coefficient (ICC) are examples.

Pearson correlation is a statistical technique used to determine the relationship between scores obtained when the same individuals take the same test multiple times. This correlation is used to assess the precision and dependability of the measuring instrument. Because the Pearson correlation coefficient value indicates the extent of the relationship between two measurements.

ICC is a statistical method that is most commonly employed in research designs to evaluate the scope and consistency of a measurement instrument across repeated measurements (25, 27). ICC indicates the repeatability of measurements by the measuring instrument. ICC has a value between 0 and 1, and a value of 0.70 or higher indicates that the measurement instrument is reliable and yields stable results in repetitive measurements (28). ICC's computation procedure evaluates 10 distinct hypotheses. It is essential to indicate which of these techniques was employed (27).

In reliability studies, ICC is more effective than Pearson correlation analysis because it incorporates both the correlation between measurements and the agreement between absolute results (27, 29). ICC, two-way mixed model with absolute fit was preferred for reliability in this analysis, contingent on the type of mean calculation. However, the study also included Pearson correlation analysis results in order to compare the two values. The analysis determined that the intra-class correlation coefficient is 0.952. This value indicates that the scale's reliability is outstanding. When Test–Retest Analysis Based on Pearson Correlation Coefficient is applied regarding the reliability of the scale; It was determined that there was a positive, highly strong, statistically significant relationship between

TABLE 5 Final version of the Bisphenol A exposure scale in adults.

Previous number No.	Last number No.	Questions
1.	1	Have you heard of a chemical called BPA or Bisphenol?
Factor 1: Personal BPA Exposure		
39.	2	Do you use cosmetic products such as lipstick, blush, foundation?
35.	3	Do you use sun protection cream?
37.	4	Do you use hair dye, hair styler, conditioner for cosmetic purposes?
36.	5	Would you use a face mask for cosmetic purposes?
38.	6	Do you use perfume, deodorant, roll-on for cosmetic purposes?
Factor 2: BPA Exposure in the Home Environment		
24.	7	Do you consume soft drinks such as soda, fizzy drinks, and fruit juice in plastic packages?
13.	8	Do you consume canned drinks at home or outside?
25.	9	Do you consume drinks with plastic straws?
23.	10	Do you consume products such as milk, cream and kefir in plastic packages?
8.	11	Do you drink hot liquid foods in plastic cups?
Factor 3: BPA Exposure to Shopping Attitudes		
18.	12	Can you use vinegar in plastic containers?
17.	13	Do you use oils in plastic containers?
19.	14	Would you consume pickles in plastic containers?
40.	15	Have you had a dental filling?

the first measurement and the second measurement ($r = 0.912$, $p < 0.001$). This correlation indicates the consistency and dependability of the scale over time.

4.1 Limitations and future research

These findings were derived from a convenience sample with limited generalizability. Academic and administrative personnel working at a foundation university were included in the sample. Consequently, the current scale will require additional research and the incorporation of various professional groups. Additionally, profession-specific research should be conducted. Also intriguing would be a study of factorial invariance by occupational category and associated socioeconomic status.

5 Limitations

The study has some limitations worth noting. It primarily involved academic and administrative personnel in Turkey, which may affect the generalizability of the findings to broader populations. Additionally, cultural and economic variations in different regions were not specifically addressed. The "BESA" scale is designed for adults and does not evaluate exposure in other age groups. Furthermore, reliance on self-reported data could influence the accuracy of the results. Acknowledging these factors can help guide future research and improve the scale's applicability.

6 Conclusion

As a consequence, most people in modern society are involved in business and consume prepared foods. In addition, cosmetic products and plastic and resin-coated materials used in the home pose a high risk of Bisphenol A exposure. Despite the availability of BPA-protection options, people continue to unknowingly use BPA-containing products. No exposure measurement scale for Bisphenol A could be identified in the literature review. The validity and reliability of the scale indicate that it can be used to determine the exposure status of adults to Bisphenol A. In this regard, it is recommended that the Adult Bisphenol A Exposure Scale, which was developed as a result of this study, be utilized in scientific studies to ascertain in detail the issues and problems associated with adult Bisphenol A exposure.

Moreover, it is anticipated that the "Bisphenol A Exposure Scale in Adults (BESA) "will be applicable in various nations. However, this research was conducted with academic and administrative personnel from Turkey. Therefore, additional research is required to validate the scale in other nations.

7 Future implications

Based on the findings of this study, future research should focus on validating the Adult Bisphenol A Exposure Scale (BESA) in different cultural and demographic contexts to enhance its global applicability. Additionally, longitudinal studies could explore the long-term health impacts of Bisphenol A exposure, using the BESA to monitor exposure levels. This scale could also serve as a foundation for developing public health interventions aimed at reducing BPA exposure, particularly in high-risk populations such as those heavily reliant on packaged foods and plastic products.

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 humans were approved by Individuals who voluntarily consented to participate gave their informed consent. This investigation adhered to the Declaration of Helsinki, and the protocol was authorized by the ethics committee of Hasan Kalyoncu University (number 2022/092). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

BK: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TO: Methodology, Project administration, Validation, Writing – review & editing. EA: Data curation, Resources, Visualization, Writing – review & editing.

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The influence of NOx, temperature, wind and total radiation on the level of ozone concentration in the Upper Silesian agglomeration

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In 2019, ozone was responsible for about 365,000 premature deaths worldwide (6.21 million healthy life years lost) and acute ozone exposure led to 16,800 premature deaths in the European Union. The aim of the study was to estimate the influence of NO, NO_2, wind direction (WD) wind speed (WS), air temperature (TA), and total radiation (GLR) on ozone concentration levels. Data provided by 3 automatic air quality monitoring stations of the Regional Environmental Protection Inspectorate in Katowice, were used in this study. The measurements were conducted in from January 1 2009 to December 31 2017. The data obtained from the measuring stations were statistically analysed. The study showed that the strongest influencing factors for O_3 values are air temperature and total radiation, with each showing a high correlation with ozone concentration. NO and NO_2 had a dual effect on O_3 concentration, causing an increase in ozone concentration at low NO and NO_2 concentrations and a decrease in ozone concentration at higher NO and NO_2 concentrations. We noted that the direction of the wind had very little effect on the concentration of O_3. The influence of wind speed on the O_3 level was also small, but stronger than that of the wind direction. The research shows that in the analysed years for selected measuring stations the strongest factors influencing O_3 concentration are air temperature and total radiation, the NO and NO_2 concentrations had a dualistic effect on the O_3 concentration.

KEYWORDS

air pollution, ozone, environmental health, environmental policy, population health

Introduction

Indoor and outdoor air pollution is one of the leading threats to human life especially in low-and middle-income countries, therefore it is indicated as one of the main public health concerns (1–3). In 2019, air pollution led to 6.75 million early deaths (1 in 9 deaths globally) and 213 million years of healthy life lost (the 4th major mortality risk factor worldwide) (4).

Recent studies have confirmed that the high number of annual excess deaths are associated with high levels of ozone (O_3), in 2019, for example, ozone accounted globally for about 365,000 early deaths (6.21 million years of healthy life lost) and acute ozone exposure led to 16,800 premature deaths in the European Union (5, 6). The European Environmental Agency report, 'Air Quality in Europe 2022,' indicated that ozone exposure above 70 μg/m^3 led to 24,000 early deaths in the EU in 2020 (7). Ozone-related mortality could be decreased if stricter air quality standards are introduced (4).

Ozone (O_3) consists of three oxygen atoms (an allotropic form of oxygen). Ninety-five percent of ozone is located in the stratosphere, at an altitude of 10–50 kilometres. Due to solar radiation, oxygen molecules (O_2) are broken down into single atoms of oxygen (O). These single atoms react with other oxygen molecules to create ozone molecules. Due to the third atom of oxygen, ozone is a firm photochemical oxidant (8, 9). Stratospheric ozone significantly screens the lower atmospheric layers and the Earth's surface from ultraviolet radiation (mostly UV-c and UV-b and half of the UV-a), but the tropospheric ozone, classified as one of the greenhouse gases, is proven to negatively influence human health (8, 9).

Tropospheric ozone (ground-level ozone) is synthesised by photochemical reactions between O_3 precursors, such as nitrogen oxides (NOx), methane, carbon monoxide and volatile organic compounds (VOCs). Due to the importance of high temperatures and solar radiation, meteorological factors significantly influence the formation of ozone (9–11). Nowadays, the domination of anthropogenic emissions of ozone precursors into the atmosphere (for instance, due to industrial and construction activities, combustion processes, and vehicle traffic) is observed, thus a high concentration of tropospheric ozone is more likely in suburban areas than in city centres (10, 12, 13). The ozone precursor, methane (CH4), is the second most abundant greenhouse gas after carbon dioxide (CO_2), and its atmospheric levels have increased significantly in recent years. Methane has natural and man-made sources (e.g., wetlands, peatlands and livestock) (14). Indirect sources of ozone are nitrogen oxides from forest fires, soil microbiological processes, and volatile organic compounds of vegetations (i.e., pinenes, terpenes), which increase the level of both NOx and VOC (15, 16). Meteorological conditions significantly affect ozone production at the regional and national levels (11, 12, 17). Long-range wind transportation of the tropospheric ozone and its precursors can occur (12, 14, 16, 18, 19).

Aim

The aim of the study was to estimate the influence of NO, NO_2, wind direction (WD), wind speed (WS), air temperature (TA), and total radiation (GLR) on ozone concentration levels.

Methods

Data obtained from the Regional Environmental Protection Inspectorate in Katowice, capital of the Silesian province, and collected in the scope of National Environmental Monitoring were used in this study.

Data were provided by 3 automatic air quality monitoring stations of the Voivodeship Inspectorate for Environmental Protection, one station each in Katowice, Zloty Potok and Bielsko-Biała. The measurements were conducted in from January 12,009 to December 312,017.

The details of the station located in Złoty Potok, Częstochowa powiat, Janów commune are as follows: international code: PL0243A; measurement zone: Silesian agglomeration, urban background station; measurement target: plant protection; surroundings of the station: natural rural area, agricultural; location of the station: the area belonging to a Kamienna Góra forester's lodge in Złoty Potok. The Janów commune is located approx. 20 km southeast of Częstochowa and approx. 25 km north of Zawiercie. The immediate surroundings of the station are meadows and plant-cultivated fields. At a distance of 150 m from the station, there is a forester's lodge and several wood-fired summer cottages.

The details of the station located in Katowice (Kossutha St. 6, 40–844) are as follows: international code: PL0008A; measurement zone: Silesian agglomeration, urban background station; measurement target: human health protection; station surroundings: urban, residential; type of area: city (250–500 thousand inhabitants); surroundings of the station: to the north, blocks of flats, a railway line, a Motorway and the "Tysiąclecia" housing estate, to the east, commercial areas, to the south, residential buildings of the "Witosa" estate, and to the west, residential buildings and, further, post-mining areas of the Mine Hard Coal "Kleofas."

The details of the station located in Bielsko-Biała, (Kossak-Szczuckiej St. 19, 43–300) are as follows: international code: PL0234A; measurement zone: Silesian agglomeration, urban background station; measurement target: human health protection; station surroundings: urban, residential; type of area: city (50–250 thousand inhabitants); location of the station: central part of Bielsko-Biała. The station is surrounded by high-and low-rise residential buildings. The surrounding buildings are heated from the heating network and individually.

The three monitoring stations were specifically selected for this research because of the different types of areas they are located in: one of the stations is located in a rural area, the other in a medium-sized city, and the station in Katowice is representative of the situation of a large city.

The data obtained from the measuring stations (NO, NO_2, WD, WS, TA and GLR variables for ozone concentration O_3) were statistically analysed using StatSoft, Statistica 13.1 software. A correlation analysis was performed. Pearson's coefficient of linear correlation (R) and the partial correlation coefficient (R-part) were analysed. In addition to the multiple regression analysis (stepwise forward regression), the standardised regression coefficient β was calculated and analysed. When creating multiple regression models, the lagged variable O3 (d - 1) was used, whose values were the previous day's O_3 concentrations.

Map

Location of the measurement stations (PL0234A PL0008A, PL0243A).

Health effects

A study conducted in 21 East Asian cities between 1979 and 2010 showed significant associations between short-term ozone exposure and higher daily mortality rates. The results varied significantly from season to season, with a significant decrease recorded in winter at temperatures below 5°C, which is consistent with results obtained in Western European and North American countries (20).

Global warming significantly increases ground-level ozone and, in turn, the number of days with high concentrations of ozone (ozone seasons). As a highly reactive oxidant, ozone can interact with the cells of the cardiovascular and respiratory systems (21, 22).

The inflammation of the respiratory tract cells and the lungs is immune-dependent. Ozone exposure contributes to increased expression of mRNA of tumour necrosis factor-α (TNF-α), interleukin-1β (IL-lβ), interleukin-6 (IL-6) and interleukin-8 (IL-8) in human alveolar macrophages, and to increased concentrations of IL-6, IL-8 and fibrinogenic proteins in human airway epithelial cells (22).

Asthma is the commonest chronic respiratory disease in the world (23). In 2015, there were 9–23 million emergency visits globally due to the worsening of asthma symptoms (23). Exposure to ground-level ozone could increase acute hospital admissions of children and adolescents regardless of the geographical context (12). The examination of 3.959 children treated for acute asthma attack in the years 2016–2019 in Xiamen, China led to the conclusion that ozone concentration above 80 μg/m3 (O_3-8 h) contributes to an increased risk of asthma attacks in children aged 0–14 (24). Short-term ozone exposures in urban areas (New York City, US) were significantly associated with asthma-related emergency department visits and hospitalisations in children aged 5–17 years (25). Human exposure to tropospheric ozone could intensify the severity of symptoms of respiratory tract infection like coughing or throat irritation (26).

Immune-dependent inflammation due to ozone exposure is also observed in the cardiovascular system (22). Increased levels of inflammatory cytokines, oxidative stress and immune-dependent inflammation of the endothelium could lead to a higher risk of cardiovascular diseases (CVD) due to ozone exposure (22, 27). Long-term exposure of 96,955 patients to ozone (89.7 μg/m^3) was positively correlated with stroke, ischaemic heart disease and overall cardiovascular diseases (28). Long-term exposure to ozone was, however, also found to have inverse associations with CVD and respiratory mortality (29). The connection between short-term ozone exposure and cardio-respiratory mortality together with out-of-hospital cardiac arrest was evaluated for both first-time acute myocardial infarction patients and previously hospitalised patients (30, 31). Ozone exposure could be significantly associated with an increase in the number of years of life lost due to hypertension. A higher association was observed in elderly individuals born in autumn months. A statistically significant association was found for 0.68 year of life lost for every 10 μg/m^3 increase in the ozone level (32).

A surface ozone level above 30 μg/m^3 could cause epigenetic alterations and genotoxic effects, resulting in potentially severe health effects (33).

In vitro and *in vivo* tests confirmed that the ocular surface (i.e., its epithelial cells), which is directly exposed for external examination, could be easily damaged by ground-level ozone (34).

Ozone regulations

According to the WHO, the daily concentration of O_3 (daily maximum 8-h average) should not exceed 100 μg/m^3 and a 0.3–0.5% growth in daily mortality has been observed for every 10 μg/m^3 increase in 8-h ozone concentrations above 70 μg/m^3 (35, 36).

It is important to note that the WHO guidelines are more restrictive than those implemented in the European Union.

The European Commission has recommended the acceptable level for O_3 concentration as 120 μg/m^3 (maximum daily 8-h mean), with permitted exceedances of up to 25 days per year (37).

The European Ozone Regulation No. 1005/2009 on ozone-depleting substances layer is a key piece of legislation in European Union (38). The act has two objectives: to implement the obligations of the Montreal Protocol on substances that deplete the O_3 layer and to provide a higher level of protection in certain areas in the EU. The act is the basis for other European Commission regulations; Commission Regulation No. 537/2011 (39), Commission Regulation No. 291/2011 (40) and Commission Decision No. 2010/372/EU (41). The rules regarding the location and number of sampling points for air quality assessment, reference ozone measurement methods and data validation are regulated by Directive 2015/1480/EC of 28 August 2015 (37, 42). Issues of mutual exchange of information and reporting on air quality are regulated by the Commission Implementing Decision of 12 December 2011, which implemented Directives 2004/107/EC and 2008/50/EC of the European Parliament and Council (No. C/2011/9068) (43).

Based on the EU directives in Poland, the Regulation of the Ministry of Environment (44) clearly defines the terms assigned to individual ozone concentration levels by introducing the notion of target level, information level and alert level.

Target level is the level to which a substance in the air must decline within a certain period of time in order to reduce, avoid or prevent the harmful effects of the substance on human health and the environment. The target O_3 level for a maximum daily average of 8 h is 120 μg/m^3, with permissible exceedances for 25 days a year.

Information level is the level of a substance in the air above which there is a danger to human health deriving from short-term exposure. The information level for ozone-1-h average is 180 μg/m^3.

Alert level is the level of a substance in the air above which there is a high risk to the health of the local population from short-term exposure to pollutants, and about which European Union States should take sudden action. The alarm level for O_3-1-h average is 240 μg/m^3.

If the O_3 concentration in the air exceeds the alert level, it has a negative impact on human health. In such situations, vulnerable people, especially those affected by respiratory diseases, also children and the elderly, should avoid staying outside, while healthier people should reduce staying outside to the minimum.

Results

The study showed that the strongest influencing factors for O_3 values are air temperature (TA) and total radiation (GLR), with each showing a high correlation with ozone concentration (Tables 1–3). The regression coefficients (β coefficients) of TA and GLR in the multiple regression model were higher than those of the other variables.

NO and NO_2 had a dual effect on O_3 concentration, causing an increase in ozone concentration at low NO and NO_2 concentrations and a decrease in ozone concentration at higher NO and NO_2 concentrations. From January to June, the level decreased and the O_3 concentration increased in all selected measuring stations, however, from July to December, there was an increase in the level of NO_2 and a decrease in the concentration of O_3, a similar relationship occurred for NO and O_3. As an example we present graphically the concentration level of O_3, NO_2 and NO in 2014 comparing to 2017 for the station located in Katowice (Figures 1–6). The relationships were

TABLE 1 The bilateral linear relationship between NO, NO_2, wind direction, wind speed, total radiation and air temperature on O3 values in Bielsko Biała measuring station PL0234A.

Measuring station	Year	Semester	R (O_3 vs. Data)	R (O_3 vs. NO)	R (O_3 vs. NO_2)	R (O_3 vs. WD)	R (O_3 vs. WS)	R (O_3 vs. GLR)	R (O_3 vs. TA)	R [O_3 vs. O_3(d-1)]
PL0234A	2009	I–VI	0.62	−0.62	−0.74	−0.13	0.25	MD	0.7	0.79
PL0234A	2009	VII–XII	−0.68	−0.63	−0.71	0.01	0.18	MD	0.78	0.79
PL0234A	2010	I–VI	0.55	−0.54	−0.72	−0.06	0.34	MD	0.68	0.77
PL0234A	2010	VII–XII	−0.63	−0.44	−0.6	−0.05	−0.03	MD	0.7	0.78
PL0234A	2011	I–VI	0.62	−0.56	−0.68	−0.17	0.1	MD	0.66	0.76
PL0234A	2011	VII–XII	−0.59	−0.56	−0.69	−0.13	0.12	MD	0.8	0.74
PL0234A	2012	I–VI	0.75	−0.68	−0.69	−0.17	−0.1	MD	0.83	0.79
PL0234A	2012	VII–XII	MD	−0.6	−0.63	−0.01	−0.08	MD	0.88	0.84
PL0234A	2013	I–VI	0.56	−0.63	−0.67	MD	MD	MD	MD	0.81
PL0234A	2013	VII–XII	−0.63	−0.57	−0.69	MD	MD	MD	MD	0.79
PL0234A	2014	I–VI	0.55	−0.6	−0.65	0.34	0.13	MD	0.76	0.7
PL0234A	2014	VII–XII	−0.54	−0.62	−0.75	0.38	0.3	MD	0.55	0.76
PL0234A	2015	I–VI	0.48	−0.61	−0.64	0.12	0.25	MD	0.67	0.69
PL0234A	2015	VII–XII	−0.72	−0.51	−0.64	−0.05	0.07	MD	0.86	0.85
PL0234A	2016	I–VI	0.66	−0.53	−0.74	−0.1	0.06	MD	0.76	0.72
PL0234A	2016	VII–XII	−0.56	−0.52	−0.69	0.14	0.14	MD	0.74	0.72
PL0234A	2017	I–VI	0.63	−0.63	−0.75	0.23	0.33	MD	0.73	0.76
PL0234A	2017	VII–XII	−0.62	−0.65	−0.7	0.01	0.13	MD	0.76	0.78

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

TABLE 2 The bilateral linear relationship between NO, NO_2, wind direction, wind speed, total radiation and air temperature on O3 values in Katowice measuring station PL0008A.

Measuring station	Year	Semester	R (O_3 vs. Data)	R (O_3 vs. NO)	R (O_3 vs. NO_2)	R (O_3 vs. WD)	R (O_3 vs. WS)	R (O_3 vs. GLR)	R (O_3 vs. TA)	R (O_3 vs. O_3 [d-1)]
PL0008A	2009	I–VI	0.65	−0.49	MD	−0.07	0.07	MD	0.66	0.81
PL0008A	2009	VII–XII	−0.73	−0.4	MD	0.05	−0.03	MD	0.77	0.82
PL0008A	2010	I–VI	0.64	−0.47	−0.62	0.19	0.15	0.69	0.64	0.7
PL0008A	2010	VII–XII	−0.76	−0.44	−0.51	0.11	−0.02	0.77	0.76	0.8
PL0008A	2011	I–VI	0.72	−0.43	−0.56	−0.07	0.02	0.69	0.62	0.76
PL0008A	2011	VII–XII	−0.68	−0.43	−0.44	−0.29	−0.2	0.81	0.81	0.8
PL0008A	2012	I–VI	0.78	−0.46	−0.61	−0.14	−0.06	0.78	0.78	0.8
PL0008A	2012	VII–XII	−0.84	−0.47	−0.46	0.13	−0.09	0.86	0.85	0.89
PL0008A	2013	I–VI	0.64	MD	MD	MD	MD	MD	MD	MD
PL0008A	2013	VII–XII	−0.65	−0.42	−0.36	−0.01	−0.06	0.73	0.78	0.79
PL0008A	2014	I–VI	0.7	−0.37	−0.45	0.16	−0.21	0.76	0.74	0.79
PL0008A	2014	VII–XII	−0.62	−0.44	−0.4	−0.02	0.28	0.75	0.55	0.71
PL0008A	2015	I–VI	0.69	−0.39	−0.51	0.31	0.36	0.78	−0.22	0.79
PL0008A	2015	VII–XII	−0.77	−0.41	−0.37	−0.19	−0.01	0.83	MD	0.84
PL0008A	2016	I–VI	0.72	−0.46	−0.5	−0.15	−0.01	0.78	0.74	0.75
PL0008A	2016	VII–XII	MD	−0.43	−0.31	0.13	−0.01	0.75	0.76	0.8
PL0008A	2017	I–VI	0.76	−0.51	−0.71	0.03	0.37	0.76	0.75	0.81
PL0008A	2017	VII–XII	−0.72	−0.45	−0.41	−0.12	0.08	0.79	0.8	0.81

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

TABLE 3 The bilateral linear relationship between NO, NO_2, wind direction, wind speed, total radiation and air temperature on O3 values in Złoty Potok measuring station PL0243A.

Measuring station	Year	Semester	R (O_3 vs. Data)	R (O_3 vs. NO)	R (O_3 vs. NO_2)	R (O_3 vs. WD)	R (O_3 vs. WS)	R (O_3 vs. GLR)	R (O_3 vs. TA)	R (O_3 vs. O_3 [d-1)]
PL0243A	2009	I–VI	0.62	−0.23	−0.43	0.01	0.02	MD	0.69	0.77
PL0243A	2009	VII–XII	−0.73	−0.45	−0.63	0.18	−0.07	MD	MD	0.8
PL0243A	2010	I–VI	0.28	−0.42	−0.36	0.001	0.25	MD	MD	0.67
PL0243A	2010	VII–XII	−0.69	−0.5	−0.57	0.09	0.04	MD	MD	0.78
PL0243A	2011	I–VI	0.62	−0.38	−0.63	−0.18	−0.26	MD	MD	0.67
PL0243A	2011	VII–XII	−0.67	−0.44	−0.72	−0.73	−0.26	MD	0.82	0.74
PL0243A	2012	I–VI	0.64	−0.34	−0.49	−0.24	0.48	MD	0.66	0.74
PL0243A	2012	VII–XII	−0.79	−0.57	−0.56	0.13	−0.08	MD	0.84	0.84
PL0243A	2013	I–VI	0.41	−0.48	−0.39	MD	MD	MD	MD	0.76
PL0243A	2013	VII–XII	−0.67	−0.45	−0.7	−0.37	0.24	0.26	0.75	0.7
PL0243A	2014	I–VI	0.53	−0.3	−0.5	0.1	0.03	0.74	0.58	0.74
PL0243A	2014	VII–XII	−0.65	−0.4	−0.54	0.2	0.14	0.74	0.64	0.78
PL0243A	2015	I–VI	0.6	−0.5	−0.5	0.1	−0.06	0.78	0.67	0.77
PL0243A	2015	VII–XII	−0.84	−0.4	−0.6	0.02	−0.25	0.82	0.88	0.89
PL0243A	2016	I–VI	0.69	−0.64	−0.7	0.06	−0.08	0.8	0.66	0.76
PL0243A	2016	VII–XII	−0.61	−0.49	−0.53	0.2	−0.04	0.72	0.76	0.8
PL0243A	2017	I–VI	0.6	−0.44	−0.56	0.14	0.28	0.69	0.62	0.68
PL0243A	2017	VII–XII	−0.65	−0.5	−0.6	0.06	−0.02	0.79	0.78	0.71

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

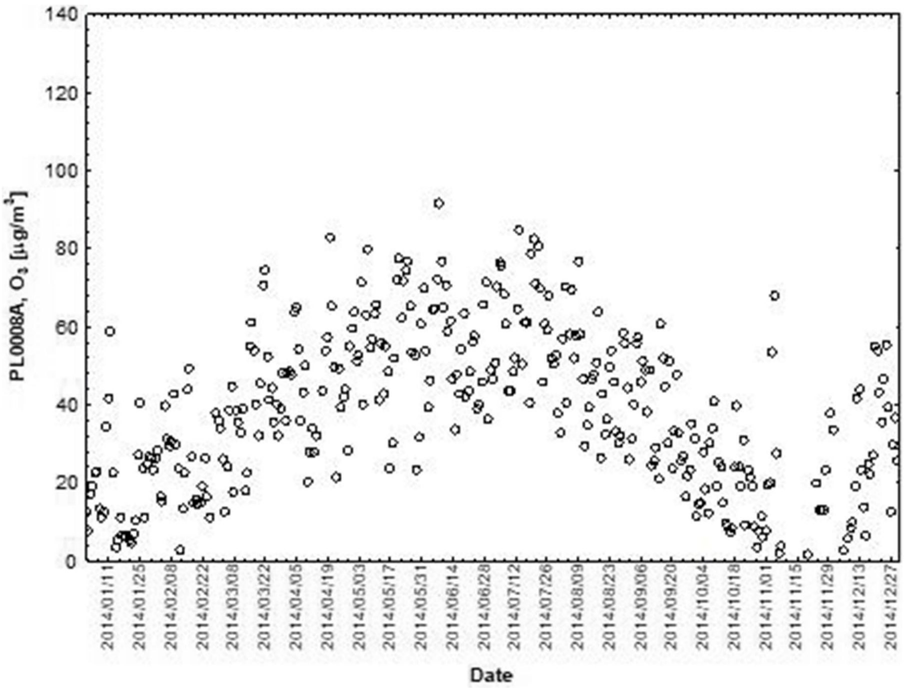

FIGURE 1
The concentration level of O_3 (µg/m^3) in 2014, PL0008A.

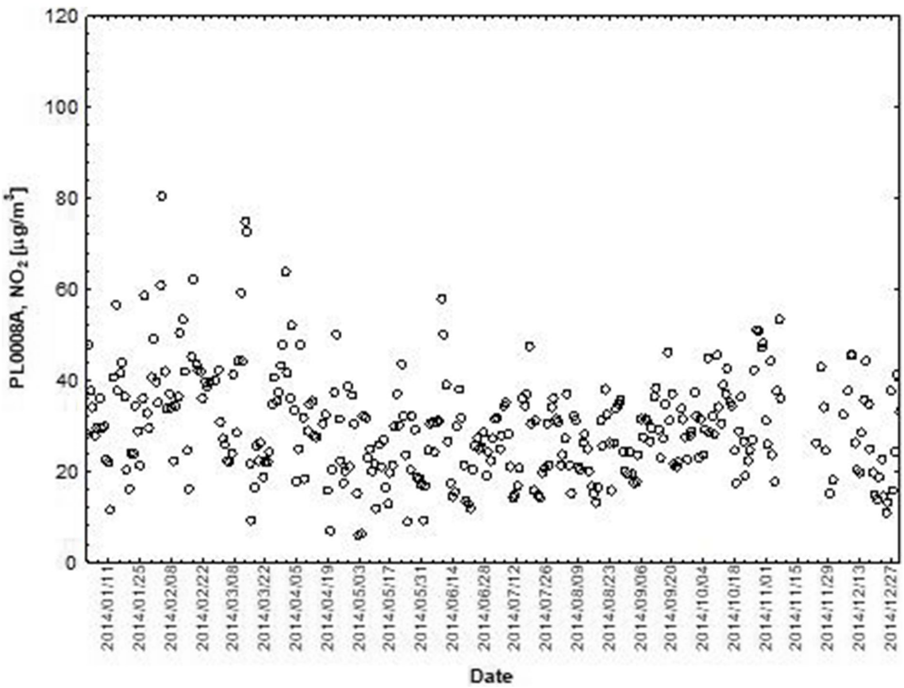

FIGURE 2
The concentration level of NO_2 (μg/m³) in 2014, PL0008A, author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

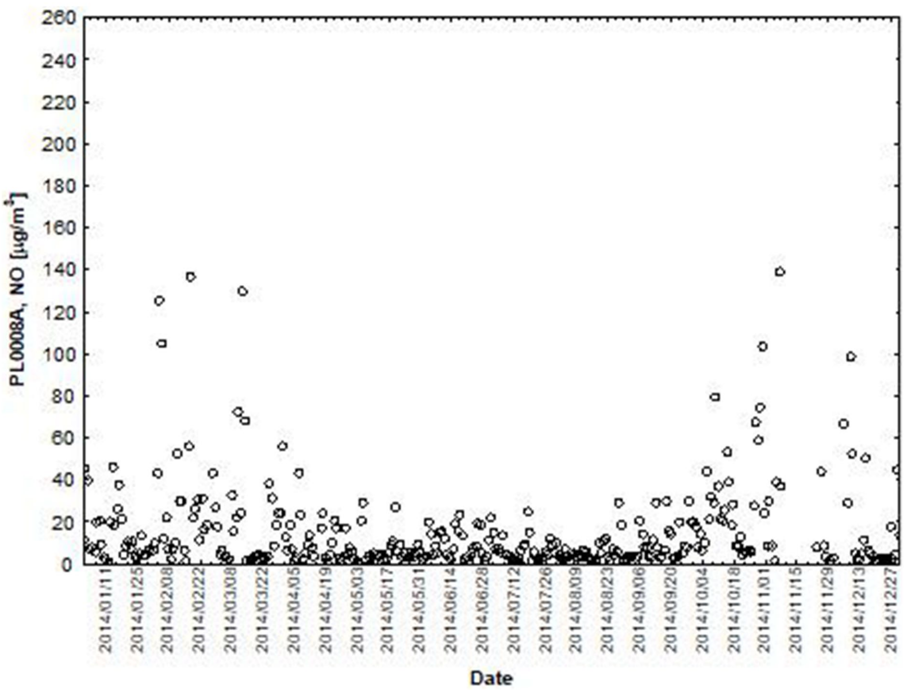

FIGURE 3
The concentration level of NO (μg/m³) in 2014, PL0008A author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

confirmed by the values of the standardised regression coefficient β in the multiple regression model (Tables 4–6) and the R-part coefficient of partial correlation (Tables 7–9). We noted that the direction of the wind had very little effect on the concentration of O_3. The influence of wind speed on O_3 content was also small, but stronger than the wind direction. This can be seen from the values of the correlation

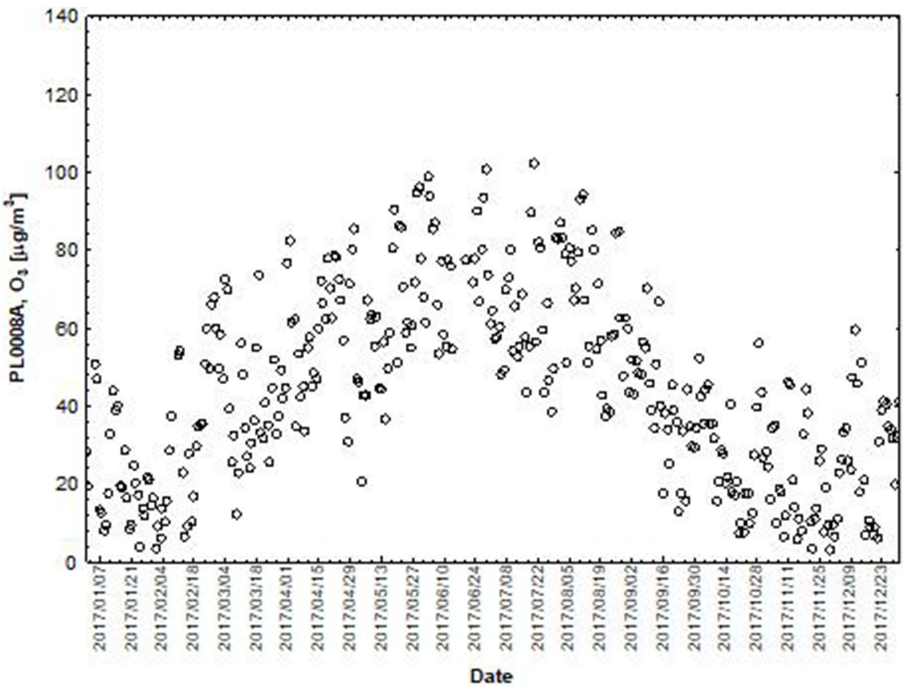

FIGURE 4
The concentration level of O_3 (μg/m³) in 2017, PL0008A, author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

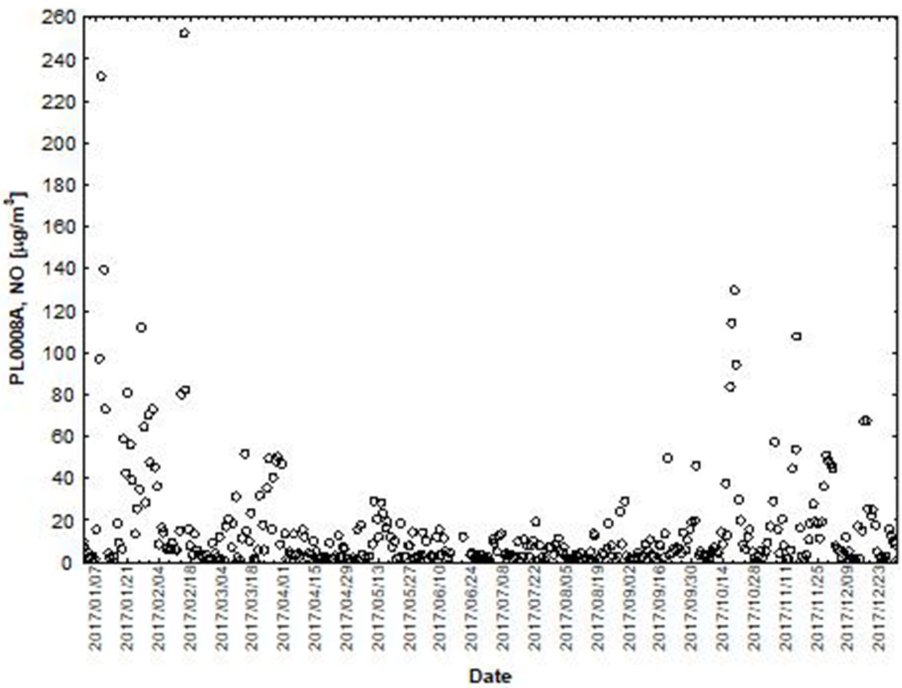

FIGURE 5
The concentration level of NO_2 (μg/m³) in 2017, PL0008A, author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

coefficient R and the R-part (Tables 1–3, 7–9) for the statistical characteristics O_3 and WS in comparison to O_3 and WD. The values of the standardised regression coefficient β1 (Tables 4–6) confirm the above results.

Discussion

The concentration of ozone near the earth's surface depends on the processes of ozone formation and dispersion. The process of

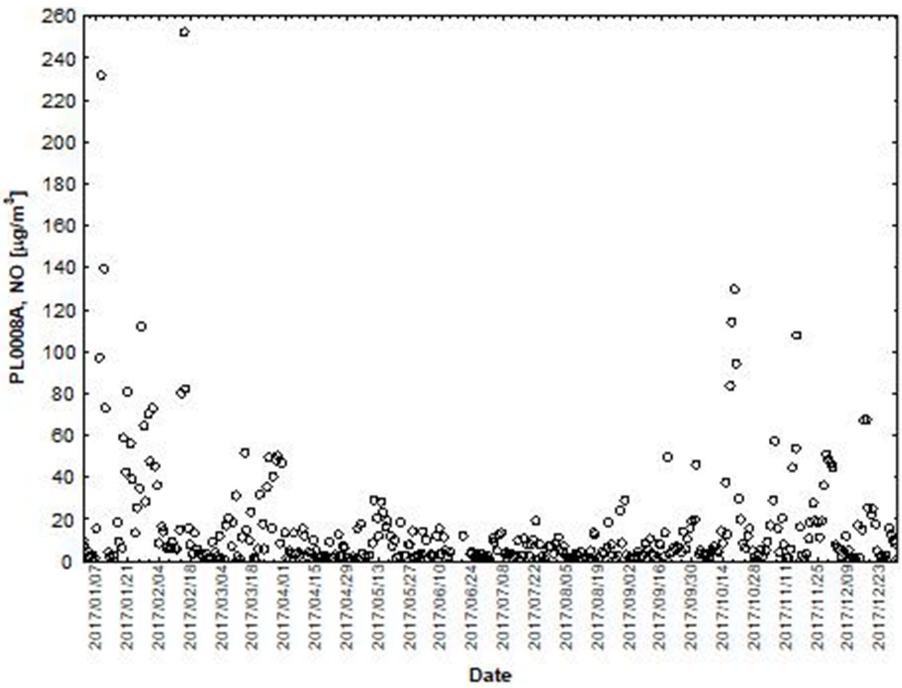

FIGURE 6
The concentration level of NO (μg/m^3) in 2017, PL0008A, author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

TABLE 4 The value of the standardised regression coefficient β of NO, NO_2, wind direction, wind speed, total radiation and air temperature on O_3 values in Bielsko Biała measuring station PL0234A.

Measuring station	Year	Semester	(NO)	(NO_2)	(WD)	(WS)	(GLR)	(TA)	[O_3(d-1)]
PL0234A	2009	I–VI	MD	−0.31	MD	0.1	MD	0.21	0.47
PL0234A	2009	VII–XII	−0.07	−0.2	−0.07	0.14	MD	0.35	0.42
PL0234A	2010	I–VI	MD	−0.21	−0.1	0.21	MD	0.27	0.46
PL0234A	2010	VII–XII	MD	−0.17	MD	0.07	MD	0.21	0.56
PL0234A	2011	I–VI	−0.16	−0.25	−0.13	MD	MD	0.14	0.44
PL0234A	2011	VII–XII	MD	−0.21	−0.13	0.15	MD	0.51	0.2
PL0234A	2012	I–VI	−0.25	MD	−0.14	MD	MD	0.41	0.33
PL0234A	2012	VII–XII	−0.09	MD	−0.11	0.17	MD	0.64	0.32
PL0234A	2013	I–VI	MD	MD	MD	MD	MD	MD	MD
PL0234A	2013	VII–XII	MD	MD	MD	MD	MD	MD	MD
PL0234A	2014	I–VI	−0.18	MD	MD	0.21	MD	0.54	0.28
PL0234A	2014	VII–XII	MD	−0.39	0.11	0.09	MD	0.13	0.45
PL0234A	2015	I–VI	−0.17	−0.06	MD	0.27	MD	0.43	0.33
PL0234A	2015	VII–XII	0.07	−0.25	MD	0.07	MD	0.44	0.41
PL0234A	2016	I–VI	0.07	−0.48	−0.07	MD	MD	0.22	0.37
PL0234A	2016	VII–XII	MD	−0.12	0.11	0.24	MD	0.49	0.38
PL0234A	2017	I–VI	MD	−0.25	MD	0.18	MD	0.36	0.32
PL0234A	2017	VII–XII	−0.11	−0.14	0.11	0.21	MD	0.47	0.33

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

ozone formation depends mainly on ozone precursors, while ozone dispersion depends on meteorological conditions. In recent years, tropospheric ozone levels in many parts of the world have shown significant regional and global responses to meteorological (climatic) changes (45). Our research shows that temperature and radiation are important factors that strongly affect the level of O_3

TABLE 5 The value of the standardised regression coefficient β of NO, NO_2, wind direction, wind speed, total radiation and air temperature on O_3 values in Katowice measuring station PL0008A.

Measuring station	Year	Semester	(NO)	(NO_2)	(WD)	(WS)	(GLR)	(TA)	[O_3(d-1)]
PL0008A	2009	I–VI	−0.14	MD	MD	0.18	0.52	MD	0.41
PL0008A	2009	VII–XII	−0.08	MD	0.04	0.17	0.49	0.1	0.41
PL0008A	2010	I–VI	MD	−0.28	0.06	0.21	0.48	MD	0.33
PL0008A	2010	VII–XII	MD	−0.19	0.07	0.12	0.5	MD	0.41
PL0008A	2011	I–VI	MD	−0.39	−0.06	0.04	0.43	MD	0.34
PL0008A	2011	VII–XII	0.09	−0.23	−0.16	0.28	0.48	0.26	0.3
PL0008A	2012	I–VI	MD	−0.3	−0.07	0.09	0.42	0.14	0.3
PL0008A	2012	VII–XII	−0.06	−0.05	MD	0.09	0.39	0.16	0.43
PL0008A	2013	I–VI	MD	MD	MD	MD	MD	MD	MD
PL0008A	2013	VII–XII	MD	−0.11	0.05	0.25	0.36	0.34	0.34
PL0008A	2014	I–VI	0.06	−0.26	MD	0.01	0.48	MD	0.45
PL0008A	2014	VII–XII	−0.06	−0.31	MD	MD	0.58	−0.06	0.35
PL0008A	2015	I–VI	−0.22	−0.21	0.09	0.3	0.16	MD	0.42
PL0008A	2015	VII–XII	MD	MD	MD	MD	MD	MD	MD
PL0008A	2016	I–VI	MD	−0.33	MD	0.09	0.58	MD	0.3
PL0008A	2016	VII–XII	MD	−0.11	0.07	0.24	0.4	0.25	0.38
PL0008A	2017	I–VI	0.24	−0.5	−0.05	0.13	0.44	MD	0.3
PL0008A	2017	VII–XII	MD	−0.21	−0.04	0.16	0.4	0.19	0.36

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

TABLE 6 The value of the standardised regression coefficient β of NO, NO_2, wind direction, wind speed, total radiation and air temperature on O_3 values in Złoty Potok measuring station PL0243A.

Measuring station	Year	Semester	(NO)	(NO_2)	(WD)	(WS)	(GLR)	(TA)	[O_3(d-1)]
PL0243A	2009	I–VI	−0.17	−0.08	0.1	0.18	MD	0.43	0.46
PL0243A	2009	VII–XII	MD	MD	MD	MD	MD	MD	MD
PL0243A	2010	I–VI	MD	MD	MD	MD	MD	MD	MD
PL0243A	2010	VII–XII	MD	MD	MD	MD	MD	MD	MD
PL0243A	2011	I–VI	MD	MD	MD	MD	MD	MD	MD
PL0243A	2011	VII–XII	MD	MD	MD	MD	MD	MD	MD
PL0243A	2012	I–VI	−0.3	MD	−0.11	0.39	MD	0.57	0.23
PL0243A	2012	VII–XII	MD	MD	MD	0.07	MD	0.49	0.47
PL0243A	2013	I–VI	MD	MD	MD	MD	MD	MD	MD
PL0243A	2013	VII–XII	MD	MD	MD	MD	MD	MD	MD
PL0243A	2014	I–VI	−0.11	−0.15	MD	0.23	0.58	MD	0.4
PL0243A	2014	VII–XII	−0.13	MD	0.11	0.28	0.54	MD	0.33
PL0243A	2015	I–VI	−0.2	MD	0.05	0.22	0.51	MD	0.42
PL0243A	2015	VII–XII	−0.1	MD	MD	0.05	0.21	0.33	0.45
PL0243A	2016	I–VI	−0.21	−0.09	0.14	0.16	0.58	−0.08	0.3
PL0243A	2016	VII–XII	−0.05	−0.17	0.13	0.21	0.34	0.12	0.43
PL0243A	2017	I–VI	−0.23	MD	−0.04	0.24	0.58	−0.13	0.37
PL0243A	2017	VII–XII	−0.19	−0.09	0.07	0.18	0.46	0.17	0.24

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

TABLE 7 The partial correlation of NO_2, wind direction, wind speed, total radiation and air temperature and O_3 values in Bielsko Biała measuring station PL0234A.

Measuring station	Year	Semester	R (O_3 vs. Data)	R_{part} (NO)	R_{part} (NO_2)	R_{part} (WD)	R_{part} (WS)	R_{part} (GLR)	R_{part} (TA)	R_{part} [O_3(d-1)]
PL0234A	2009	I–VI	0.62	0.47	0.34	0.62	0.69	MD	0.01	0.24
PL0234A	2009	VII–XII	−0.68	−0.57	−0.52	−0.68	−0.77	MD	−0.06	−0.33
PL0234A	2010	I–VI	0.55	0.43	0.19	0.57	0.67	MD	−0.12	0.24
PL0234A	2010	VII–XII	−0.63	−0.53	−0.35	−0.63	−0.66	MD	0.02	−0.28
PL0234A	2011	I–VI	0.62	0.53	0.39	0.64	0.68	MD	0.18	0.27
PL0234A	2011	VII–XII	−0.59	−0.48	−0.42	−0.62	−0.65	MD	0.2	−0.29
PL0234A	2012	I–VI	0.75	0.68	0.69	0.75	0.8	MD	0.24	0.4
PL0234A	2012	VII–XII	MD	MD	MD	MD	MD	MD	MD	MD
PL0234A	2013	I–VI	0.56	0.39	0.31	MD	MD	MD	MD	0.22
PL0234A	2013	VII–XII	−0.63	−0.51	−0.49	MD	MD	MD	MD	−0.3
PL0234A	2014	I–VI	0.55	0.4	0.42	0.52	0.65	MD	−0.09	0.26
PL0234A	2014	VII–XII	−0.54	−0.37	−0.31	−0.51	−0.69	MD	0.02	−0.18
PL0234A	2015	I–VI	0.48	0.28	0.31	0.51	0.65	MD	−0.22	0.24
PL0234A	2015	VII–XII	−0.72	−0.67	−0.67	−0.72	−0.78	MD	0.01	−0.29
PL0234A	2016	I–VI	0.66	0.56	0.49	0.66	0.77	MD	0.03	0.36
PL0234A	2016	VII–XII	−0.56	−0.45	−0.32	−0.59	−0.69	MD	0.23	−0.24
PL0234A	2017	I–VI	0.63	0.46	0.37	0.62	0.78	MD	−0.04	0.3
PL0234A	2017	VII–XII	−0.62	−0.49	−0.5	−0.62	−0.75	MD	0.15	−0.27

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

TABLE 8 The partial correlation of NO_2, wind direction, wind speed, total radiation, air temperature and O_3 values in Katowice measuring station PL0008A.

Measuring station	Year	Semester	R (O_3 vs. Data)	R_{part} (NO)	R_{part} (NO_2)	R_{part} (WD)	R_{part} (WS)	R_{part} (GLR)	R_{part} (TA)	R_{part} [O_3(d-1)]
PL0008A	2009	I–VI	0.65	0.59	MD	0.67	0.71	0.2	0.23	0.26
PL0008A	2009	VII–XII	−0.73	−0.69	MD	−0.73	−0.76	−0.1	−0.18	−0.34
PL0008A	2010	I–VI	0.64	0.57	0.46	0.63	0.72	0.29	0.19	0.34
PL0008A	2010	VII–XII	−0.76	−0.72	−0.69	−0.76	−0.78	−0.35	−0.25	−0.38
PL0008A	2011	I–VI	0.72	0.69	0.67	0.72	0.74	0.39	0.46	0.38
PL0008A	2011	VII–XII	−0.68	−0.63	−0.63	−0.68	−0.73	−0.17	0.1	−0.28
PL0008A	2012	I–VI	0.78	0.77	0.75	0.78	0.82	0.43	0.38	0.41
PL0008A	2012	VII–XII	−0.84	−0.81	−0.81	−0.83	−0.85	−0.36	−0.34	−0.36
PL0008A	2013	I–VI	0.64	0.62	0.64	MD	MD	MD	MD	0.27
PL0008A	2013	VII–XII	−0.65	−0.63	−0.66	−0.65	−0.72	−0.07	0.07	−0.31
PL0008A	2014	I–VI	0.7	0.69	0.65	0.69	0.69	0.27	0.25	0.33
PL0008A	2014	VII–XII	−0.62	−0.57	−0.66	−0.55	−0.52	0.1	−0.19	−0.29
PL0008A	2015	I–VI	0.69	0.66	0.65	0.67	0.66	0.2	−0.22	0.32
PL0008A	2015	VII–XII	−0.77	−0.75	−0.76	−0.76	−0.8	−0.15	MD	−0.36
PL0008A	2016	I–VI	0.72	0.69	0.7	0.72	0.8	0.23	0.22	0.38
PL0008A	2016	VII–XII	MD	MD	MD	MD	MD	MD	MD	MD
PL0008A	2017	I–VI	0.76	0.71	0.66	0.76	0.81	0.35	0.33	0.39
PL0008A	2017	VII–XII	−0.72	−0.69	−0.72	−0.71	−0.79	−0.17	−0.02	−0.32

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

TABLE 9 The partial correlation of NO_2, wind direction, wind speed, total radiation, air temperature and O_3 values in Złoty Potok measuring station PL0243A.

Measuring station	Year	Semester	R (O_3 vs. Data)	R_{part} (NO)	R_{part} (NO_2)	R_{part} (WD)	R_{part} (WS)	R_{part} (GLR)	R_{part} (TA)	R_{part} [O_3(d-1)]
PL0243A	2009	I–VI	0.62	0.7	0.52	0.63	0.64	MD	−0.09	0.26
PL0243A	2009	VII–XII	−0.73	−0.71	−0.55	−0.72	−0.75	MD	MD	−0.35
PL0243A	2010	I–VI	0.28	0.07	0.02	0.28	0.36	MD	MD	0.11
PL0243A	2010	VII–XII	−0.69	−0.55	−0.4	−0.69	−0.72	MD	MD	−0.33
PL0243A	2011	I–VI	0.62	0.6	0.33	0.61	0.57	MD	MD	0.23
PL0243A	2011	VII–XII	−0.67	−0.69	−0.5	MD	MD	MD	0.11	−0.33
PL0243A	2012	I–VI	0.64	0.64	0.55	0.2	0.41	MD	0.26	0.34
PL0243A	2012	VII–XII	−0.79	−0.7	−0.69	−0.79	−0.81	MD	−0.19	−0.37
PL0243A	2013	I–VI	0.41	0.54	0.47	MD	MD	MD	MD	0.18
PL0243A	2013	VII–XII	−0.67	−0.58	−0.42	MD	MD	MD	MD	−0.3
PL0243A	2014	I–VI	0.53	0.5	0.26	0.54	0.57	0.04	0.15	0.23
PL0243A	2014	VII–XII	−0.65	−0.68	−0.49	−0.64	−0.76	−0.07	−0.2	−0.3
PL0243A	2015	I–VI	0.6	0.49	0.46	0.6	0.65	0.07	0.08	0.27
PL0243A	2015	VII–XII	−0.84	−0.82	−0.74	−0.84	−0.84	−0.42	−0.4	−0.37
PL0243A	2016	I–VI	0.69	0.52	0.36	0.69	0.71	0.14	0.31	0.35
PL0243A	2016	VII–XII	−0.61	−0.51	−0.42	−0.62	−0.63	−0.08	0.21	−0.25
PL0243A	2017	I–VI	0.6	0.53	0.4	0.59	0.66	0.13	0.16	0.32
PL0243A	2017	VII–XII	−0.65	−0.62	−0.47	−0.65	−0.7	−0.04	0.12	−0.34

MD, missing data; author's own study based on data of Regional Environmental Protection Inspectorate in Katowice.

concentration. Research conducted in Nicosia, Cyprus form 2007 to 2014 provided similar results. It examined how ozone levels changed during a heat wave (defined as 4 consecutive days with a daily maximum temperature above 39°C) compared to summer conditions without a heat wave. There was a medium to strong positive correlation between ozone and temperature, as well as between ozone and daytime UVA and UVB radiation, which increased by about 35% in heat wave conditions (46). The results of another study, using data from 17 measurement stations in Sydney, Australia, showed that during periods of extreme heat, the impact of temperature on air quality was as large as the impact of biogenic emissions (eucalyptus trees are key to biogenic emissions in Australia) (47). Studies carried out in Lithuania showed that the concentration of ozone increased with increasing temperature; however, ozone concentration was not significantly related to relative air humidity, and a decrease in ozone concentration was observed during the rainy season (48). Similarly, in a study conducted in the Ciuc Basin, Romania, the intensity of sunlight and increase in temperature had a significant impact on the increase in ozone pollution (49). The relationship between the maximum daily temperature and changes in ground-level ozone concentrations was investigated in the state of Terengganu, Malaysia, using data from 2000 to 2010 (excluding 2008); measurements made at two stations representing urban and industrial areas were analysed. The study found a positive linear correlation between the maximum daily temperature and the maximum daily ozone concentration, with levels higher in the industrial area than in the urban area (50). The Terengganu results also confirmed that temperature played a key role in shaping ground-level ozone concentrations. In addition, ozone concentrations were highest in dry and warm air masses during the southwest monsoon and were usually associated with haze episodes in the Malaysian peninsula (50). Similarly, the direct relationship between temperature and ozone was confirmed by studies carried out in Porto (51).

However, not all studies provide such unambiguous results. For example, studies conducted in eastern Texas showed that the temperature in this area rarely had any effect on ozone concentrations, perhaps due to the small spatial variation (52).

Measurements of the solar ultraviolet index (UVI) in Arica, Chile from 2006 to 2015 indicated that 16.6% of the maximum daily UVI measured at solar noon during the summer season was high and very high (8 < UVI < 10) while 83.1% of the measured maximum daily UVI was extreme (> 11 UVI), according to the WHO scale (53). Hourly and daily changes in ground-level ozone were also analysed in relation to meteorological parameters (UVB radiation) in the Baltic Sea region in Lithuania. A close correlation was established between ground-level ozone concentration and UVB radiation intensity (48).

In our research, we also tried to estimate the influence of wind strength and direction on ozone concentration. The influence of wind speed on the O_3 level was small but stronger than the influence of wind direction. A similar analysis in Cyprus showed a slight decrease in wind speed during heat waves, leading to stagnant weather conditions. The same study analysed a diurnal cycle of wind speeds that peaked at noon when ozone levels were highest (46). In studies conducted in Porto, the highest concentrations of O_3 were observed at high wind speeds (51). On the other hand, studies carried out in Lithuania showed that the dominance of wind direction had a significant impact on the variability of ozone concentrations. An unusual situation was observed in terms of wind dominance, namely the wind from the continent was twice as frequent as the wind from the sea. Meteorological parameters such as relative humidity, wind speed and direction had different effects on the ozone concentration at the ground level of the atmosphere. Wind direction had the greatest impact on the variability of ozone concentration. Higher concentrations of ozone in the boundary layer of the atmosphere were found when the wind was blowing from the Baltic towards the continent, perhaps due to the low rate of ozone decomposition (48). Modelling and statistical analyses described three important variables that could affect O_3 concentration, *viz.*: wind speed, temperature and NO_2 concentration (51).

Our research showed that from January to June in all the measurement stations, the level of NO_2 and NO decreased while the concentration of O_3 increased. In contrast, we observed an increase in NO_2 and NO levels but a decrease in O_3 concentrations from July to December. Similar results were obtained in a study conducted in 2005–2010 for four different types of stations in central Poland. On the basis of daily averages, it was found that the seasonal maximum of ozone occurred in spring and early summer, and the minimum in autumn (54). In addition, the same study showed that the lowest ozone concentration occurred in the early morning and the maximum in the afternoon. Moreover, ozone concentrations differed significantly on weekends and weekdays. The measurement results also showed that the concentration of surface ozone was higher in rural areas than in urban or suburban areas (54).

In the above-mentioned study conducted in Cyprus during the heat wave period, a negative correlation of NOx concentration with ozone levels was observed, increasing during the heat wave conditions, leading to steeper ozone minima in the morning (46). Also, the research carried out in Porto (Jan 2012–Dec 2013) confirmed unequivocally that the highest O_3 concentrations were observed for low NOx concentrations (51).

The results of the East Texas study showed that the spatial mean of ground-level ozone concentrations was strongly related to the spatial mean of NO_2 concentrations, although the spatial distributions of NO_2 and ozone concentrations were not uniform throughout the study period due to uneven wind speeds and directions. Thus, this study confirmed that wind speed and direction also played a significant role in ozone spread (52). Interesting conclusions were provided by the results of research on the sources of surface ozone in Switzerland in the summer (June–August) of 2018, one of the warmest years in Europe. The largest share in the formation of surface ozone was border import (65%), followed by off-road traffic (11%) and road traffic (8%). Compared to 2000, lower emissions were recorded in 2018, leading to a reduction in ozone levels in most areas of the country with the exception of some urban areas, with the largest decrease being in emissions due to road traffic. The results indicated that reduced anthropogenic emissions were the main reason for the reduction of high ozone concentrations during the hot summer in Switzerland (55). The so-called border import is quite important in many countries, especially transit countries. In Romania, for instance, the air masses flowing through the Ciuc Basin in 2008–2017 came from neighbouring Central and Eastern European countries. Local sources of NOx emissions in this region are car exhaust fumes emitted in the form of NO and burning biomass in cold winter periods (49).

Currently, ozone probes, satellites and commercial aircraft provide information on the distribution of tropospheric ozone. Long-term surface observations have limited global spatial coverage, but data from various locations indicate that ozone concentrations in the 21st century are higher than in the 1970s and 1980s, and we have seen an increase in tropospheric ozone concentrations since the 1990s. Some highly polluted regions of East Asia have seen increases in ozone concentrations since 2000, while many other regions have seen decreases, so there is no clear global trend in surface ozone concentrations since 2000. Satellite data can estimate the global effect of long-wave ozone radiation, but this assessment is difficult due to the limited number of observations in places where the radiation effect is greatest (56). Extensive air quality monitoring and analysis has shown that reductions in ozone precursor emissions have reduced extreme levels of ozone across much of Europe, both in rural and urban areas, as well as in North America (57). Between 2000 and 2017, rural areas across Europe showed an overall decline in ozone concentrations while highly urbanised areas showed an increase in ozone (58, 59).

Recent modelling projections predict that future climate change will increase surface ozone levels in polluted regions and decrease global ozone levels due to stronger chemical ozone loss (45). However, uncertainties in climate–ozone responses and limitations in the capabilities of model analyses still pose challenges to such predictions. Experts highlight the growing importance of future increases in stratosphere–troposphere exchange in modulating tropospheric ozone, which can largely offset the predicted chemical loss of tropospheric ozone load. They also highlight that uncertainties in isoprene chemistry, biogenic emissions associated with changing CO_2 levels and vegetation, and interactions between ozone and vegetation can greatly influence surface ozone levels and, consequently, climate change (45). Our results will contribute to more targeted environmental policies and improve the health risk assessment of the effects of ozone pollution on local populations.

Conclusion

The research shows that in the analysed years for selected measuring stations, the NO and NO_2 concentrations had a dualistic effect on the O_3 concentration, leading to an increase in the O_3 concentration level at low concentrations and a decrease in the O_3 level at higher concentrations. The strongest factors influencing O_3 concentration are air temperature and total radiation. The local policy makers responsible for environmental policy should take it into consideration.

Limitations of the study

It should be emphasised that analysing the correlation between statistical characteristics is not tantamount to strictly comparing their physical and chemical properties and thus may lead to false conclusions, including the finding of illusory correlation, which indicates a relationship between variables when no relationship exists. The observed statistical relationships do not necessarily imply true cause-and-effect relationships between the components of the atmosphere.

Recommendations

Further studies are needed to explain the dual effect of NOx on O3 concentration and its dependence on atmospheric conditions.

Data availability statement

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

Author contributions

JK: Conceptualization, Investigation, Writing – original draft, Funding acquisition, Project administration. LD: Data curation, Methodology, Software, Validation, Writing – original draft. MG: Formal analysis, Project administration, Supervision, Writing – original draft.

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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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Prediction of respiratory diseases based on random forest model

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In recent years, the random forest model has been widely applied to analyze the relationships among air pollution, meteorological factors, and human health. To investigate the patterns and influencing factors of respiratory disease-related medical visits, this study utilized data on medical visits from urban areas of Tianjin, meteorological observations, and pollution data. First, the temporal variation characteristics of medical visits from 2013 to 2019 were analyzed. Subsequently, the random forest model was employed to identify the dominant influencing factors of respiratory disease-related medical visits and to construct a statistical forecasting model that relates these factors to the number of visits. Additionally, a predictive analysis of medical visits in Tianjin for the year 2019 was conducted. The results indicate the following: (1) From 2013 to 2019, the number of medical visits exhibited seasonal fluctuations, with a significant decline observed in 2017, which may be directly related to adjustments in hospital policies. (2) Among the meteorological factors, average temperature, relative humidity, precipitation, and ozone concentration significantly influenced the variation in medical visits, while wind speed, precipitation amount, and boundary layer height were of lesser importance. Furthermore, different linear relationships exist among the meteorological factors; specifically, meteorological factors show a negative correlation with pollutant elements, and there is a strong correlation among the pollutant factors. (3) When the number of medical visits ranged from 50 to 200, the predictions made by the random forest model closely matched the actual values, demonstrating strong predictive performance and the ability to effectively forecast daily variations in medical visits over extended periods, thus exhibiting good stability and generalization capability. (4) However, since the random forest model relies on a large amount of data for model validation, it has limitations in capturing extreme variations in medical visit numbers. Future research could address this issue by integrating different models to enhance predictive capabilities.

KEYWORDS

random forest, prediction, meteorological factors, human health, pollutant

1 Introduction

Over the past century, fossil fuel combustion and unequal, unsustainable energy and land use have caused a global temperature increase of 1.1°C above pre-industrial levels (1–3). This rise has led to more frequent and intense extreme weather events, along with increasingly severe impacts on nature and people in all regions. Further increases in global temperature are expected to intensify these hazards. More severe heatwaves, heavier rainfall, and other extreme weather events pose greater risks to human health and ecosystems. Extreme heat has resulted in deaths in every region. As the planet continues to warm, the negative effects of climate change on food and water security will grow. When these risks combine with other challenges, such as epidemics and conflicts, the situation becomes even harder to manage. The focus on loss and damage highlights that the most vulnerable people and ecosystems experience the greatest losses and damages (4).

A growing body of research shows that climate change is creating widespread health risks globally. It is intensifying heatwaves, increasing wildfires, raising flood risks, and worsening droughts (5). These changes contribute to higher rates of heat-related mortality, pregnancy complications, and cardiovascular diseases. As with many climate-related issues, the risks and hazards are most severe in regions with the least capacity to adapt (6, 7).

Hospitals worldwide have faced significant challenges due to extreme weather (8). Many are increasingly unprepared to handle storms, high temperatures, and other climate-related events that are becoming more frequent. Floods claimed the lives of COVID-19 patients at a hospital in Mexico (9). Severe flooding affected hospitals in India. Hospitals on the West Coast struggled to maintain indoor air quality during wildfires. Hurricanes damaged the roof of a rural hospital in Louisiana (10–12).

In recent years, as living standards have improved, health has become an important focus of daily life (13–15). The desire for better health and longer lives has become increasingly urgent. Traditional weather forecasts are no longer sufficient to meet public needs, leading to a growing demand for more specific and professional forecasting. Because of the strong link between meteorological conditions and health, it is essential to conduct in-depth research on medical meteorology (16, 17). This includes developing meteorological indicator systems and prediction models tailored to local health needs. Medical meteorological forecasting aims to help individuals take preventive measures and assist medical institutions in preparing for disease prevention and control in a more targeted and timely manner (18).

The relationship between the meteorological environment and human health is complex. It often follows a nonlinear pattern and is influenced by additional non-environmental factors. In recent years, the promotion and application of random forest models have significantly advanced the understanding of this correlation (19). Random forest is an algorithm designed to control the overfitting tendency of decision trees. It achieves this through bagging (bootstrap aggregation), which involves sampling the training set with replacement. This method effectively handles collinearity and interactions among variables, including other independent variables and external factors. It also compensates for missing or incomplete inputs, making it a flexible tool for analyzing the impact of intervention measures on air quality time series (20–23).

The random forest model is particularly useful when the number of explanatory variables is large, the relationship between the response and explanatory variables is unclear, or the response variable does not conform to specific distribution requirements (24). While relatively few studies have applied random forest models for prediction, existing research highlights their strong fitting performance. In China, medical meteorological forecasting is still in its early stages. Advancements in science and technology, along with increasing environmental awareness, are expected to drive further research in this area. These developments will likely promote the growth of medical meteorological forecasting and its broader practical applications (25).

Currently, research on predicting patient numbers using machine learning models and examining the effects of climate conditions (e.g., temperature, humidity, pressure, wind, and pollutants) on respiratory diseases primarily focuses on average monthly data and short-term forecasts. Most studies rely on ARIMA, GAM, and GLM models (26). However, these methods often struggle to capture the complexity of non-linear relationships and interactions among multiple environmental factors (27, 28). In contrast, ARIMA excels at modeling time series with strong temporal patterns, but its capacity to handle nonlinear relationships is limited, making it more suitable for univariate or low-dimensional datasets. GAM provides a balance between nonlinear modeling and interpretability, but it requires careful selection of smoothing functions and struggles with temporal dependencies without extensions. In the study of urban heatstroke found that the evaluation and indicate that the random forest model stands out among all the compared models with its smallest MSE, RMSE, and R^2 value closest to 1, which suggests that it has higher accuracy in predicting the number of heatstroke victims per day (29). Our study addresses these limitations by employing the Random Forest (RF) model, which is better equipped to handle these challenges. By doing so, we aim to improve predictive accuracy and deepen the understanding of how environmental variables influence respiratory health (30).

The random forest model offers several advantages over other statistical models and is particularly effective in fitting the nonlinear effects of meteorological factors (31–35). First, it accounts for interactions between variables and handles datasets with a large number of features efficiently. Second, by introducing double randomness—random sampling of training data and random selection of variable subsets—it enhances resistance to overfitting (36). Third, it is highly robust to missing values and outliers, reducing the influence of outliers by averaging the results of all regression trees. Fourth, it requires relatively few parameters for model construction. Finally, the model-building process inherently includes cross-validation, enhancing reliability (37). These features make the random forest model a powerful tool for analyzing complex environmental and health data.

Tianjin is situated in the northern temperate zone, on the east coast of the Eurasian continent in the mid-latitudes (38). Its climate is primarily influenced by the East Asian monsoon circulation, resulting in a warm temperate semi-humid monsoon climate. Proximity to Bohai Bay further amplifies the influence of the marine climate. As a major city in one of China's three key economic regions along the eastern coast and one of the three major metropolitan areas in Northeast Asia, Tianjin plays a pivotal role in regional development (39, 40). It serves as a modern port city, a vital hub for sea-land transport in Northeast Asia's urban corridors, and a key connection point for the "Belt and Road" initiative. Investigating the effects of meteorological changes and pollutant concentrations on respiratory diseases in Tianjin provides critical insights into the relationships between human activities, meteorological factors, and atmospheric environmental quality. Moreover, these findings have significant practical applications for environmental planning, urban development, pollution control, and public health management in the Beijing-Tianjin-Hebei region (41). Employing random forest models to forecast outpatient respiratory disease caseloads enables more effective public health interventions within urban environments. These projections facilitate crucial actions including the optimization of healthcare resource allocation, the dissemination of timely public health advisories, and the implementation of preventative measures designed to mitigate the impact of predicted increases in respiratory disease.

2 Methods and data

2.1 Data

The data used in this article include respiratory outpatient medical data, meteorological data, and pollutant data. Respiratory outpatient medical data includes the number of outpatient visits to the respiratory department, patient age and gender during the period from April 2013 to December 2019. Meteorological data comes from the Tianjin Meteorological Bureau, including observation data of meteorological elements such as temperature, relative humidity, wind speed, and precipitation. The hourly concentration monitoring data of pollutants (NO_2, SO_2, O_3, $PM_{2.5}$, PM_{10}) comes from the National Urban Air Quality Real-time Publishing Platform.[1]

To ensure the accuracy of the research results, strict adherence was maintained to the "Ambient Air Quality Standards" (GB3095-2012). Quality control was applied to the original data from the monitoring stations, which involved removing missing values and outliers from the environmental variables. Ultimately, a total of 414,887 valid data points were selected, resulting in a data missing rate of 0.12%.

2.2 Random forest

Random forest is an ensemble learning method that combines multiple decision trees, where each tree is built using independently sampled random vectors from the original data (Bagging algorithm) (42). The algorithm optimizes node selection for each independent variable based on the residual sum of squares (RSS). At each node, it splits the data to minimize the residuals of the two resulting subsets, thereby enhancing predictive accuracy.

The training dataset for the random forest model included daily records of outpatient visits to the respiratory department from April 2013 to December 2018. The validation dataset, used for evaluating model performance, consisted of daily outpatient data from 2019. The model inputs included meteorological variables, pollutant variables and temporal variables (date_unix, day of the year, weekday, and hour of the day). The date_unix variable represents the number of seconds since January 1, 1970 (43). It was used to explain hourly mean concentrations of pollutant data. This approach allowed for the integration of temporal and meteorological factors, providing a robust framework for analyzing air quality data. The random forest model was implemented using the latest "rmweather" R package.

2.3 Feature importance analysis using the SHAP algorithm

SHAP (Shapley Additive Explanations) is a widely adopted method in interpretable machine learning, designed to explain the prediction outcomes of complex models. The SHAP framework assigns an importance weight to each feature, quantifying its contribution to the model's predictions. This approach provides insights into how individual features influence model behavior, making it a valuable tool for understanding machine learning models (42).

Compared to other interpretable machine learning methods, SHAP offers several distinct advantages:

1. Consistency: SHAP ensures both global and local consistency in its explanations, which enhances the reliability and stability of the results.
2. Local Accuracy: SHAP provides feature importance at the individual sample level, enabling detailed explanations for single predictions.
3. Feature Importance Ranking: SHAP ranks features by their importance, helping users identify the most significant predictors and facilitating feature selection.

3 Results

3.1 Statistical description

3.1.1 Change characteristics of the number of medical visits

The cumulative number of respiratory system consultations in Tianjin from April 2013 to December 2019 was 414,887. Figure 1 illustrates the time series of outpatient visits during this period, revealing a cyclical annual pattern. Each year, the number of visits typically peaked at the beginning and end of the year, with lower numbers in the middle months.

Daily outpatient visit data were collected for the 81-month period from April 2013 to December 2019. The average number of daily visits was 225.50, with a minimum of 9 and a maximum of 847 cases per day. The trend in daily visits, shown in Figure 1, exhibits significant fluctuations. Notably, there are two peak periods annually. However, a marked decline in the number of visits occurred from 2016 to 2017. Analysis suggests that this decline coincided with institutional changes at the hospital, including a reduction in doctors' weekend consultation hours. These external factors substantially affected the number of patients and must be accounted for in the modeling process to minimize their impact on predictions.

Seasonal analysis (Figure 2) highlights distinct patterns in outpatient visits. A minor peak occurs in July, while a sharp increase begins in October as temperatures drop during winter. This seasonal trend indicates a higher frequency of medical consultations in both summer and winter. Box plot analysis for each month further reveals significant variability in outpatient visits during July and the winter months, with both higher patient numbers and larger fluctuations observed.

The COVID-19 pandemic in early 2020 profoundly disrupted hospital outpatient services. As of July 2021, the monthly number of visits had not returned to pre-pandemic levels. February also consistently shows a decline in outpatient visits each year due to the Chinese Lunar New Year, during which fewer people seek medical care. Given the significant impact of the pandemic on outpatient numbers after January 2020, only data from 2013 to 2018 were used to develop the predictive model. Data from 2019 were subsequently employed for model validation.

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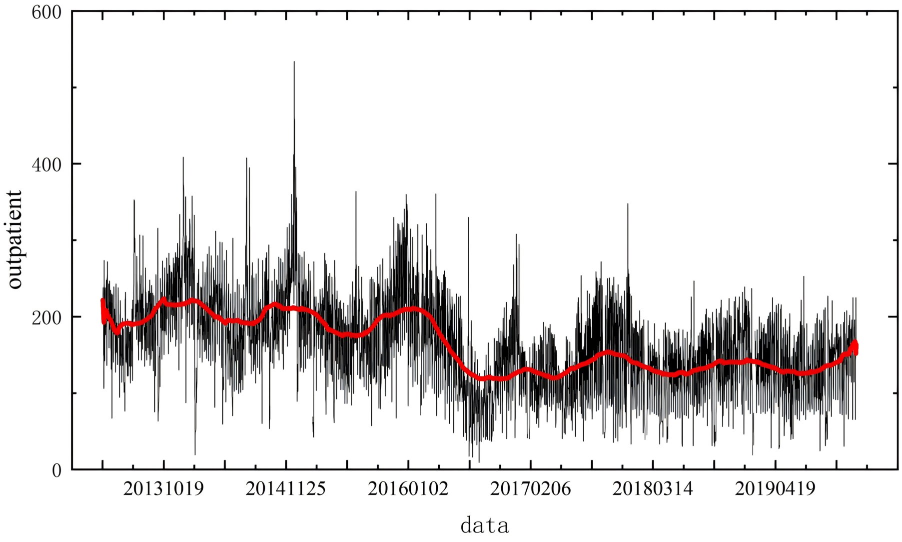

FIGURE 1
Daily average changes in the number of outpatient visits to the respiratory department.

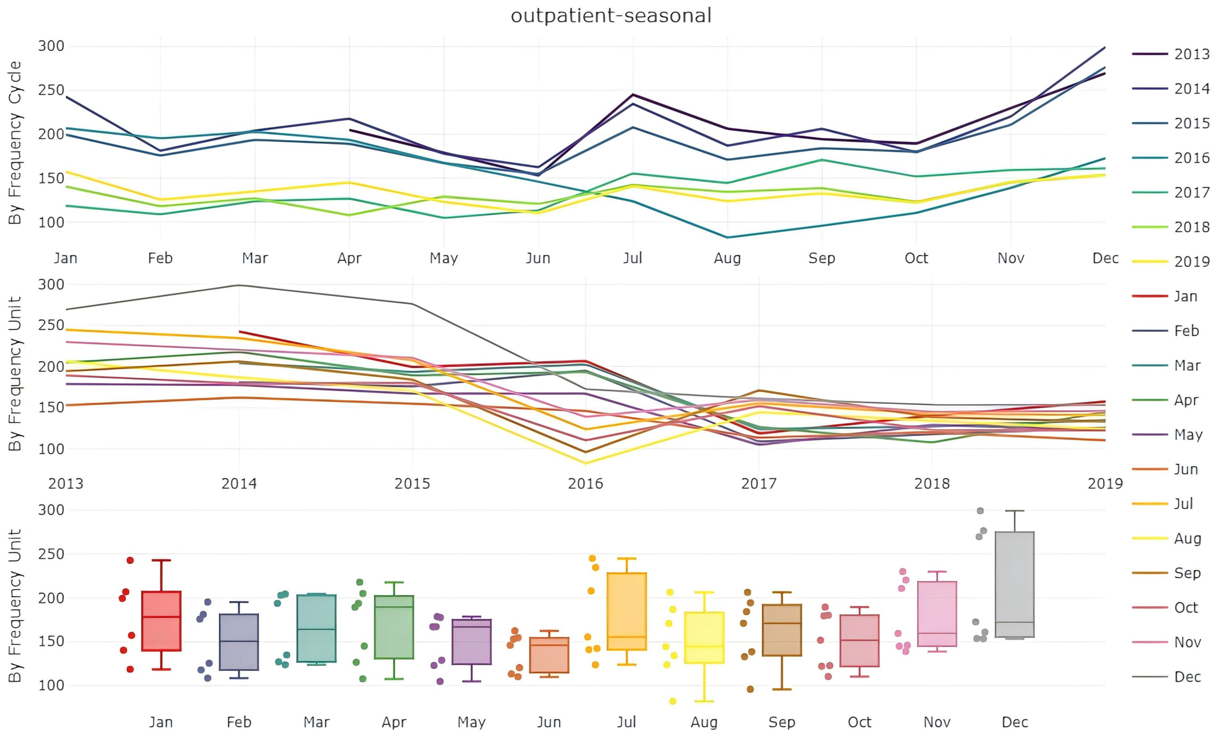

FIGURE 2
Analysis of the monthly average number of patients.

3.2 Analysis of changes in meteorological elements and pollutant concentrations

The summary statistics for patient numbers, daily average meteorological factors, and pollutant concentrations from 2013 to 2018 are presented in Table 1. The data indicate that the average temperature, maximum temperature, and minimum temperature in Tianjin during this period were 289 K, 309.9 K, and 259.6 K, respectively. The average relative humidity was 44.70%, and the average wind speed was 4.28 m/s. Regarding air pollutants, the average concentrations of PM_{10} and $PM_{2.5}$ were 110.15 and 68.45 mg/m^3, respectively. The average concentrations of O_3, NO_2, SO_2, and CO were 57.30, 47.27, 25.11, and 1.36 mg/m^3, respectively.

TABLE 1 Frequency distribution of main meteorological elements and air pollution in Tianjin from 2013 to 2018.

	Mean	Minimum	P25	Median	P75	Maximum
Wind_speed (m/s)	4.28	0.82	3.19	4.10	5,015	11.77
Temperature (K)	289	259.60	277.90	291.10	299.2	309.90
Relative-humidity (%)	44.70	6.09	29.58	43.70	57.91	94.25
Planetary-boundary-layer-height (m)	520.01	42.28	347.69	489.56	647.4	2048.84
Precipitation (mm)	18.54	0.73	5.93	13.55	28.39	72.62
Pm_{10} (μg/m^3)	110.15	10.66	63.55	93.84	138.55	483.60
$Pm_{2.5}$ (μg/m^3)	68.45	6.86	34.30	55.15	87.36	383.98
O_3 (μg/m^3)	57.30	2.81	26.55	50.56	79.57	191.07
No_2 (μg/m^3)	47.27	9.14	31.20	43.08	59.62	176.20
So_2 (μg/m^3)	25.11	2.41	9.26	15.41	29.03	237.13
Co (mg/m^3)	1.36	0.29	0.88	1.18	1.62	8.46

From 2013 to 2019, the average temperature in Tianjin was 289 K, with a maximum temperature of 309.90 K and a minimum temperature of 259.60 K. These data suggest that Tianjin experiences a relatively mild climate with pronounced seasonal variations. The average relative humidity was 44.702%, indicating a moderately dry environment that could influence public health and daily life. The average wind speed of 4.28 m/s reflects relatively stable wind conditions, which may play a role in the dispersion and dilution of air pollutants.

Tianjin's air quality indicators reveal significant pollution levels. The average PM_{10} concentration was 110.15 μg/m^3, and the average $PM_{2.5}$ concentration was 68.45 μg/m^3, both of which exceed the safety thresholds set by many countries. These particulate matters are known to irritate the respiratory system. PM10 particles, when inhaled, can cause conditions such as asthma and chronic bronchitis. PM2.5, due to its smaller size, can penetrate deeper into the alveoli and bloodstream, potentially impacting the cardiovascular system.

The average concentrations of other air pollutants further highlight the severity of Tianjin's air quality challenges. Ozone (O_3) averaged 57.30 μg/m^3, nitrogen dioxide (NO_2) 47.27 μg/m^3, sulfur dioxide (SO_2) 25.19 μg/m^3, and carbon monoxide (CO) 1.39 μg/m^3. These gases, particularly in industrial and high-traffic areas, contribute to poor air quality. Elevated levels of ozone and nitrogen oxides are known to irritate the respiratory tract and may trigger asthma attacks or exacerbate lung diseases.

Tianjin's geographical location and rapid industrialization have created favorable conditions for air pollution. As a northern coastal city, Tianjin has a dense industrial infrastructure, including numerous manufacturing plants, petrochemical enterprises, and energy industries, which release substantial pollutants during production. Additionally, the increasing use of motor vehicles has made exhaust emissions a major source of urban air pollution. Growing traffic volumes have further deteriorated air quality, particularly in the city center.

In addition, as urbanization progresses, the green coverage rate remains relatively low, and the urban heat island effect is becoming more prominent. This effect leads to higher temperatures, which in turn promote the formation of ozone. Elevated temperatures facilitate chemical reactions, resulting in increased ozone concentrations. At the same time, high humidity conditions may cause pollutants to accumulate and form haze. This phenomenon is particularly noticeable during the autumn and winter months, often leading to reduced visibility and, in some cases, meteorological disasters.

Extended exposure to such environmental conditions significantly increases health risks. Studies have shown that poor air quality is directly linked to the incidence of chronic respiratory diseases, cardiovascular diseases, and lung cancer. Children and the older adult are especially vulnerable to these pollutants, often experiencing allergic reactions or acute health issues. Pregnant women living in highly polluted environments may face risks to fetal development, including complications such as low birth weight. In recent years, Tianjin has faced a severe air pollution problem, which is closely related to its climate, geographical features, and human activities. In rapidly developing cities, it is essential for the government to implement effective policies to improve air quality. The public's health and quality of life must be prioritized. Only through raising environmental awareness and strengthening pollution control measures can a healthier living environment be created for citizens.

3.3 Correlation between main meteorological factors and daily emergency room visits for respiratory diseases in Tianjin from 2013 to 2019

Figure 3 presents the Spearman's correlation between key meteorological elements and the number of daily emergency department visits for respiratory diseases in Tianjin from 2013 to 2019. Temperature, relative humidity, precipitation, and ozone are all negatively correlated with the number of outpatient visits for respiratory diseases to varying degrees. Among these, the correlation between average temperature and ozone is the strongest, followed by the effect of precipitation.

Overall, the influence of temperature is particularly significant. Current research indicates that among various meteorological factors, temperature and humidity are closely related to the incidence of respiratory diseases. A recent study conducted by scholars from Finland and the United Kingdom found that when room temperature ranges from 18 to 26°C and relative humidity is between 17 and 40%, increasing humidity helps alleviate dryness in the nose, reduces nasal

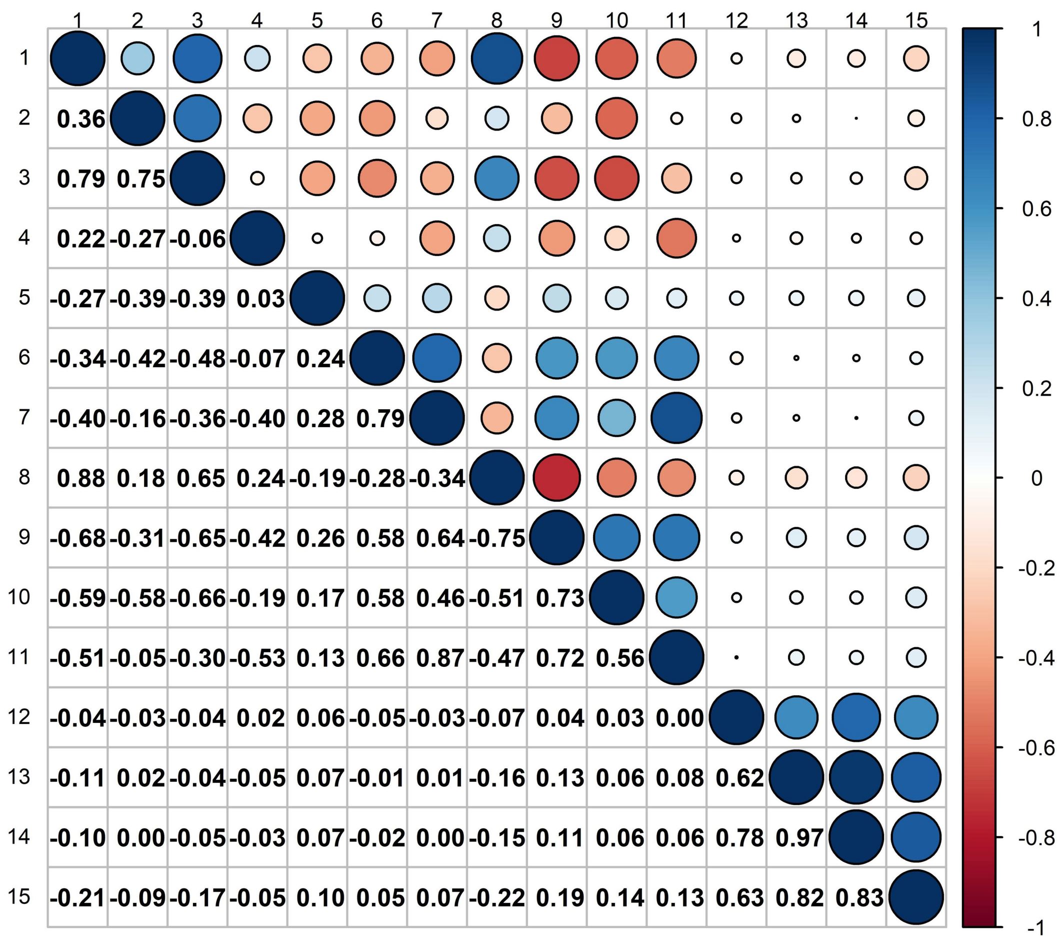

FIGURE 3
Correlation analysis of various factors on the number of patients. 1. Average temperature, 2. Relative humidity, 3. Precipitation, 4. Wind speed, 5. Boundary layer height, 6. Pm_{10}, 7. $Pm_{2.5}$, 8. o_3, 9. No_2, 10. So_2, 11. co, 12. Clinic hours, 13. Number of doctors, 14. Medical resources (the product of clinic hours and number of doctors), 15. Number of patients; the value range is between −1 and 1, where −1 indicates a complete negative correlation, 1 indicates a complete positive correlation, and 0 indicates no linear relationship; the area of the circle indicates the absolute value of the correlation coefficient, and the color depth indicates the strength of the correlation.

congestion, and relieves symptoms of a dry throat. Conversely, an increase in room temperature can exacerbate dry throat symptoms. This suggests that there is an optimal range for the effects of temperature and humidity on the respiratory system. Extremes in either temperature or humidity, whether too high or too low, can have detrimental effects on respiratory health. This implies that the combined effects of temperature and humidity on the respiratory system are nonlinear. Furthermore, short-term exposure to high concentrations of ozone can lead to respiratory irritation, including symptoms such as sore throat, cough, and wheezing. Prolonged exposure to ozone may result in reduced lung function and an increased risk of chronic respiratory diseases. Additionally, ozone exposure can cause lung tissue inflammation, impair alveolar function, and reduce the efficiency of oxygen exchange. Therefore, it is crucial to protect the respiratory system by minimizing exposure to ozone.

(1) The impact of individual meteorological factors on the number of patient visits: In this study, we calculated the Spearman correlation coefficients between 14 factors and the number of patients to assess the strength of their relationships. The coefficients for the number of doctors and the operating time of medical resources were 0.82 and 0.83, respectively, indicating a strong positive impact on patient visits. As the number of doctors increases or medical resources expand, patients are more likely to seek treatment due to reduced waiting times and improved satisfaction. The correlation between time and the number of patients was 0.63, suggesting that longer time provide more opportunities for patients to seek care. In contrast, environmental factors, such as air pollution and climate conditions, exhibited relatively low correlations with patient visits, most of which were negative. For instance, the Spearman coefficients for PM_{10} and $PM_{2.5}$ were 0.05 and 0.07, indicating minimal effects. Negative correlations were also observed for relative humidity (−0.09), precipitation (−0.17), wind speed (−0.05), and boundary layer height (0.10), suggesting that adverse weather conditions may discourage hospital visits. Higher humidity and precipitation could deter individuals from going out, while strong winds might negatively affect physical health, leading people to stay home.

Furthermore, the coefficients for pollutants such as O_3, NO_2, SO_2, and CO were − 0.22, 0.19, 0.14, and 0.13, respectively, with the negative correlation for O_3 indicating that higher ozone levels may reduce the likelihood of seeking medical treatment, particularly for individuals with pre-existing respiratory conditions. Additionally, the correlation coefficient for average temperature and patient visits was −0.21, revealing a significant negative relationship. This suggests that extreme temperatures, both high and low, may discourage individuals from seeking medical attention. Hot weather may prompt people to remain indoors, thereby reducing healthcare visits, while sudden temperature fluctuations could exacerbate seasonal health conditions, leading to temporary increases in patient numbers. Overall, extreme temperature conditions tend to negatively impact medical-seeking behavior.

(2) The linear relationships among meteorological factors: The correlation coefficient is a statistic used to measure the strength and direction of the linear relationship between two variables. Based on the correlation coefficients shown in Figure 3, it can be observed that the lighter the color of the number, the weaker the linear relationship between the two meteorological factors. Among these factors, the boundary layer height has a relatively weak correlation with other factors (correlation coefficient < 0.5). The average temperature and precipitation have a more pronounced effect on pollutant factors compared to other meteorological variables. Additionally, there is a strong correlation among the pollutant factors.

The combined influence of environmental factors and medical resources provides an important context for changes in patient numbers. A complex interaction exists between the availability of medical resources, doctors' work schedules, and the impact of environmental factors on public health. Environmental risks may drive people to seek medical services, while the availability of healthcare resources determines their access to care. Thus, enhancing the allocation of medical resources and improving environmental quality are critical for promoting better health outcomes and healthcare utilization. Together, these factors interact through various mechanisms, influencing individuals' decisions to seek medical attention and, ultimately, contributing to changes in patient numbers.

3.4 Establishment of respiratory disease prediction model

A prediction model was developed using daily emergency department visit data for respiratory diseases in Tianjin from 2013 to 2018. The model accounts for various factors, including long-term trends, weekly and holiday effects, as well as meteorological variables such as average temperature, relative humidity, average wind speed, boundary layer height, and precipitation. Additionally, air pollution levels (PM_{10}, O_3, SO_2, NO_2, etc.) were incorporated to assess their combined impact. Figure 4 presents a regression scatter plot of the model fitting. The data points are evenly distributed around the solid line, indicating that the random forest model explains more than 80% of the variation in patient numbers, demonstrating its strong predictive performance. The model exhibits a small error between predicted and observed values, further confirming its reliability and providing a solid foundation for future research.

The goodness-of-fit analysis evaluates the existing predictive model. In this study, we employed linear regression to test the model (Figure 4a). By inputting the original data into the model, we obtained the fitted values and compared these results with the actual observed values. The figure indicates a close linear relationship between the predicted values and the actual values. Most data points are concentrated near the regression line, suggesting a good fit between the predicted and actual values. Additionally, the slope of the regression line is close to 1, indicating an accurate proportional relationship between the predicted and actual values. However, there are a few outliers, which may result from not considering all influencing meteorological factors or from random errors in the data.

The residual plot can be used to assess whether the model's residuals are consistent with random errors. Figure 4b presents the density plot of the model's predicted residuals, which helps evaluate the model's fit. The horizontal axis represents the magnitude of the residuals, while the vertical axis indicates the corresponding

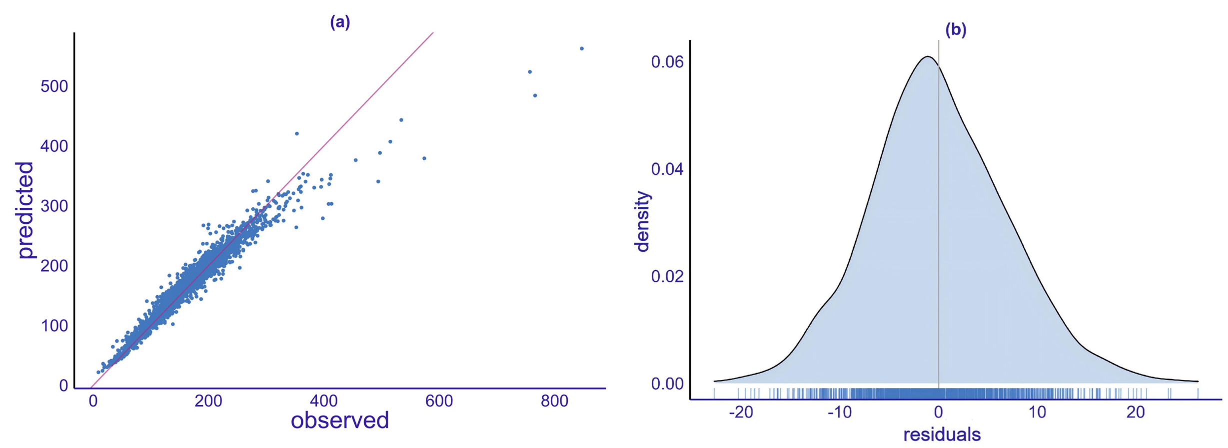

FIGURE 4
Model fitting analysis. **(a)** Quantile-quantile plot. **(b)** Density plot of the model's predicted residuals.

density of the residuals. The height of the density reflects the proportion of the residuals and allows for a visual assessment of their distribution, providing a preliminary judgment of the model's fit. The results in Figure 4B show that the distribution of the model's residuals follows a unimodal, bell-shaped curve, consistent with a normal distribution.

3.5 Establishm model interpretability analysis

3.5.1 SHAP analysis

To evaluate the importance of different meteorological variables, the SHAP model was applied. Figure 5 illustrates the importance ranking of individual variables, while Figure 6 shows the distribution of SHAP values derived during the construction of the random forest model.

Variable importance plays a critical role in selecting predictors for the random forest model. In this study, meteorological data were used as pre-selected influencing factors. Redundant variables with weak correlations were eliminated based on their importance, thereby streamlining the prediction model and enhancing its operational efficiency. For the case of Tianjin, the pre-selected influencing factors were evaluated, as shown in Figure 5. This ranking indicates that the higher the influence of a factor, the greater its importance. Specifically, sulfur dioxide (SO_2), ozone (O_3), and temperature were identified as significantly more important than other meteorological factors. The findings suggest that the number of patients in Tianjin is most sensitive to variations in SO_2, O_3, and temperature.

When predicting the number of patients, the ranking of variables provides valuable insights into the influence of different factors. Among these, sulfur dioxide (SO_2) and ozone (O_3) ranked first and second, respectively, highlighting their significant impact on the number of patients. Sulfur dioxide, a major air pollutant, is strongly linked to respiratory diseases. Elevated concentrations of SO_2 can irritate the airways, leading to symptoms such as coughing and wheezing, which may increase the demand for medical treatment. Ozone, a byproduct of chemical reactions between pollutants in the presence of sunlight, is more prevalent during the summer months. High ozone concentrations also have substantial negative effects on public health, with many individuals experiencing difficulty breathing, further contributing to an increase in medical visits. Thus, the high importance of these two pollutants can be understood as a direct threat to public health.

Temperature ranks closely behind other variables in its influence on the number of medical visits. Changes in temperature can affect the immune system and overall physiological condition. Cold weather often leads to an increase in respiratory infections, while hot climates may cause heat-related illnesses such as heat stroke. Consequently, temperature changes are a key factor influencing both people's health and their medical behavior.

The variable "doctor" also emerged as an important factor. The number of doctors and their distribution significantly impact the frequency of medical visits. When there are fewer doctors in a region, patients may delay seeking treatment due to difficulties in accessing healthcare. Even when symptoms become severe, individuals may wait until the condition worsens before seeking medical attention. Thus, the availability of medical professionals directly influences patients' willingness and ability to seek care.

Precipitation is another relevant factor. Heavy rainfall often leads people to stay indoors, reducing outdoor activities, which in turn can

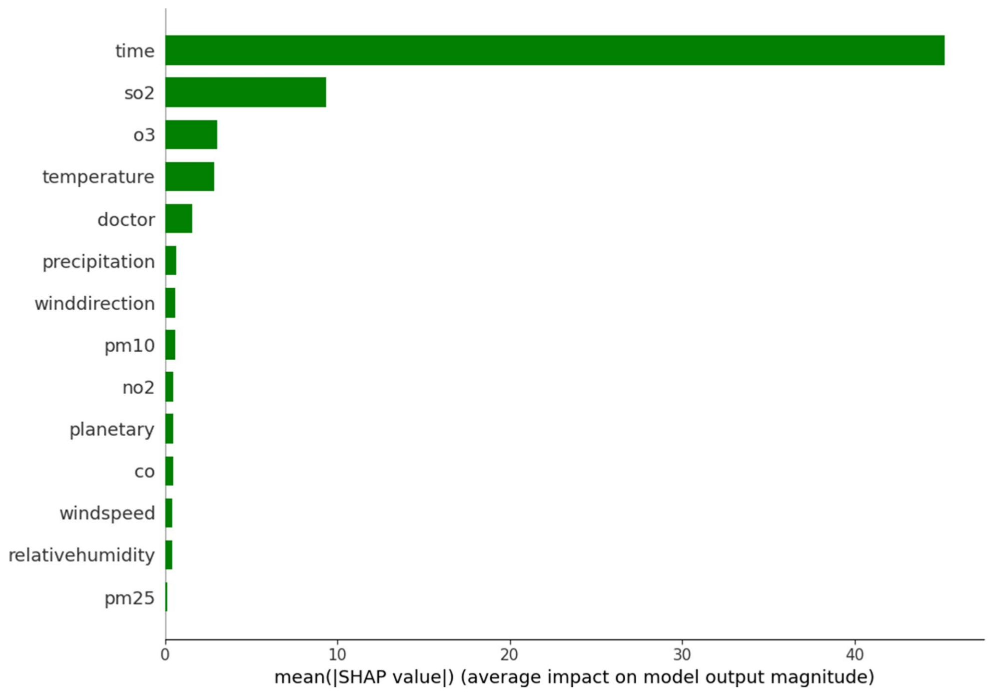

FIGURE 5
Importance of single factor variables.

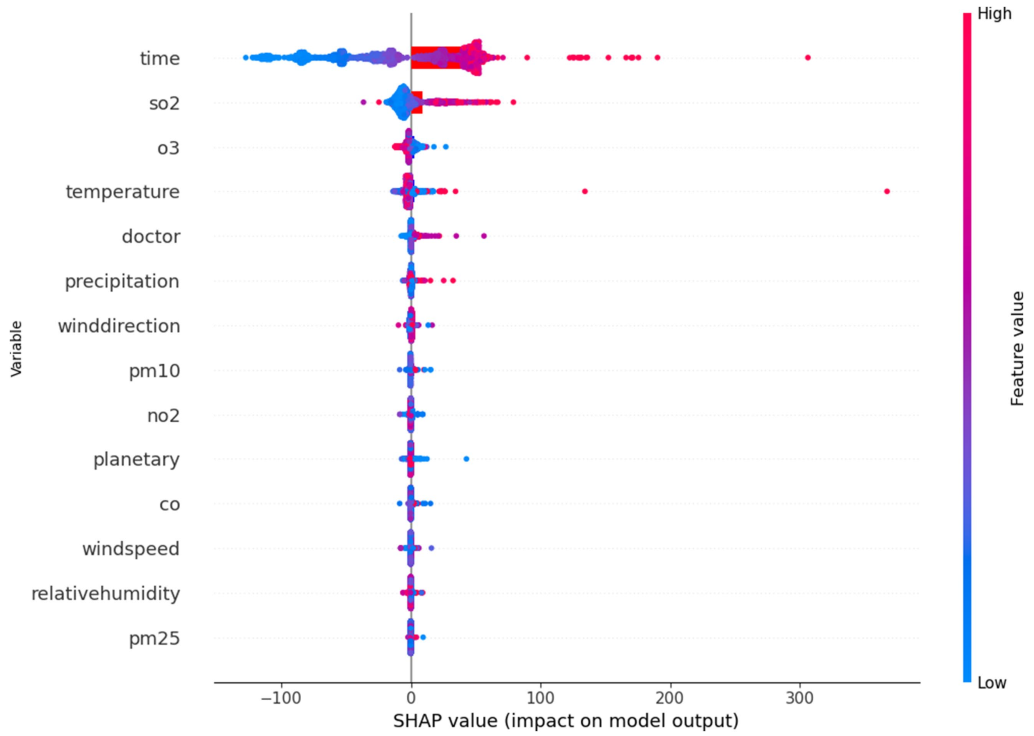

FIGURE 6
SHAP analysis.

impact the spread of respiratory diseases. However, in cases of extreme weather, such as heavy storms, transportation disruptions may affect people's ability to access medical services. Additionally, precipitation can influence the transmission of certain infectious diseases. For example, during the rainy season, increased mosquito breeding can lead to outbreaks of diseases like dengue fever, thereby driving an increase in medical visits.

Particulate matter and gaseous pollutants, such as PM_{10} and NO_2, also rank highly in their importance. These pollutants have well-established negative effects on both the respiratory and cardiovascular systems. PM_{10} particles can penetrate the lungs and cause a variety of health issues, while nitrogen dioxide (NO_2) often exacerbates respiratory conditions such as asthma when combined with other pollutants. This highlights the strong connection between air quality and public health.

As a professional environmental parameter, the planetary boundary layer appears in the variable importance ranking, highlighting its impact on local air quality. The height of the planetary boundary layer influences the diffusion of pollutants. A lower boundary layer results in higher pollutant concentrations, which degrade air quality and increase the number of medical visits. In contrast, a higher boundary layer aids in the dilution of pollutants, reducing their harmful effects on public health.

Wind speed and relative humidity are also relevant factors. High wind speed facilitates the dispersion of pollutants, reducing their concentration in a given area, which can alleviate pollution-related health issues. Relative humidity interacts with respiratory health, as a high humidity environment may promote the growth of mold and bacteria, leading to an increased number of visits for allergies or respiratory conditions.

Although fine particulate matter ($PM_{2.5}$) ranks lower in the importance ranking, its health impacts should not be underestimated. $PM_{2.5}$ can penetrate deep into the alveoli and even enter the bloodstream, causing significant damage to the heart and lungs. Despite its lower rank, its influence on the number of medical visits may vary across different regions and time periods.

Analyzing the importance ranking of these variables provides valuable insights into the complex relationship between environmental factors and public health. This model not only offers a scientific basis for health policy development but also provides essential information for managing and preventing medical needs. Factors such as pollutant levels, temperature, and the availability of medical professionals interact to shape individuals' health status, which, in turn, influences changes in the number of medical visits. This underscores the importance of considering multiple environmental and social factors in public health management.

SHAP (SHapley Additive exPlanations) values quantify the impact of a specific feature value by comparing it to the prediction made when the feature assumes a baseline value.

Variables with high SHAP values are considered important, while meteorological variables with SHAP values close to zero are of lesser importance. As illustrated in the figure, the doctor's sitting time contributes significantly to changes in the number of patients. Among the meteorological variables, temperature is shown to have a major impact on patient numbers. Additionally, sulfur dioxide and ozone, as pollutants, demonstrate a substantial contribution, highlighting the importance of addressing ozone pollution and acid rain in the context of respiratory diseases. Although rainfall is less important, it is associated with low SHAP values, which aligns with the concept of wet deposition of aerosols.

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3.5.2 Partial dependence analysis

Partial dependence plots are a useful tool for visualizing how specific features affect model predictions. Like permutation importance, partial dependence plots are computed after model fitting and applied to real, unmodified data. By examining the relationship between variations in environmental factors and hospital visits, the results suggest that the relationship between pollutant concentrations and health outcomes is complex. These findings highlight a strong connection between air quality and public health. For example, nitrogen dioxide (NO_2) concentrations exhibit a dual effect. At low concentrations (0–50 μg/m^3), NO_2 is negatively correlated with the number of hospital visits, suggesting that improved air quality in this range may reduce respiratory disease incidences. However, as concentrations increase to 50–125 μg/m^3, a positive correlation emerges, indicating that higher pollution levels are linked to a greater demand for medical treatment. This shift may be due to the heightened health risks associated with higher pollutant concentrations.

Similarly, ozone (O_3) demonstrates a comparable dual effect. In the range of 0–50 μg/m^3, O_3 is negatively correlated with the number of patients, indicating better public health at lower pollution levels. However, as O_3 concentrations rise to 125–150 μg/m^3, a positive correlation emerges, which may be due to the severe health risks posed by high ozone concentrations in the air. The negative correlation observed with relative humidity suggests that high humidity causes physical discomfort, particularly for individuals with respiratory diseases.

Regarding particulate matter, both PM_{10} and $PM_{2.5}$ show a clear positive correlation with hospital visits. Increases in PM_{10} concentrations correlate with higher patient numbers, underscoring the adverse effects of fine particulate matter on public health. $PM_{2.5}$, in particular, demonstrates the closest relationship with patient visits within the concentration range of 100–125 μg/m^3. These particles can penetrate deep into the lungs, enter the bloodstream, and impair cardiopulmonary function. A similar positive correlation was observed for sulfur dioxide (SO_2), further reinforcing the detrimental health effects of airborne pollutants.

The boundary layer height also revealed a significant negative correlation with hospital visits within the range of 0–500 meters. Lower boundary layer heights may trap pollutants near the ground, worsening air quality and increasing respiratory disease-related visits. Precipitation generally shows a negative correlation with patient numbers at 0–50 mm, but turns positive at higher precipitation levels (50–70 mm). Precipitation helps reduce airborne pollutants, leading to fewer health issues. Additionally, complex interactions between increased humidity and changes in precipitation patterns contribute to public health outcomes.

Temperature also exhibits a clear positive correlation with hospital visits. High temperatures often exacerbate respiratory diseases, and hot weather increases ozone levels, further raising the demand for medical treatment. Wind speed has a more nuanced effect, showing a negative correlation at low wind speeds (0–5 m/s) and a positive correlation at higher wind speeds (5–9 m/s). This likely reflects the various mechanisms involved in wind-driven pollutant dispersion. At lower wind speeds, pollutants can accumulate in a specific area, negatively impacting public health. However, at higher wind speeds, pollutants may disperse or be diluted, improving air quality and reducing medical treatment needs (Figure 7).

3.6 Research on prediction and forecast of respiratory diseases

To assess the prediction accuracy of the random forest model for ozone (O_3) in estimating the number of daily emergency patients in Tianjin, the model was tested using data from 2013 to 2018 as the training set. The model incorporated 13 influencing factors, including average temperature, relative humidity, precipitation, wind speed, PM_{10}, $PM_{2.5}$, O_3, NO_2, SO_2, CO, sitting time, number of doctors, and medical resources, to predict the daily number of respiratory patients for 2019. The predicted values were compared with the actual observed values (Figure 8). Figure 8 illustrates the distribution of the observed and predicted values for the number of respiratory patients in Tianjin in 2019. The high degree of consistency between the two suggests that the model performs well in predicting daily fluctuations in patient numbers. The strong goodness of fit indicates that the random forest model is effective for forecasting long-term daily changes in the number of respiratory patients in Tianjin.

4 Conclusion

(1) This study analyzed the temporal and seasonal variations in the number of outpatient visits for respiratory conditions in Tianjin from 2013 to 2019. The number of visits exhibited fluctuations with the seasons, with significantly higher numbers in summer and winter compared to spring and autumn. A notable decline occurred in 2017, which may be directly related to adjustments in hospital policies. Considering the trends in meteorological factors and pollutants, there is a clear overlap between the peaks in outpatient visits and temperature and precipitation during the summer. This suggests that the increase in outpatient visits may be associated with meteorological factors.

(2) The changes in outpatient visits show a nonlinear relationship with both meteorological and pollutant factors. Among these, average temperature, relative humidity, precipitation, and ozone have a strong correlation with the number of visits. The correlation between boundary layer height and other factors is weaker. The impact of average temperature and precipitation on pollutant factors is more pronounced compared to other meteorological elements. Additionally, there is a strong correlation among the pollutant factors. In the analysis of the importance of meteorological factors, it was found that sulfur dioxide, ozone, average temperature, and precipitation significantly influence the model's predictions of outpatient visit numbers, while wind speed, precipitation, and boundary layer height have a smaller effect.

(3) When the number of outpatient visits is between 50 and 200, the random forest model demonstrates a high goodness of fit between predicted and actual values, indicating good predictive performance. This model effectively predicts the long-term daily variations in outpatient visits. Future work should focus on further optimizing model parameter selection and improving the model's temporal resolution to achieve more accurate predictions.

(4) Although the random forest model effectively predicts long-term daily variations in outpatient visits, it lacks the ability to

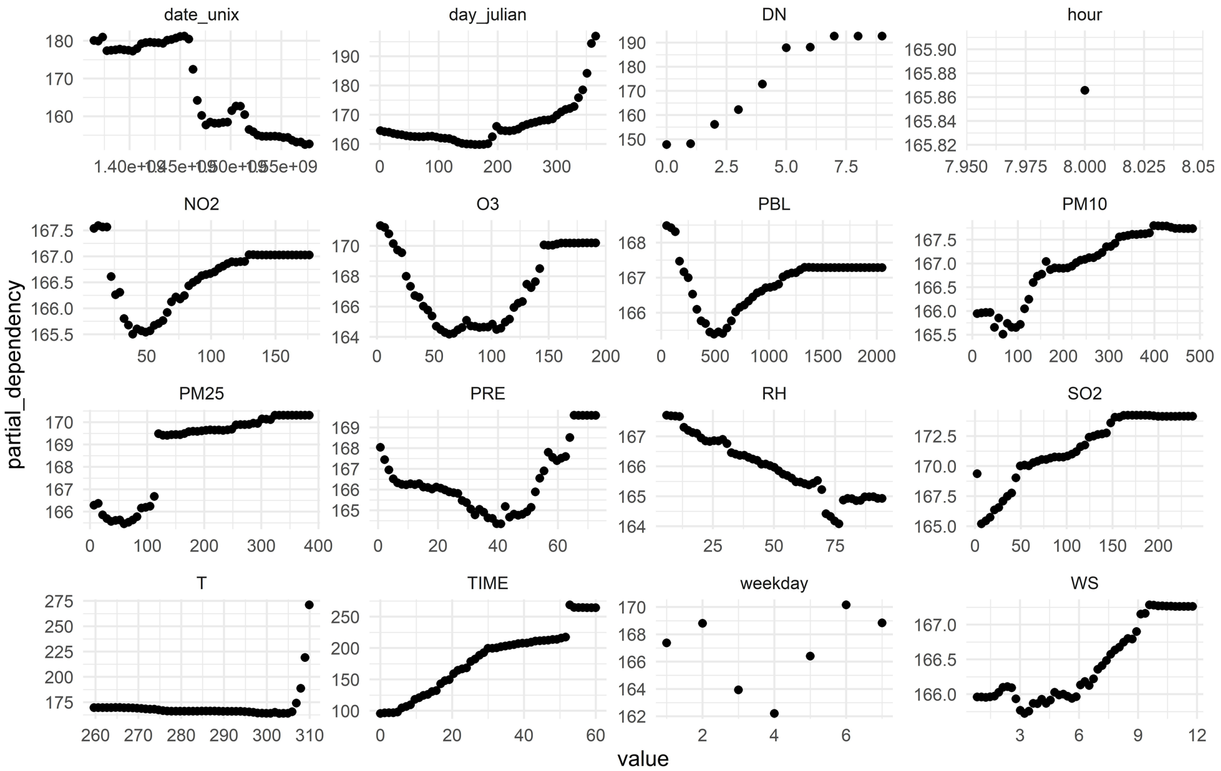

FIGURE 7
Partial dependence analysis of each factor on the number of patients.

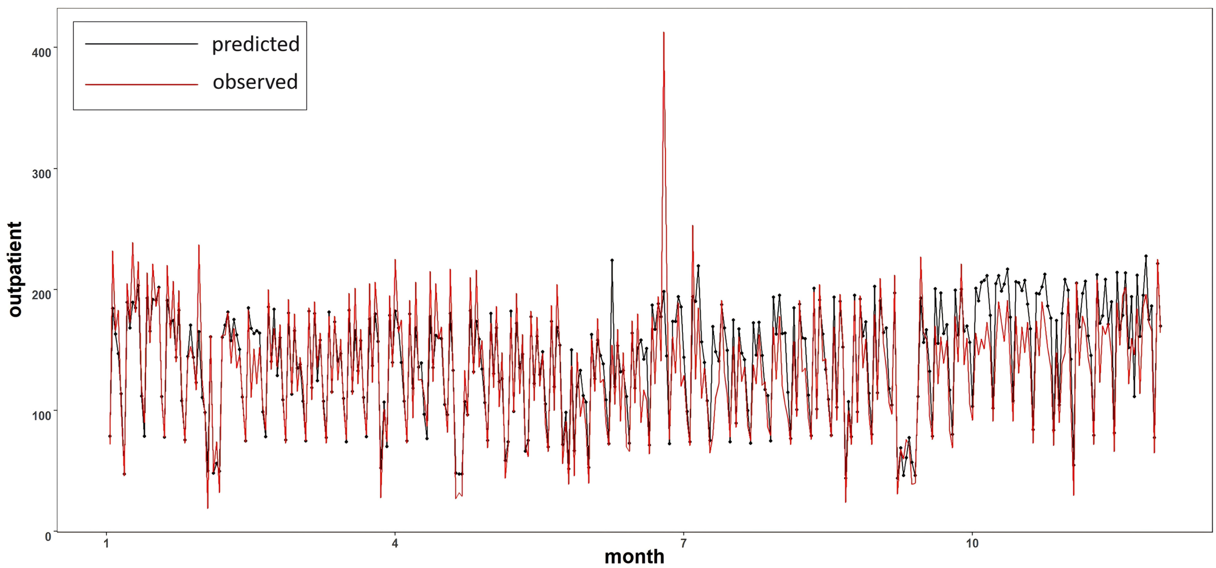

FIGURE 8
Comparison of predicted value and actual value in 2019.

capture extreme values. This limitation arises because the random forest model relies heavily on large datasets for modeling and validation; insufficient sample sizes for extreme value data directly affect the model's predictive accuracy. Therefore, to enhance the prediction of outpatient visits for respiratory conditions, future research could combine different models to improve predictive capabilities. Additionally, integrating this method with traditional mechanistic models, such as ARIMA, may yield more precise predictions while reducing time costs.

Data availability statement

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

Ethics statement

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

Author contributions

XY: Writing – original draft. LL: Writing – review & editing. YL: Writing – review & editing. ZZ: Writing – review & editing.

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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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Prevalence and risk factors of elevated blood lead levels in 0-6-year-old children: a national cross-sectional study in China

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Aims: To evaluate the prevalence and risk factors of elevated blood lead levels (EBLL) among the pediatric population in China.

Methods: Questionnaire investigation about Lead exposure information, venous blood samples collection and BLL detection are conducted. A total of 32,543 subjects aged 0–6 years old (from 1 month old to under 7 years old) were recruited from May 2013 to March 2015 in 15 provinces of China.

Results: The overall weighted prevalence of EBLL which is defined as BLL ≥ 50 μg/L in this study is 4.1%, as for different geographical regions, with lowest prevalence in the western region of China, lowest prevalence in Shaanxi province and highest in Hebei province. In 0–3-Year-old children, female weighted prevalence of EBLL (4.0%) is higher than male (2.4%), while in 3–6-Year-old children, male (8.3%) is higher than female (6.3%). Bad hygienic habits, some kind of custom, using folk prescriptions, living on the ground floor, poor drinking water quality, indoor air pollution and passive smoking exposure remain risk factors of EBLL (BLL ≥ 50 μg/L) of 0–6-year-old (from 1 month old to under 7 years old) children in China, after adjustment of gender, age, geographical region, annual household income, educational background and occupation of the parents and caregivers.

Conclusion: This study reveals the prevalence and risk factors for EBLL (BLL ≥ 50 μg/L) in 0–6-Year-old Children of China. We hope this study will help public health education and inform policy for preventing and eradicating children's lead poisoning in China.

KEYWORDS
children, elevated blood lead levels, prevalence, risk factors, China

1 Introduction

Lead naturally occurs in the earth's crust and has been used in industry, paint, gasoline, construction, pottery, folk medicines, and herbal remedies for centuries. Lead is pervasively present in the environment, slowly impacting health from early childhood and throughout life (1). When lead is absorbed in different ways, it enters the body, attaches to soft tissue, easily assimilated into the nervous system (2). Lead poisoning causes toxicity in several organ systems, such as central nervous system impairment what needed special attention, mainly manifested as impairing neurological development, reducing intelligence quotient, and generating negative behavior (3, 4). The adverse effects of childhood lead exposure have been well-documented, such as learning issues (5), behavior problems (6, 7), worsened cognition (8, 9), and the like (10–12). Even blood lead levels less than 50 μg/L are associated with irreversible neurocognitive and behavioral development impairments in infants and children who are more susceptible to lead toxicity (13, 14).

Lead poisoning has been recognized for centuries for its extensive application and environmental persistence (1, 13); however, lead exposure is still a critical public health problem globally, especially in developing countries (15), as poverty may lead to significant ongoing exposures (16).

As a developing country, China has experienced dramatic industrial and economic growth over the past decades, becoming one of the largest lead producers and consumers worldwide. Different sources of children lead exposure are reported in different countries affected by the economic, social and cultural levels. Children still face risks of lead exposure from coal burning, petroleum fuel consumption, e-waste recycling piles (17–19), ore and metal processing, lead-containing folk remedies (20–22), and poor living environment (19, 23–26).

In 2006 public guideline for the prevention of high BLLs and lead poisoning in children issued by the Ministry of Health in China stated that high blood lead syndrome in children should be recognized if the venous blood lead level reaches 100–199 μg/L two consecutive times. Furthermore, lead poisoning in children should be diagnosed if venous blood lead level is ≥200 μg/L two consecutive times (27). Since leaded gasoline was prohibited in 2000 in China, the children BLLs and the prevalence of lead poisoning have dramatically declined over the past 20 years (28, 29). However, the American Centers for Disease Control reports that there is no acceptable level of lead in the human body and that even minimal levels of lead can cause neurological damage to children (30). The Council of State and Territorial Epidemiologists'(CSTE) blood lead reference value is 3.5 μg/dL which is used to identify adults and children whose blood lead levels are higher than the 97.5th percentile of adults and children nationwide (30). Considering sensitivity to lead toxicity in children's neurocognitive and behavioral development, even BLLs less than 50 μg/L, we defined BLL ≥ 50 μg/L as EBLL in this study, referring to acceptable children's blood lead levels in 2012 by the American Centers for Disease Control.

For the lack of national epidemiological investigation of blood lead levels and Pb exposure risk factors of 0–6-Year-old children (from 1 month old to under 7 years old) in China, we conduct this national population-based cross-sectional survey. This study explores the prevalence of EBLL, defined as BLL ≥ 50 μg/L, and the risk factors of EBLL. We aim to reveal the epidemiological characteristics of EBLL and provide a theoretical basis for targeted preventive measures of lead exposure for children.

2 Materials and methods

2.1 Study design

The study population is selected using a multi-stage stratified cluster random sampling technique. The survey methods and sampling details have been published elsewhere (31). The sampling steps are as follows: First, every five provinces were selected from Eastern China, Central China and Western China by the simple random sampling (SRS) method. According to the classification by the National Bureau of Statistics, Shanghai, Jiangsu, Hebei, Guangdong, and Fujian are categorized as eastern regions; Shanxi, Henan, Hunan, Jilin, and Hubei as central regions; and Shaanxi, Yunnan, Qinghai, Guangxi, Xinjiang as western regions. Second, within each selected province, a probabilistic proportional to size (PPS) sampling method was used to choose districts of major cities, medium and small cities and towns/villages of rural areas based on the population. According to the "China Small and Medium City Development Report (63)" and the "Regulations on the Statistical Division of Urban and Rural Areas," cities with a resident population of over 1 million are classified as major cities, while those with a resident population of 1 million or less are categorized as small and medium-sized cities. Areas outside these designated urban regions are defined as rural areas. Third, children from 1 to 2 neighborhoods chosen by the SRS method within each selected district/village were investigated.

2.2 Sample size calculation

The study uses a multi-stage stratified cluster random sampling method. The formula $n = \frac{Z^2 \cdot P \cdot (1-P)}{d^2} \times deff$ is used to calculate the sample size for each stratification, in which as for 95% CI, Z sets to 1.96, p as expected prevalence rate set to 6%, based on the results of we previous meta-analysis that the pool lead poisoning rate of Chinese population aged 0–18 years old was 5.3% and the pool lead poisoning rate of children was from 4.7 to 9.5% of different age groups under 7 years old (excluding newborn) (29). The allowable error d setting to 2% is applied here. Design effect deff is applied when considering representativeness of 15 provinces of three regions (i.e., Eastern China, Central China, Western China), rural and urban areas (i.e., major cities, medium and small cities and rural areas), gender (i.e., male and female) and age (i.e., 0–36 months and 36–84 months) which are the stratified analysis factors. Consequently, this calculation resulted in a sample size of 24,390 Taking response rate of 90% into account, the final sample size was targeted at 27100. At last, there were over 30,000 samples collected.

2.3 Data collection procedure

The survey is strictly quality-controlled. All investigators undertaken by experienced medical professional, are well trained by project team to ensure using standardized questionnaire instructions, standard sample collection, preservation and transportation. Each questionnaire undergoes double scanning and entry, with 10% of the questionnaires being reviewed by the project quality control officers. We obtain sociodemographic information (gender, date of birth, nationality, education level, occupation, and annual family income), self-reported behavior tendencies (smoking, physical activity, hand-to-mouth activity, and washing hands before eating), and living environment for estimating potential lead exposure (folk prescriptions for treatment, customs and habits leading to potential lead exposure, industry around the house, and house location). We obtain the information through face-to-face interviews using a questionnaire of mostly closed-ended questions. We survey Uyghur participants jointly with a Uyghur language translator using a questionnaire translated into Uyghur language. The participants' confidentiality and privacy are assured. After completion of the interview, anthropometric measurements and blood samples are obtained.

2.4 Blood sample collection and detection

A trained nurse drew 3 milliliters of venous blood into a vacuum blood tube. EDTA (Na_2) is used as an anticoagulant, and samples were stored at 4°C. Refrigerated batches of 100 tubes are sent in a box of ice to the central laboratory at the local site and stored at −20°C before measurement. Blood sample collection is performed in a clean room, far from pollution sources. Children are required to clean their hands with soap before blood collection. Blood lead concentration is measured using an atomic absorption spectrometry-graphite furnace (PerkinElmer Company, 900Z, United States). Quality control is performed using a sample test. The laboratory protocol includes daily calibration with five standards (1–50 μg/L; agreement <5%) and standard reference materials (Contox, Kaulson Laboratories, Inc., NJ, United States) to ensure the accuracy of the assay. The method's limit of detection (LOD) is 1 ug/dL for BLL. No sample has a BLL less than the LOD. All plastic tubes used for blood lead tests are washed thoroughly, soaked with dilute nitric acid, rinsed with deionized water, and dried before use.

2.5 Ethics approval

The study is approved by Ethics Committee of Xinhua Hospital affiliated with Shanghai Jiao Tong University School of Medicine (XHEC-C-2013-008). Signed consent forms are collected from the guardians of all children who participated in the study.

2.6 Statistical analysis

Data weighting is used as a statistical technique to adjust survey data to represent the target population. The design weight for adjusting the probability of being sampled for each individual unit of the smallest survey unit is computed by multiplying the sampling weight of each stage. As describing in study design section of this article, we applied three sampling steps and stratified sampling which divided the sample into subgroups as below: different provinces, urban areas and rural areas, different genders and different age groups. The formula $Wh = \frac{N_h / N}{n_h / n}$ is applied. N in formula is the total population, Nh represents the number of people in layer h of the population, n is the sample population, n_h represents the population of layer h in the sample. We adjust the design weight using the no-answer factor, which is the reciprocal of the response rate. Given the known stratification structure of the population (such as urban and rural areas, age, gender, etc.), the sample is re-stratified and the weights of each stratum are adjusted to match the overall proportion. Population information refers to the data from The Sixth National Population Census of China in 2010. In this survey, the post-stratification weights were adjusted according to age and gender stratification.

Sample characteristics are summarized using descriptive statistics (n, mean, median, p25, p75). A threshold of 50 μg/L for BLLs is used to categorize BLLs into two groups. The socioeconomic status, residence characteristics, and potential risk factors for lead exposure among children are compared between different BLL groups. A logistic regression analysis is performed to estimate odds ratios (OR), 95% confidence intervals (CI), and *p*-values. IBM SPSS version 22 is used for statistical analysis. Statistical significance is set at a *p*-value of 0.05 (two-tailed test).

3 Results

This population-based cross-sectional study is conducted to examine the prevalence and associated risk factors of EBLL (BLL ≥ 50 μg/L) among Chinese children aged 0–6 years old (from 1 month old to under 7 years old), and their blood samples are also obtained. We finally recruited 32,543 0–6-year-old children (from 1 month old to under 7 years old) from 15 provinces of China from May 2013 to March 2015 with 16,997 (52.2%) males and 15,546 (47.8%) females.

3.1 The prevalence of children with BLL ≥ 50 μg/L (EBLL) in different geographical regions of China

The weighted prevalence with BLL ≥50 μg/L (EBLL) in 0–6-year-old children (from 1 month old to under 7 years old) is 4.1%. There is significant difference of prevalence among different geographical regions of China with 2.7% in the western region much lower than the other two regions in China.

Considering geographic factor, children in rural areas of eastern (12.4%) and western (7.4%) regions have higher prevalence of EBLL than urban areas, while children in urban areas of middle or small-sized city in central region (7.4%) have higher prevalence of EBLL.

And prevalence of EBLL differs significantly by province, with the lowest in Shaanxi province (0.5%) and highest in Hebei province (18.5%) (Figure 1). There is significant difference in children EBLL prevalence of urban areas in major cities (1.8%), urban areas in medium and small cities (7.2%) and in rural areas (8.5%). However, there are significant differences in prevalence among different districts in some provinces. In Qinghai, highest prevalence of urban areas in major city (21.9%) and in middle or small-sized city (16.2%) are observed. In Hebei, highest prevalence of rural areas (41%) is observed (Table 1).

3.2 The prevalence of children with BLL ≥ 50 μg/L (EBLL) by different ages and genders

The weighted prevalence of children with BLL ≥50 μg/L (EBLL) is higher in female (4.9%) than in male (3.7%). However, the situation varies among different age groups.

In 0–3-Year-old children, female weighted prevalence of EBLL (4.0%) is higher than male (2.4%), while in 3–6-Year-old children,

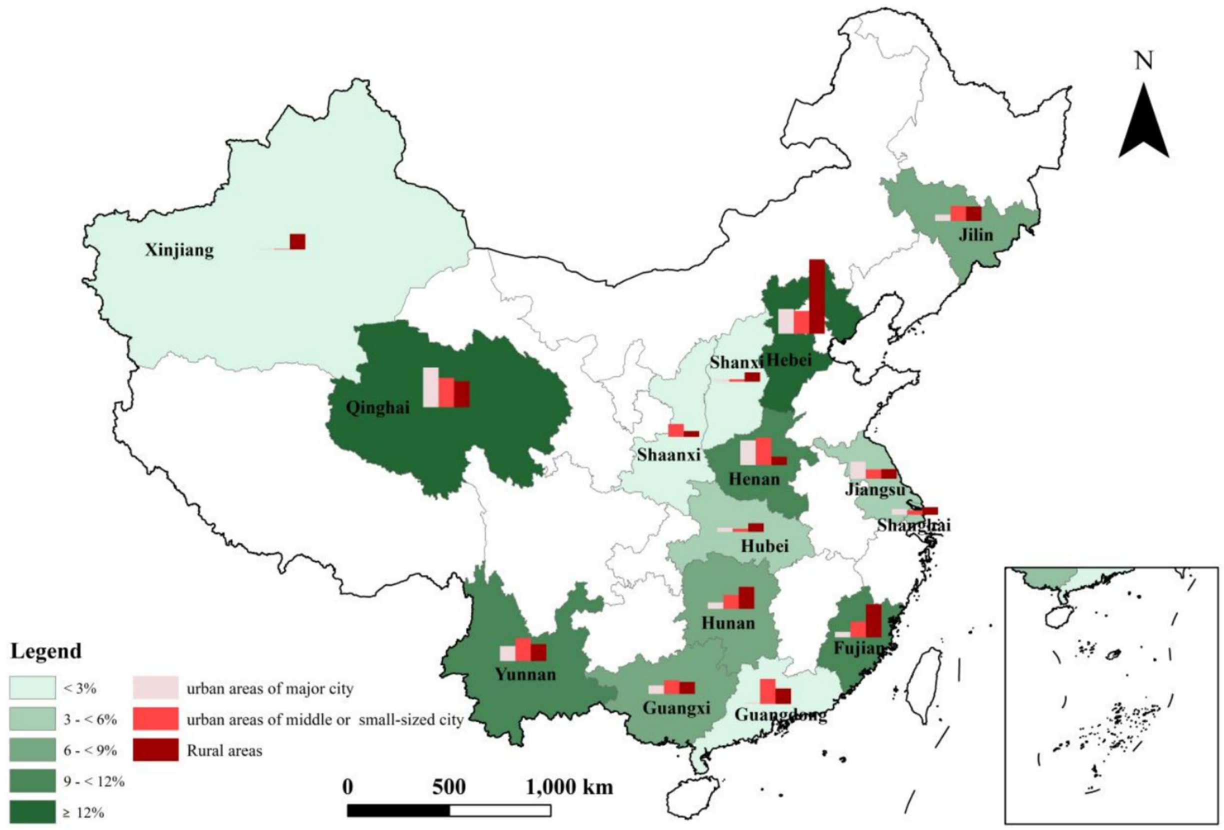

FIGURE 1
Distribution and EBLL prevalence in 0–6-year-old children of fifteen provinces in China.

male (8.3%) is higher than female (6.3%). Among different areas, female EBLL weighted prevalence in urban area of major cities (3.5%) is higher, while male EBLL weighted prevalence in urban area of middle or small-sized city (8.7%) and in rural areas (10.4%) are higher (Table 2; Figure 2).

3.3 Proportion of EBLL in children by demographic characteristics

Table 3 shows the EBLL (BLL ≥50 μg/L) proportion of 0–6-year-old (from 1 month old to under 7 years old) children in China by demographic characteristics. A specific population of mothers with low educational levels ($OR_{illiterate} = 6.43$, $OR_{primary\ school} = 4.55$, $OR_{middle\ school} = 3.46$, $OR_{high\ school} = 2.47$), fathers ($OR_{illiterate} = 8.28$, $OR_{primary\ school} = 6.99$, $OR_{middle\ school} = 4.86$, $OR_{high\ school} = 3.57$), primary caregivers ($OR_{illiterate} = 2.71$, $OR_{primary\ school} = 1.93$, $OR_{middle\ school} = 1.76$) refering to the person who lived with the child and was mainly responsible for the child's daily living arrangements, mother's occupation worker (OR = 1.53) or peasantry (OR = 1.31), father's ($OR_{worker} = 1.24$, $OR_{peasantry} = 1.25$), primary caregivers' ($OR_{worker} = 1.19$, $OR_{peasantry} = 1.23$), low economic income ($OR_{<50,000\ yuan} = 3.3$, $OR_{50,000–250,000\ yuan} = 2.11$) is at risk of EBLL compared to other groups.

3.4 Risk factors of children's behavior habits associated with EBLL

Information on children's behavioral habits is also collected, including taking nutritional supplements, health habits, local customs, taking traditional Chinese medicine or folk prescriptions, and drinking water. Logistic regression analysis shows that risk factors of EBLL include unfrequently nail trimming (OR = 1.23, 1.35), sometimes/frequently hand-to-mouth activity (OR = 1.20, 1.39), frequently playing with dirt (OR = 1.37), contacting or burning tinfoil paper 3 times or more per year (OR = 1.24, 2.17), applying lead tetroxide (OR = 1.61), sometimes/frequent using traditional dinnerware such as tin pots (OR = 1.47, 1.85), using tap water, surface water, ground water (OR = 1.15, 1.60, 2.10). In contrast, protection factors include sometimes/frequently taking Zinc (OR = 0.75, 0.73), Iron (OR = 0.90, 0.83), Calcium (OR = 0.74, 0.61), Vitamin D supplements (OR = 0.72, 0.61), sometimes/frequently washing hands using soap or hand sanitizer before meals (OR = 0.76, 0.61).

After adjustment of gender, age, geographical region, annual household income, educational background and occupation of the parents and caregivers, risk factors concerning children's behavior habits of EBLL include unfrequently nail trimming (OR = 1.14, 1.24), sometimes/frequently hand-to-mouth activity (OR = 1.23,

TABLE 1 The EBLL prevalence of children in different geographical regions of China.

Geographical region	Province	*N* (%)	Weighted prevalence of province (%)	Different districts						
				N (%)	Weighted prevalence of urban areas of major city (%)	*N* (%)	Weighted prevalence of urban areas of middle or small-sized city (%)	*N* (%)	Weighted prevalence of rural areas (%)	*p*
Eastern region	Shanghai	2,255 (6.9)	3.1	680 (30.2)	3.1	792 (35.1)	2.4	783 (34.7)	4.1	0
	Jiangsu	3,257 (10.0)	6	1,274 (39.1)	9.4	806 (24.7)	5.2	1,177 (36.1)	5.3	0
	Hebei	1,492 (4.6)	18.5	506 (33.9)	13.6	716 (48)	12.5	270 (18.1)	41	0
	Guangdong	1,791 (5.5)	2.8	150 (8.4)	1	782 (43.7)	13.8	859 (48)	8.6	0
	Fujian	1,977 (6.1)	9.3	575 (29.1)	3	708 (35.8)	8.6	694 (35.1)	18.2	0
	total of Eastern region	10,772 (33.1)	5.2*	3,185 (29.6)	2.6	3,804 (35.3)	7.8	3,783	12.4 (35.1)	0
Central region	Shanxi	2,554 (7.8)	2.8	772 (30.2)	1.4	849 (33.2)	1.3	933 (36.5)	5.1	0
	Henan	2095 (6.4)	10.3	622 (29.7)	13.6	712 (34)	15.1	761 (36.3)	4.6	0
	Jilin	2,140 (6.6)	6.5	702 (32.8)	3.4	350 (16.4)	8.2	1,088 (50.8)	7.9	0
	Hunan	2,314 (7.1)	7	697 (30.1)	3.6	940 (40.6)	7.7	677 (29.3)	12.2	0
	Hubei	2,269 (7.0)	3.1	716 (31.6)	2.3	730 (32.2)	1.8	823 (36.3)	4.8	0
	Total of Central region	11,372 (34.9)	6.1*	3,509 (30.9)	5	3,581 (31.5)	7.4	4,282 (37.7)	5.9	0
Western region	Shaanxi	1,681 (5.2)	0.5	309 (18.4)	0	625 (37.2)	7.1	747 (44.4)	3.2	0
	Yunnan	2,241 (6.9)	10.3	639 (28.5)	8.2	840 (37.5)	12.6	762 (34)	9.3	0
	Qinghai	2,465 (7.6)	17.2	882 (35.8)	21.9	779 (31.6)	16.2	804 (32.6)	14.2	0
	Guangxi	1,936 (5.9)	6.2	789 (40.8)	4.7	593 (30.6)	7.5	554 (28.6)	6.6	0
	Xinjiang	2,076 (6.4)	2.5	886 (42.7)	0.6	104 (5)	0.3	1,086 (52.3)	8.5	0
	Total of Western region	10,399 (32.0)	2.7*	3,505 (33.7)	1	2,941 (28.3)	6.5	3,953 (38)	7.4	0
Total		32,543 (100)	4.1	10,199 (31.3)	1.8	10,326 (31.7)	7.2	12,018 (36.9)	8.5	0

* Means $p < 0.05$.

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TABLE 2 EBLL prevalence of children with different ages and genders in China.

	Male	Female
N (%)	16,997 (52.2%)	15,546 (47.8%)
Weighted prevalence of EBLL	3.70%	4.90%
OR (95%CI)	Reference	1.36 (1.33,1.38)
p value		0
0–3-year-old		
N (%)	6,056 (52.1%)	5,571 (47.9%)
Weighted prevalence of EBLL	2.40%	4.00%
OR (95%CI)	Reference	1.68 (1.64,1.73)
p value		0
3–6-year-old		
N (%)	10,941 (52.3%)	9,975 (47.7%)
Weighted prevalence of EBLL	8.30%	6.30%
OR (95%CI)	Reference	0.75 (0.73,0.77)
p value		0
Urban areas of major city		
N (%)	5,364 (52.6%)	4,835 (47.4%)
Weighted prevalence of EBLL	1.30%	3.50%
OR (95%CI)	Reference	2.82 (2.71,2.92)
p value		0
Urban areas of middle or small-sized city		
N (%)	5,385 (52.1%)	4,941 (47.9%)
Weighted prevalence of EBLL	8.70%	5.60%
OR (95%CI)	Reference	0.62 (0.60,0.64)
p value		0
Rural areas		
N (%)	6,248 (52%)	5,770 (48%)
Weighted prevalence of EBLL	10.40%	6.50%
OR (95%CI)	Reference	0.60 (0.58,0.63)
p value		0

1.42), sometimes/frequently playing with dirt (OR = 1.12, 1.15), contacting or burning tinfoil paper 3 times or more per year (OR = 1.27, 1.96), applying lead tetroxide (OR = 1.56), sometimes/frequent using traditional dinnerware such as tin pots (OR = 1.34, 1.68), using folk prescriptions (OR = 1.23), using ground water (OR = 1.52). At the same time, sometimes/frequently taking Calcium (OR = 0.88, 0.82), Vitamin D supplements (OR = 0.86, 0.81), sometimes/frequently washing hands using soap or hand sanitizer before meals (OR = 0.87, 0.79) are protection factors (Table 4).

3.5 Risk factors of children's living environment associated with EBLL

Logistic regression analysis shows that risk factors of children's living environment associated with EBLL include living on the ground floor/The 2nd–3rd floor (OR = 1.93, 1.32), never/sometimes disusing first section of over night water (OR = 1.54, 1.35), frequently/sometimes passive smoking (OR = 1.32, 1.15), using coal or coal products/wood straw for cooking fuel (OR = 1.87, 1.41), using coal or coal products/wood straw for heating fuel (OR = 2.00, 1.55), none/chimney/window ventilated (OR = 1.60, 1.40, 1.28). There is no difference among houses of different distance to main road.

After adjustment of gender, age, geographical region, annual household income, educational background and occupation of the parents and caregivers, living on the ground floor (OR = 1.25), never/sometimes disusing first section of over night water (OR = 1.19, 1.16), frequently/sometimes passive smoking (OR = 1.24, 1.13), using coal or coal products for cocking fuel (OR = 1.50), using coal or coal products for heating fuel (OR = 1.68) remain risk factors of EBLL of 0–6-year-old children (Table 5).

4 Discussion

Phasing out leaded petrol in 2000 and a series of environmental protection measures have dramatically decreased children's BLL and the prevalence of lead poisoning in China over the past 20 years (28, 29); however, the CDC (2022) reported that there is no acceptable level of lead in the human body and that minimal lead levels can cause neurological damage to children (30). Lead exposure remains an important public health problem in China because of its extensive use in the manufacturing industry with rapid economic growth (20). This study assesses the prevalence and risk factors of EBLL in 0–6-year-old children in China. This group has more susceptibility to lead exposure for frequent hand-to-mouth activity and higher sensitivity to lead toxicity due to an immature nervous system.

The prevalence of EBLL, defined in this study as BLL ≥ 50 μg/L, among 0–6-year-old children in China is 4.1%. The Council of State and Territorial Epidemiologists' (CSTE) blood lead reference value is 35 μg/L in the United States. This value is used to identify adults and children whose blood lead levels are higher than the 97.5th percentile of adults and children nationwide (32, 33).

This study explores the prevalence of EBLL in different geographic regions of China. The weighted prevalence of EBLL in the central region is much higher than the other two regions in China, which is consistent with the result that the pool rate of lead poisoning in China's central region is higher than those in eastern and western regions as previous research showed (29). This change might be interpreted as the western region gradually reducing pollution industries with increasing awareness of environmental protection (34). The increasing support for primary medical and health care in western China from the central and local governments also contributes to the improving of children's health. However, among provinces of western region, the children prevalence of EBLL in Qinghai Province is at a high level, especially the prevalence of EBLL in urban areas of major city (21.9%) and in urban areas of middle or small-sized city (16.2%), which both ranked first in their respective categories. The investigation sites of children in urban areas in Qinghai province are

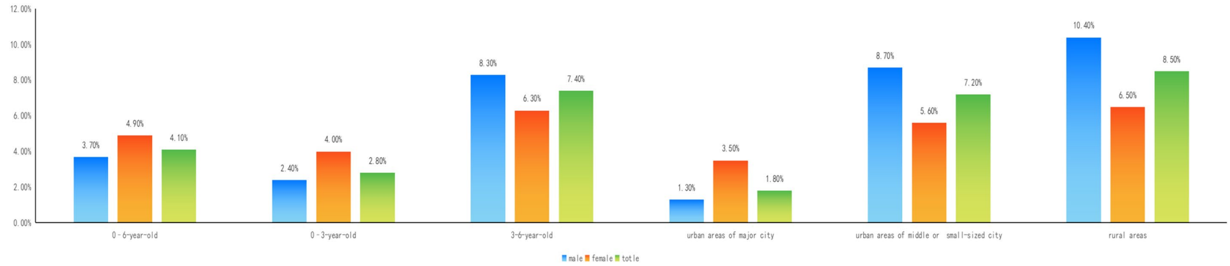

FIGURE 2
EBLL prevalence of children with different ages and genders in China.

located in Xining City, Delingha and Geermu City, where coal resources are abundant, and the proportion of manufacturing and mining industries is rising year by year. Delingha and Geermu City belong to Mongolian and Tibetan Autonomous Region, where multi-ethnic population lives together. Environment pollution caused by industrial development, different national cultures and living habits bring a great challenge of the improvement of children's living environment and health habits in such areas. Those results in the study suggest that we should pay more attention to monitoring children's blood lead levels and strengthening health education in areas with different national culture and rapid industrial development.

This survey reveals the prevalence of children EBLL of rural areas in China is much higher than of urban areas, which suggests that children in rural areas is at high risk of lead exposure. Considering geographic factor, children in rural areas of eastern and western regions is at high risk of EBLL, while children in urban areas of middle or small-sized city in central region should be pay more attention of possible lead exposure.

Some studies reveal the association between controlling environmental lead pollution in the atmosphere and considerable and sustained reduction of a population's blood lead level (16, 35). We found that prevalence of EBLL differed significantly by province with the highest in Hebei province (18.5%), which dominated by industry with proportion accounts for 53.5%, especially the iron and steel industry as the first pillar industry in Hebei Province in 2011. Among different districts, weighted prevalence of EBLL in rural area of Hebei province, where mineral resources such as coal and coal bed methane were abundant, is high up to 41.0%. This result suggests that we should pay attention to screening the blood lead levels of children in mineral rich areas.

In this study, we observed weighted prevalence of children with BLL ≥50 μg/L (EBLL) is higher in female than in male, which seems inconsistent with previous results with higher proportion of BLL ≥50 μg/L in male than in female (31). However, in consideration of multi-stage sampling method of the survey, the proportion does not represent prevalence. In order to make the sample better reflect the overall characteristics, weighting issue should be taken into account when prevalence is mainly discussed in this paper. Though boys has higher BLLs compared to girls as previous results, the prevalence of girls with BLL ≥50 μg/L is higher. When subgroups are discussed, the situation varies among different age groups and area groups. In 0–3-Year-old children, female weighted prevalence of EBLL is higher than male, while in 3–6-Year-old children, male is higher than female. Also, in major city districts, female weighted prevalence of EBLL is higher than male, while in middle or small-sized city districts and in rural areas, the situation is on the contrary. The same phenomenon has been reported about age-dependent manner of EBLL prevalence increasing with age growth (36). In this survey, EBLL prevalence is higher in 3–6-year-old children, and BLL is also higher compared to 0–3-year-old children which published in our previous article (31). More boys' bad habits and outdoor activity in 3–6-year-old children or in rural areas are likely to increase the risk of lead exposure (18, 35, 37).

As far as demographic characteristics are concerned, this study shows that mothers with low educational levels, fathers, caregivers, low socioeconomic family income and mother's occupation worker or peasantry, fathers, caregivers seemed to have a higher prevalence of EBLL. However, the trends of both BLL and EBLL prevalence increased significantly in an age-dependent manner was not observed in this study, which was needed further research and exploration. As for family socioeconomic status, parents or caregivers with higher educational levels are better aware of avoiding lead exposure and promoting children's good hygiene habits, reducing opportunities for children suffering from lead poisoning (26). Children living in poverty are more likely to reside in older houses with lead-based paint and lead-containing plumbing and have a higher likelihood of having nutritional imbalances such as iron deficiency (38).

This study examined risk factors related to children's behavioral tendency toward EBLL. The results show that unfrequently nail trimming, sometimes/frequently hand-to-mouth activity, sometimes/frequently playing with dirt were the risk factors of EBLL, as previous research has shown (39–43).

In this study we also explored local traditional custom and folk prescription impacting on EBLL incidence. We found that contacting or burning tinfoil paper 3 times or more per year, sometimes/frequent using traditional dinnerware such as tin pots, applying lead tetroxide, using folk prescriptions were risk factors of children EBLL. Local customs and traditions (such as contacting or burning tinfoil paper several times or using tin pots as dinnerware) might be related to lead exposure. Tinfoil paper is a complex of tin and lead with a surface layer of metal-containing lead. According to local customs in East China, during funerals, people often fold or burn tinfoil paper at home, and lead on the surface layer releases polluting indoor air, which might result in lead exposure (44). Another study showed that tinfoil paper manufacture in family workshops seriously impacts the BLLs of operators and their family members (45). We also found that tin pots, a traditional vessel containing lead, may cause EBLL if children use them (46). Traditional Chinese medicine believes that the

TABLE 3 Proportion of EBLL in children by demographic characteristics.

Demographic characteristics		*N* (%)	Proportion of EBLL	OR (95% CI)	*p* value
Maternal educational degree	Illiterate	269 (0.8%)	18.20%	6.43 (3.67, 11.3)	0
	Primary school	2,198 (6.8%)	13.60%	4.55 (2.8, 7.39)	0
	Middle school	12,528 (38.9%)	10.70%	3.46 (2.16, 5.55)	0
	High school	7,971 (24.8%)	7.90%	2.47 (1.53, 3.97)	0
	College/University	8,689 (27%)	4.60%	1.38 (0.85, 2.23)	0.19
	Higher education	538 (1.7%)	3.30%	Reference	
Paternal educational degree	Illiterate	99 (0.3%)	17.20%	8.28 (4.11, 16.7)	0
	Primary school	1,651 (5.2%)	14.90%	6.99 (4.3, 11.38)	0
	Middle school	12,063 (37.7%)	10.80%	4.86 (3.03, 7.78)	0
	High school	8,297 (25.9%)	8.20%	3.57 (2.22, 5.74)	0
	College/University	9,190 (28.7%)	4.90%	2.05 (1.27, 3.3)	0.003
	Higher education	737 (2.3%)	2.40%	Reference	
Caregiver's educational degree	Illiterate	1,390 (4.5%)	14.70%	2.71 (2.11, 3.47)	0
	Primary school	4,713 (15.2%)	10.90%	1.93 (1.55, 2.4)	0
	Middle school	11,244 (36.2%)	10.10%	1.76 (1.43, 2.17)	0
	High school	7,064 (22.8%)	7.00%	1.18 (0.95, 1.47)	0.146
	College/University	4,925 (15.9%)	4.10%	0.68 (0.53, 0.87)	0.002
	higher education	1706 (5.5%)	6.00%	Reference	
Maternal occupation	Worker	2,382 (7.4%)	11.90%	1.53 (1.31, 1.79)	0
	Peasantry	6,342 (19.8%)	10.40%	1.31 (1.16, 1.48)	0
	Merchant	12,900 (40.3%)	8.20%	1.01 (0.91, 1.13)	0.814
	Technicians or administrator	4,425 (13.8%)	5.40%	0.64 (0.55, 0.75)	0
	Others or unknowing	5,970 (18.6%)	8.10%	Reference	
Paternal occupation	Worker	3,990 (12.5%)	10.60%	1.24 (1.09, 1.42)	0.001
	Peasantry	6,060 (19.1%)	10.60%	1.25 (1.11, 1.41)	0
	Merchant	8,574 (27%)	8.30%	0.95 (0.84, 1.06)	0.344
	Technicians or administrator	6,782 (21.3%)	5.70%	0.63 (0.55, 0.72)	0
	Others or unknowing	6,399 (20.1%)	8.70%	Reference	
Caregiver's occupation	Worker	1798 (6.1%)	10.00%	1.19 (0.99, 1.42)	0.061
	Peasantry	6,982 (23.8%)	10.30%	1.23 (1.09, 1.38)	0.001
	Merchant	11,641 (39.7%)	8.30%	0.98 (0.87, 1.09)	0.663
	Technicians or administrator	2,821 (9.6%)	4.90%	0.55 (0.46, 0.67)	0
	Others or unknowing	6,065 (20.7%)	8.50%	Reference	
Annual household income (CNY)	<50,000 yuan	14,388 (45.7%)	10.70%	3.3 (2.51, 4.35)	0
	50,000–250,000 yuan	15,499 (49.3%)	7.10%	2.11 (1.6, 2.78)	0
	>250,000 yuan	1,579 (5%)	3.50%	Reference	

rational use of lead can treat various difficult and complicated diseases, but modern traditional Chinese medicine rarely uses it. Lead poisoning caused by lead containing drugs often comes from folk remedies. Lead tetroxide (chemical formula Pb_3O_4) is popular in some remote rural areas of southern China (47) for treating skin diseases, such as prickly heat and eczema; it is typically applied on children's necks, armpits, and groin areas. A case report covered that a 3-year-old boy with BLL 303 μg/L and his 6-month-old sister with BLL 385 μg/L had used lead tetroxide instead of baby power (21). An investigation of approximately 222 children living in a Chinese rural area showed that lead-containing powder use is significantly associated with EBLL (47). Other folk remedies that are significantly correlated with higher BLL are also reported, such as folk remedies for treating epilepsy (48–50). Although the medicinal value of lead was

TABLE 4 Risk factors of children's behavior habits associated with EBLL.

Factors of behavioral habits		*N* (%)	Proportion of EBLL	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)#	*p* value
Taking Zinc supplementation	Never	10,640 (33.4%)	10.10%	Reference		Reference	
	Sometimes	16,689 (52.4%)	7.70%	0.75 (0.69, 0.81)	0.00	0.86 (0.78, 0.94)	0
	Frequently	4,519 (14.2%)	7.60%	0.73 (0.65, 0.83)	0.00	0.88 (0.77, 1.02)	0.08
Taking Iron supplementation	Never	14,643 (46.3%)	9.00%	Reference		Reference	
	Sometimes	13,885 (43.9%)	8.10%	0.90 (0.83, 0.97)	0.01	0.99 (0.90, 1.08)	0.74
	Frequently	3,115 (9.8%)	7.60%	0.83 (0.72, 0.96)	0.01	0.95 (0.81, 1.12)	0.53
Taking Calcium supplementation	Never	4,596 (14.4%)	11.20%	Reference		Reference	
	Sometimes	17,574 (55.1%)	8.50%	0.74 (0.67, 0.83)	0.00	0.88 (0.79, 0.99)	0.04
	Frequently	9,751 (30.5%)	7.10%	0.61 (0.54, 0.69)	0.00	0.82 (0.71, 0.93)	0.00
Taking Vitamin D supplementation	Never	9,377 (29.4%)	10.70%	Reference		Reference	
	Sometimes	15,135 (47.5%)	7.90%	0.72 (0.66, 0.78)	0.00	0.86 (0.78, 0.95)	0.003
	Frequently	7,335 (23%)	6.80%	0.61 (0.55, 0.68)	0.00	0.81 (0.72, 0.93)	0.002
Washing hands using soap or hand sanitizer before meals	Rarely	14,215 (44.8%)	9.90%	Reference		Reference	
	Sometimes	12,613 (39.7%)	7.70%	0.76 (0.70, 0.83)	0.00	0.87 (0.79, 0.96)	0.01
	Frequently	4,915 (15.5%)	6.30%	0.61 (0.54, 0.69)	0.00	0.79 (0.69, 0.91)	0
Nail trimming	Less than every 2 weeks	19,320 (60.2%)	7.80%	Reference		Reference	
	Two weeks–one month	11,241 (35%)	9.40%	1.23 (1.14, 1.34)	0.00	1.14 (1.04, 1.25)	0
	More than 1 month	1,558 (4.9%)	10.20%	1.35 (1.13, 1.60)	0.00	1.24 (1.03, 1.50)	0.03
Hand-to-mouth activity	Rarely	14,315 (45.2%)	7.60%	Reference		Reference	
	Sometimes	13,736 (43.4%)	9.00%	1.20 (1.10, 1.31)	0.00	1.23 (1.12, 1.35)	0
	Frequently	3,596 (11.4%)	10.30%	1.39 (1.23, 1.57)	0.00	1.42 (1.24, 1.63)	0
Playing with dirt	Rarely	9,882 (31.2%)	7.90%	Reference		Reference	
	Sometimes	16,680 (52.7%)	8.20%	1.05 (0.95, 1.15)	0.34	1.12 (1.01, 1.24)	0.04
	Frequently	5,112 (16.1%)	10.50%	1.37 (1.22, 1.54)	0.00	1.15 (1.01, 1.32)	0.03
Contacting or burning tinfoil paper	0–1 times per year	28,156 (94.2%)	8.20%	Reference		Reference	
	2–3 times per year	1,234 (4.1%)	10.00%	1.24 (1.02, 1.50)	0.03	1.27 (1.03, 1.56)	0.03
	≥4 times per year	505 (1.7%)	16.20%	2.17 (1.70, 2.75)	0.00	1.96 (1.51, 2.56)	0
Applying lead tetroxide	Never	29,193 (98.5%)	8.50%	Reference		Reference	
	Yes	456 (1.5%)	12.90%	1.61 (1.22, 2.12)	0.00	1.56 (1.16, 2.09)	0
Using traditional dinnerware such as tinpots	Rarely	29,845 (94.4%)	8.30%	Reference		Reference	
	Sometimes	1,430 (4.5%)	11.70%	1.47 (1.25, 1.74)	0	1.34 (1.12, 1.61)	0
	Frequently	349 (1.1%)	14.30%	1.85 (1.37, 2.50)	0	1.68 (1.20, 2.35)	0
Using folk prescriptions	Never	28,721 (92.1%)	8.50%	Reference		Reference	
	Yes	2,454 (7.9%)	9.10%	1.09 (0.94, 1.25)	0.27	1.23 (1.05, 1.45)	0.01
Drinking water sources	Purified water	4,185 (13.4%)	6.80%	Reference		Reference	
	Tap water	22,464 (71.7%)	7.80%	1.15 (1.01, 1.31)	0.03	1.01 (0.88, 1.16)	0.91
	Surface water	591 (1.9%)	10.50%	1.60 (1.20, 2.14)	0	1.09 (0.78, 1.51)	0.63
	Ground water	4,097 (13.1%)	13.30%	2.10 (1.81, 2.45)	0	1.52 (1.29, 1.80)	0

Adjusted by gender, age, parent's and caregiver's educational degree, parent's and caregiver's occupation and geographical region.

TABLE 5 Risk factors of children's living environment associated with EBLL.

Factors of children's living environment		*N* (%)	Proportion of EBLL	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)#	*p* value
Floor of buildings	The ground floor	12,109 (37.9%)	11.00%	1.93 (1.74, 2.14)	0	1.25 (1.10, 1.42)	0
	The 2nd–3rd floor	10,402 (32.6%)	7.80%	1.32 (1.19, 1.48)	0	1.05 (0.93, 1.19)	0.43
	The 4th or above	9,419 (29.5%)	6.00%	Reference		Reference	
Disusing first section of over night water	Never	12,440 (39.3%)	9.50%	1.54 (1.36, 1.74)	0	1.19 (1.04, 1.37)	0.01
	Sometimes	13,519 (42.7%)	8.40%	1.35 (1.19, 1.52)	0	1.16 (1.02, 1.33)	0.03
	Frequently	5,665 (17.9%)	6.40%	Reference		Reference	
Passive smoking	Frequently	3,784 (12%)	10.10%	1.32 (1.17, 1.49)	0	1.24 (1.09, 1.41)	0
	Sometimes	11,469 (36.4%)	8.90%	1.15 (1.06, 1.25)	0	1.13 (1.03, 1.24)	0.01
	Never	16,229 (51.6%)	7.90%	Reference		Reference	
Cooking fuel	Coal or coal products	17,49 (5.5%)	13.70%	1.87 (1.62, 2.15)	0	1.50 (1.28, 1.76)	0
	Wood straw	3,187 (10%)	10.80%	1.41 (1.25, 1.60)	0	0.96 (0.84, 1.10)	0.59
	Clean energy	26,914 (84.5%)	7.90%	Reference		Reference	
Heating fuel	Coal or coal products	4,867 (16.5%)	13.40%	2.00 (1.81, 2.20)	0	1.68 (1.50, 1.88)	0
	Wood straw	1,506 (5.1%)	10.80%	1.55 (1.31, 1.84)	0	1.10 (0.91, 1.33)	0.31
	Clean energy	23,123 (78.4%)	7.20%	Reference		Reference	
Ventilation facilities	None	548 (1.7%)	11.30%	1.60 (1.22, 2.10)	0	1.02 (0.76, 1.36)	0.91
	Chimney	3,061 (9.7%)	10.00%	1.40 (1.22, 1.60)	0	0.91 (0.78, 1.06)	0.23
	Window ventilated	12,418 (39.6%)	9.20%	1.28 (1.17, 1.39)	0	1.01 (0.91, 1.11)	0.9
	Smoke exhaust ventilator	15,368 (49%)	7.40%	Reference		Reference	
Distance from house to main road	Along the street	4,813 (15.1%)	9.00%	1.09 (0.97, 1.22)	0.15	1.11 (0.98, 1.26)	0.09
	30–50 meters	3,238 (10.2%)	8.70%	1.05 (0.92, 1.2)	0.48	1.10 (0.95, 1.27)	0.2
	50–100 meters	7,271 (22.9%)	8.10%	0.97 (0.88, 1.07)	0.57	1.08 (0.97, 1.21)	0.15
	Above 100 meters	16,463 (51.8%)	8.40%	Reference		Reference	

Adjusted by gender, age, parent's and caregiver's educational degree, parent's and caregiver's occupation and geographical region.

recorded in the earliest Chinese pharmacological works, Shennong Classic of Materia Medica, for example, adding minerals such as lead to enhance the stability, sustainability, efficacy and storability of herbal medicines, modern Chinese medicine rarely used lead. Many studies revealed that the use of lead-containing herbs or lead-containing preparations mostly originated from folk remedies and long-term use of such lead-containing drugs may suffer from high risk of elevated blood lead levels or even lead poisoning (22, 45, 47, 51).

Furthermore, this study found that decentralized water supply was one of the risk factors for increased blood lead levels in children. In rural areas of China, decentralized water supply projects primarily utilized shallow well, mostly by household construction and management, and with the lack of water quality testing and monitoring. The findings show that the ground water with a non-central water supply was unsafe for lead exposure. Contamination of soil, water (groundwater and surface water), sediment, and air with hazardous and toxic compounds is one of the most severe and challenging problems that the industrialized world faces (52). A cross-sectional survey in Pakistan was conducted using water samples from drinking water sources. Of the 216 ground and surface water samples collected, 86% had lead levels higher than the World Health Organization's maximum acceptable concentration of 10 ppb. The mean lead concentration in groundwater was 146 ppb, significantly higher than in surface water, with a lead concentration of 77.1 ppb (53).

Previous studies also found that elevated lead concentration in water often occurs due to corrosive water effects on pipeline materials, such as plumbing, coating, solder, pipes, pipe joints, and fittings (54). That might partially explain the result in this study that never/sometimes disusing first section of over night water might increase risk of EBLL.

This study also discussed children's living environmental risk factors associated with EBLL. Lead pollution mainly comes from dust and sediment on the ground or suspended in the air. These are released by industrial metal smelting, mining enterprises, and related industrial and manufacturing industries, such as battery manufacturing, printing, mechanical manufacturing, and shipbuilding (18, 55). The results of a meta-analysis show that the corrected pooled lead poisoning rates of populations living around mining areas (70%) and industrial areas (57.5%) are much higher than those in urban areas (9.6%), suburban areas (23.6%), and rural areas (23.8%) (29). The total suspended lead particle counts in ambient air and lead concentrations are ten times higher than in the upper air above the ground where children breathe (40).

Our investigation suggested that the parents' occupational exposure to lead is a risk factor for EBLL among children. Lead dust from parents' surfaces and work clothing can be digested or inhaled by children at home (37). Parents may also carry the lead from the workplace to home in their clothing.

We find that living on the ground might increase the EBLL risk due to contacting dust, soil, or smoke. Lead in the air and the soil can enter the room of lower floors more easily than on higher floors, which leads to a higher rate of EBLL occurrence. A study tested that reducing 1,000 ppm or more lead in soil accessible to children would decrease at least 30 μg in BLLs. The results demonstrated that lead-contaminated soil or dust contributes to the lead burden in children (56).

We also verify that passive smoking as a risk factor is associated with EBLL, which is similar to the result of a previous study (37). Cigarettes contain heavy metals, such as cadmium and lead, and second-hand smoking exposure can increase the level of lead in children's blood (26, 57, 58). It is estimated that 72% of non-smokers, including 180 million children under the age of 15, who live in China are exposed to second-hand smoke (59, 60).

This study also focuses on the impact of indoor air pollution from coal burning on children EBLL. During the coal combustion process, various atmospheric pollutants can be generated, including the heavy metal element lead, which is highly volatile. The result revealed the harmfulness of indoor cooking and heating fueled by coal or coal products. Therefore, coal which is commonly used as indoor fuel in northern China, is not recommended as a household fuel to avoid lead exposure.

Unlike previous research results, we did not find an increase in the prevalence of EBLL with a decrease in the distance between the residence and the main road. Local researches in China have found that after the implementation of unleaded gasoline, automobile exhaust is no longer the main source of atmospheric lead pollution. Lead pollution in road dust is mainly controlled by coal combustion emissions and non-ferrous metallurgical emissions (61, 62). Thus, the distance between the residence and the main road is not a risk factor of EBLL in China.

The strength of this study is its reporting prevalence of EBLL in Chinese children aged 0–6 years (from 1 month old to under 7 years old) in a large sample size and exploring risk factors for children lead exposure, especially in areas of traditional Chinese customs and the use of folk remedies. These issues have been rarely addressed in previous studies. Nonetheless, this study has some limitations. While adequate for assessing the BLLs of most Chinese children aged 0–6 years, the sample size may not be sufficient to reflect the extent of overall risk associated with lead exposure. Furthermore, this study did not directly measure the lead level of pollution sauces, such as the atmosphere, drinking water, soil, house dust, diet, and others in the children's proximate environment. Moreover, as a cross-sectional study, the data reflect children's lead exposure over the study period.

5 Conclusion

This study reveals the prevalence and risk factors for EBLL (BLL ≥ 50 μg/L) in 0–6-year-old children (from 1 month old to under 7 years old) in China. The pediatric population with high-risk factors should be given attention of lifestyle habits and living environment of lead exposure. This study also indicates that lead poisoning in children is preventable by removing high-risk factors and promoting protective factors. We hope this study will help public health education and inform policy for preventing and eradicating lead poisoning in China.

Data availability statement

The data are available from the corresponding author on reasonable request.

Ethics statement

The studies involving humans were approved by Ethics Committee of Xinhua Hospital affiliated with Shanghai Jiao Tong University School of Medicine (XHEC-C-2013-008). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

M-ML: Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. X-TJ: Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. JZ: Formal analysis, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. Z-YG: Data curation, Methodology, Project administration, Software, Supervision, Writing – review & editing. JC: Data curation, Methodology, Project administration, Supervision, Writing – review & editing. J-XL: Methodology, Supervision, Writing – review & editing. Y-LY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. C-HY: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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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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Association between household solid fuel use and cognitive frailty in a middle-aged and older Chinese population

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Objectives: Our research intended to investigate the association between the solid fuels use and the risk of cognitive frailty (CF).

Methods: The research utilized data from the China Health and Retirement Longitudinal Study (CHARLS), a nationwide longitudinal study focusing on individuals aged 45 and older. A total of 8,563 participants without CF were enrolled from 2011 and followed up to 2015. Household fuel types include solid fuels (such as coal, crop residue, or wood-burning) and clean fuels (such as solar power, natural gas, liquefied petroleum gas, electricity, or marsh gas). CF was defined as the co-existence of cognitive impairment and physical frailty. Cox proportional hazards models were utilized to evaluate the relationship between the solid fuels use and the risk of CF. Furthermore, sensitivity analyses were conducted.

Results: Over a median follow-up of 4.0 years, 131 subjects were diagnosed with CF. We observed that the solid fuels use for cooking or heating increased the risk of developing CF compared to clean fuels, with HRs of 2.02 (95% CI: 1.25 to 3.25) and 2.38 (95% CI: 1.26 to 4.48), respectively. In addition, participants who use solid fuel for heating (HR: 2.38 [95% CI: 1.26, 4.48]) and cooking (HR: 2.02 [95% CI: 1.25, 3.25]) might experience an increased risk of CF. However, transitioning from solid to clean fuels for cooking could potentially reduce these risks (HR: 0.38 [95% CI: 0.16, 0.88]).

Conclusion: Household solid fuels utilization was closely associated with the risk of CF.

KEYWORDS

household solid fuel, cognitive frailty, cohort study, CHARLS, Chinese older adult individuals

Introduction

Cognitive frailty (CF) is a complex condition that gradually develops with aging (1). Previous studies have shown that cognitive impairment (CI) is significantly associated with physical frailty (PF) in older adults, as the two conditions frequently coexist (2, 3). In response to this, a consensus meeting held by members of the International Academy on Nutrition and Aging (I.A.N.A.) and the International Association of Gerontology and Geriatrics (I.A.G.G.) recently established the concept of CF (1). CF was defined as the coexistence of PF and mild CI without dementia. Global survey data indicate that the prevalence of CF among older adults in communities ranges from 1 to 5% (4), potentially affecting approximately 3.9 million older adult individuals in China (5). CF has a significant negative impact on health and is closely associated with an increased risk of disability, higher mortality rates, and a reduced quality of life (6).

PF, a key component of CF, has a global prevalence of approximately 12% and is primarily characterized by reduced walking speed and decreased muscle strength (7, 8). The impact of PF on cognitive functions is also noteworthy. Research has shown that low physical activity may further diminish cognitive reserves, triggering clinical or pathological manifestations of CI (9). Moreover, functional limitations in daily activities due to PF are closely linked to an increased risk of CI (10). CI involves declines in various cognitive domains, such as memory, visuospatial abilities, orientation, calculation, executive function, and comprehension (11). It is important to note that PF and CI frequently interact and coexist within the same individuals (12). The more holistic concept of CF integrates PF with CI, emphasizing the need for integrated healthcare strategies that address both cognitive and physical health challenges simultaneously (12, 13).

Globally, approximately 2.4 billion people depend on solid fuels, such as coal, crop residue, and wood burning, primarily for cooking and heating, which positions it as a leading cause of household air pollution (HAP) (14). Each year, over 3 million people worldwide die prematurely due to HAP (15). In typical developing countries like China, about 33% of the population remains reliant on solid fuels due to difficulties in accessing cleaner alternatives, particularly among lower-income and less-educated groups (16). The combustion of these solid fuels generates a significant amount of pollutants, including fine particulate matter ($PM_{2.5}$ and PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), black carbon, and various organic compounds that are carcinogenic (17). These harmful substances pose a serious threat to human health, potentially causing cardiovascular and respiratory diseases, severe depressive symptoms, and cognitive function in the nervous system (18). Given the widespread use of solid fuels in households and the increasing recognition of CF, there is a lack of literature explicitly linking these two variables. Therefore, it is crucial to investigate the connection between utilization of solid fuels and its impact on CF.

In light of the current dearth of research pertaining to the link between domestic use of solid fuels and CF, and considering China's evolution towards a population with a higher average age, we seek to explore if the utilization of indoor solid fuels among Chinese individuals aged 45 and older is linked to the likelihood of CF.

Methods

Study design and population

This study employed data from the China Health and Retirement Longitudinal Study (CHARLS), a comprehensive nationwide population cohort study. The research carried out within the framework of CHARLS has obtained ethical approval from the Biomedical Ethics Review Committee of Peking University (IRB 00001052–11,015), and all participants have provided their informed consent by signing consent forms. CHARLS, which was initiated in 2011 and is conducted every 2 years, has the primary objective of gathering nationally representative data from Chinese individuals aged 45 and above in order to advance gerontological research. This comprehensive study employs a meticulously designed multistage stratified probability proportional to size sampling method, which involves randomly selecting around 10,000 households across 450 villages/communities in 150 counties/districts throughout 28 provinces (19). Every participant is subjected to evaluation using standardized questionnaires, facilitating the methodical gathering of extensive data on sociodemographic characteristics, current indoor fuel exposures, lifestyle habits, and health-related information. The structured survey includes eight sections, with complete details accessible on the official CHARLS website.[1] In 2014, the CHARLS introduced a pioneering life course survey aiming to reconstruct the life histories of Chinese residents aged 45 and above by delving into their past experiences. This particular survey offers detailed insights into the previous indoor fuel usage among participants of the 2011 baseline survey. To date, comprehensive data has been available from several phases: the initial baseline survey in 2011, followed by two-year (2013), four-year (2015), seven-year (2018), and nine-year (2020) follow-ups, along with the vital data from the 2014 life course survey.

Notably, the definition of CF encompasses a range of biochemical indicators, including body mass index (BMI), the chair stand test, 2.5-meter gait speed, and the grip strength test. Concerning biochemical data collection, the CHARLS was only conducted at critical intervals: initially at baseline in 2011, then in a second wave in 2013, and a third wave in 2015. Consequently, our analysis focused on the data collected within the 2011 to 2015 period. The preliminary phase of our study involved screening 17,708 individuals from the baseline survey conducted between 2011 and 2012. The criteria for excluding participants from the further analysis were as follows: those under the age of 45 ($n = 602$), missing data on both fuel use ($n = 1909$), use of other fuel types not specified ($n = 2,864$), diagnosis of mental disorders ($n = 144$), and missing information on significant covariates ($n = 2076$). Additionally, 151 participants who had prevalent CF at baseline and 1,397 participants who were lost to follow-up were also excluded. Ultimately, 8,563 participants were deemed eligible for our study, as illustrated in Figure 1.

Definition of household solid fuel

Adapting the research methodology from Chen et al. (20), we employed two pivotal questionnaires to ascertain the predominant energy sources in households, including queries like "What is the main source of cooking fuel?" and "What is the primary heating energy source?." Solid fuels were self-reported and categorized into coal, crop residues, or wood-burning used for cooking and heating purposes. In contrast, clean fuels encompassed the habitual use of solar energy, natural gas, liquefied petroleum gas, or electricity to meet cooking and heating demands. To ensure the precision and relevance of our study, we excluded responses indicating the use of "other" fuels (21). Fuel switching is assessed when a disparity in fuel utilization exists between the life course survey and the baseline (22). For instance, if the life course survey unveils an individual's reliance on solid fuels, while the baseline indicates the adoption of clean fuels, this circumstance would be interpreted as a shift in the participant's fuel use from clean fuels to solid fuels.

1 http://charls.pku.edu.cn/en

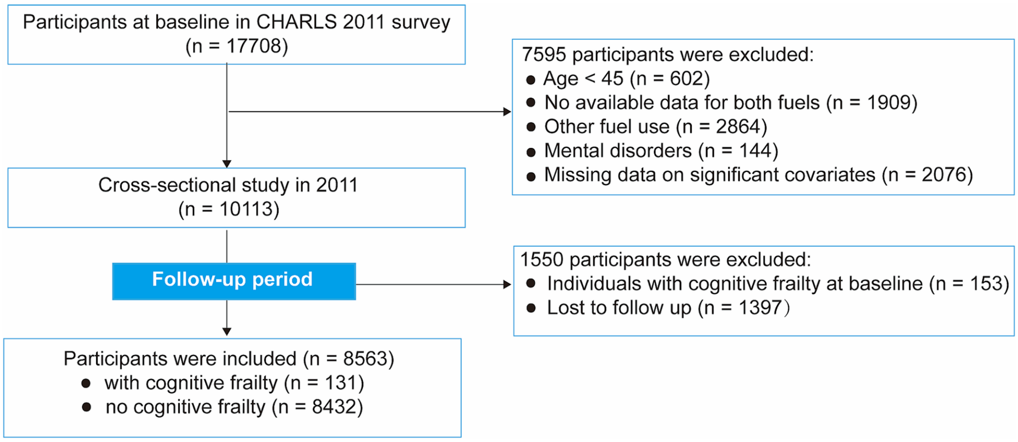

FIGURE 1
Flow chart of the study participant selection process.

Definition of PF

PF was conducted through an adapted version of the Fried phenotyping approach (23). This refined approach was adapted and validated within the CHARLS framework (24). As described previously (12, 24–26), PF encompasses five components: shrinking, weakness, slowness, low physical activity, and exhaustion. Shrinking was defined as having a BMI not exceeding 18.5 kg/m^2 or self-reporting a weight loss of 5 kg or more in the preceding year. Weakness was evaluated by measuring handgrip strength with a dynamometer for both dominant and non-dominant hands, where participants were encouraged to exert their maximum effort. The criterion for defining weakness was set at a grip strength at or below the 20th percentile, taking into account adjustments for sex and BMI. Slowness was assessed through a 2.5-meter gait speed or the chair stand test, as outlined by Wu et al. (24). Participants were classified as having low physical activity based on their responses to three specific questions regarding their engagement in vigorous activities, moderate physical effort, and walking for at least 10 min continuously during a typical week (25). Negative responses to these questions resulted in their categorization into the low physical activity group.

The level of exhaustion was evaluated using two specific questions from the 10-item Center for Epidemiological Studies Depression Scale (CESD-10): “I felt everything I did was an effort” and “I could not get going.” Participants who responded with “sometimes or half of the time (3–4 days)” or “most of the time (5–7 days)” to either of these questions were categorized as experiencing self-reported exhaustion (25). Participants meeting three or more of the specified criteria were defined as PF.

Definition of CI

Within the CHARLS, the evaluation of CI concentrated on two primary cognitive measures: episodic memory and executive function (27).

Episodic memory assessment

This is measured through immediate and delayed recall tests. The procedure involves reading 10 unrelated Chinese words to the participants, followed by an evaluation of their ability to recall these words both immediately and after a four-minute interval. The episodic memory score is calculated as the average of the immediate and delayed recall scores, with a range from 0 to 10.

Executive function assessment

This is based on the Telephone Interview for Cognitive Status (TICS) and a drawing test. The TICS involves tasks like recognizing the date (year, month, season, and day), the day of the week, and performing serial subtraction of 7 from 100 (5 times). In the drawing test, participants are asked to replicate a given image. The executive function score is the combined total of the TICS and drawing test scores, with a scale from 0 to 11.

Ultimately, the total cognitive function score is derived from adding the scores of episodic memory and executive function, with a maximum of 21 points. According to the literature, a total score below 6 is defined as indicative of CI, whereas a score above this threshold is considered indicative of normal cognitive function (27).

Definition of CF

In accordance with the definition established by the International Consensus Group (I.A.N.A/I.A.G.G) (1), and as substantiated in the literature of preceding studies (5, 12, 25), the concept of CF is identified as the concurrent presence of CI and PF.

Covariates

Based on prior research (20, 28), we included the following covariates: social activities, age (years), sex (female/male), education level (junior high school or below/senior high school or above), marital status (married/divorced/widowed/unmarried), self-reported socioeconomic status (poor/fair/good), residence (urban/rural), smoking status (non-smoker/current or former smoker), drinking status (non-drinker/current or former drinker), and the presence of hypertension, diabetes, and stroke (yes/no for each). Socioeconomic status was self-reported through the question, "How would you rate your standard of living?" with options ranging from poor to very high. Based on their responses, we classified them into three categories: "poor" (including relatively poor and poor), "fair" (equivalent to a fair standard of living), and "good" (comprising both relatively high and very high). The criteria for identifying hypertension were (29): (1) a systolic blood pressure of 140 mmHg or more, (2) a diastolic blood pressure of 90 mmHg or more, (3) a self-reported history of hypertension, or (4) the use of medication to lower blood pressure. Participants were deemed to have diabetes if they reported a diagnosis confirmed by a doctor, had fasting blood glucose levels of 126 mg/dL (7.0 mmol/L) or above, had glycosylated hemoglobin levels of 6.5% or above, or were taking medications for diabetes (30).

Statistical analyses

Based on the cooking and heating fuel type, we presented baseline characteristic data with continuous variables expressed as mean ± standard deviation (SD) and categorical variables as percentages. We calculated CF incidence rates by individual cooking or heating fuel type, expressing these with 95% confidence intervals (CIs) as events per 1,000 person-years. The Cox proportional hazards model is a statistical methods employed to analyze the relationship between one or more explanatory variables (also known as covariates) and the hazard rate of a specific event (31). In the present study, we used Cox regression to evaluate the association between the solid fuels use and the hazard risk of CF. We assessed the proportional hazards models using Schoenfeld residuals and found no violations (32).

We first analyzed the different impacts of solid fuels for heating and cooking on the risk of CF. We then investigated the collective effects of fuel combinations on the development of CF ([reference group]: both clean fuels; [exposure group]: clean fuel use for cooking and solid fuel use for heating; solid fuel use for cooking and clean fuel use for heating; solid fuel use for both cooking and heating), including transitions from solid to clean fuels and vice versa. For each analysis, we calculated hazard ratios (HRs) and their 95% CIs. Participants were followed up from baseline to CF diagnosis, death, or the end of the follow-up, whichever came first. In our study, three Cox models were constructed: Model 1 was unadjusted, Model 2 adjusted for age and sex, and Model 3 with full adjustments including age, sex, education level, marital status, smoking, drinking status, residence, self-reported socioeconomic status, social activities, hypertension, diabetes, and stroke.

We conducted a comprehensive series of sensitivity analyses to rigorously assess and confirm the robustness of our findings. (1) Firstly, considering the diversity of solid fuel used among households in the CHARLS, we separately evaluated the individual impacts of coal use and crop residue/wood burning on the risk of developing CF. (2) Moreover, the published literature reveals variations in the definition of clean fuels for heating (33). These definitions can be broadly divided into two categories: solar energy, natural gas, liquefied petroleum gas, and electricity, whereas the other includes centralized heating alongside these previously mentioned fuels. In our sensitivity analysis, we specifically considered centralized heating as a factor within clean heating fuels. (3) To minimizing the influence of confounding factors and to uncover potential modification or interaction effects of stratified variables, as well as population-specific findings, we conducted stratified analyses based on age (≤65/>65), sex (female/male), socioeconomic status (poor/fair/good), drinking (nondrinker/ Current or former drinker), and smoking (nonsmoker/ current or former smoker). The interactions between these stratified covariates and CF were estimated using the likelihood ratio test. It is noteworthy that due to the uneven distribution of disease prevalence among the baseline population, we did not conduct stratified analyses for conditions such as hypertension, diabetes, and stroke.

A statistically significant result was determined when the two-tailed p value was less than 0.05. The statistical analyses were conducted utilizing the R software (version 4.1.2).

Results

Participant's characteristics

Table 1 presents the fundamental characteristics of the included population categorized by the various types of household fuel utilization. Among the 10,232 study participants, we documented 131 incident CF, with females comprising 53.60% and males 46.40%, during a median observation period of 4.0 years. Regarding fuel usage, 62.60% of participants reported regularly using solid fuels for cooking, and 76.50% used solid fuels for heating; conversely, 37.40 and 23.50% of participants, respectively, used clean fuels for cooking and heating. Compared with participants who used clean fuels for heating or cooking, the group using solid fuels generally reported lower socioeconomic status and a higher proportion of current or former smokers and stroke patients. Furthermore, those using solid fuels for cooking or heating were often older, more likely to be unmarried or widowed, and tended to hold a junior high school diploma or lower, with a relatively higher risk of CF. Notably, urban dwellers often opted for clean fuels for heating or cooking purposes, whereas individuals in rural regions predominantly used solid fuels for these daily needs.

Associations between household solid fuel use and cognitive frailty

In the longitudinal analysis, participants who utilized solid fuels for cooking or heating exhibited a higher risk of CF when compared to those employing clean fuels. Table 2 illustrated that the use of solid fuels for cooking significantly increased the risk of CF after adjusting for all covariates (HR: 2.02, 95%CI: 1.25–3.25). A similarly significant association was observed in the use of solid fuels for heating (HR: 2.38, 95%CI: 1.26–4.48). When examining the combined exposure to fuels, individuals reporting the use of solid fuels for both cooking and heating had a significantly higher risk of CF, with HR of 3.17 (95%CI: 1.43–7.05), compared to those reporting the use of clean fuels for both. However, null associations were observed among other combinations of fuel usage.

Associations between fuel use switching and cognitive frailty

Table 3 illustrated that 1,045 individuals transitioned from solid to clean fuels for cooking and 393 for heating, with their CF incidence rates (per 1,000 person-years) recorded at 2.24 and 1.70, respectively. When compared with counterparts who continued using solid fuels

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TABLE 1 Participant characteristics by household fuel type at baseline.

Characteristic	Household heating fuel			Household cooking fuel		
	Total	Clean fuels	Solid fuels	Total	Clean fuels	Solid fuels
Number of participants, *n* (%)	8,563 (100)	2013 (23.50)	6,550 (76.50)	8,563 (100)	3,202 (37.40)	5,361 (62.60)
Age, years (mean ± SD)	58.50 ± 9.06	57.50 ± 9.05	58.70 ± 9.05	58.50 ± 9.06	57.40 ± 8.89	59.10 ± 9.10
Social activity score (mean ± SD)	1.11 ± 1.51	1.44 ± 1.75	1.00 ± 1.41	1.11 ± 1.51	1.35 ± 1.71	0.96 ± 1.35
Sex (%)						
Female	53.60	53.80	53.60	53.60	53.10	54.00
Male	46.40	46.20	46.40	46.40	46.90	46.00
Educational level (%)						
Junior high school or below	90.70	84.90	92.50	90.70	84.60	94.33
Senior high school or above	9.30	15.10	7.50	9.30	15.40	5.67
Socioeconomic status (%)						
Poor	44.70	37.00	47.10	44.70	38.30	48.50
Fair	52.60	59.20	50.60	52.60	57.90	49.40
Good	2.70	3.80	2.30	2.70	3.80	2.10
Residence (%)						
Urban	31.60	56.00	24.20	31.60	51.50	19.80
Rural	68.40	44.00	75.80	68.40	48.50	80.20
Social activity score (%)						
0 (no social activities)	55.10	47.60	57.50	55.10	49.60	58.40
1–2 (infrequent social activities)	21.70	22.20	21.50	21.70	22.10	21.50
≥3 (frequent social activities)	23.20	30.20	21.00	23.20	28.30	20.10
Smoking (%)						
Nonsmoker	61.20	64.50	60.20	61.20	62.80	60.30
Current or former smoker	38.80	35.50	39.80	38.80	37.20	39.70
Drinking (%)						
Nondrinker	61.10	59.70	61.50	61.10	59.90	61.80
Current or former drinker	38.90	40.30	38.50	38.90	40.10	38.20
Marital status (%)						
Married	88.50	89.00	88.30	88.50	89.20	88.00
Divorced	0.60	0.99	0.47	0.60	0.81	0.47
Widowed	10.10	9.74	10.20	10.10	9.78	10.30
Unmarried	0.80	0.27	1.03	0.80	0.21	1.23
Diabetes (%)						
No	93.20	92.40	93.50	93.20	92.20	93.90
Yes	6.80	7.60	6.50	6.80	7.80	6.10
Hypertension (%)						
No	72.90	73.30	72.70	72.90	72.70	73.00
Yes	27.10	26.70	27.30	27.10	27.30	27.00
Stroke (%)						
No	97.30	97.50	97.30	97.33	97.60	97.20
Yes	2.70	2.50	2.70	2.67	2.40	2.80
Cognitive frailty (%)						
No	98.50	99.50	98.20	98.50	99.30	98.0
Yes	1.50	0.50	1.80	1.50	0.70	2.00

All values are presented as proportion (%), or mean (standard deviation). SD, standard deviation.

TABLE 2 Hazard ratios and 95% CI of household solid fuel use for cognitive frailty.

Exposure	Cases	Number of events	Incidence rate per 1,000 person-years (95% CI)	Model 1[a] HR[d] (95% CI), *p*-value	Model 2[b] HR[d] (95% CI), *P*-value	Model 3[c] HR[d] (95% CI), *P*-value
Heating						
Clean fuels	2013	11	1.37 (0.72, 2.53)	**1 (Ref.)**	**1 (Ref.)**	**1 (Ref.)**
Solid fuels	6,550	120	4.63 (3.85, 5.55)	3.28 (1.82, 6.27) **<0.001**	3.10 (1.67, 5.75) **<0.001**	2.38 (1.26, 4.48) **0.007**
Cooking						
Clean fuels	3,202	22	1.72 (1.11, 2.66)	**1 (Ref.)**	**1 (Ref.)**	**1 (Ref.)**
Solid fuels	5,361	109	5.14 (4.24, 6.22)	2.99 (1.89, 4.73) **<0.001**	2.56 (1.62, 4.06) **<0.001**	2.02 (1.25, 3.25) **0.003**
Mixed fuel use						
Both clean fuels	1,589	7	1.10 (0.48, 2.38)	**1 (Ref.)**	**1 (Ref.)**	**1 (Ref.)**
Clean fuel use for cooking and solid fuel use for heating	1,598	15	2.34 (1.36, 3.95)	2.12 (0.45, 1.64) 0.10	2.15 (0.87, 5.29) 0.09	1.67 (0.66, 4.23) 0.27
Solid fuel use for cooking and clean fuel use for heating	424	4	2.38 (0.76, 6.52)	2.15 (0.63, 7.37) 0.22	1.79 (0.52, 6.18) 0.35	1.39 (0.37, 5.20) 0.62
Solid fuel use for both cooking and heating	4,937	105	5.38 (4.42, 6.54)	4.89 (2.27, 10.52) **<0.001**	4.20 (1.95, 9.03) **<0.001**	3.17 (1.43, 7.05) **0.004**

Model 1[a]: no covariates were adjusted; Model 2[b]: adjusted for age and sex; Model 3[c]: age, sex, education level, marital status, smoking, drinking status, residence, self-reported socioeconomic status, social activities, hypertension, diabetes, and stroke; HR[d]: effect value; Bolded *p*-values indicate statistical significance. HR, hazard ratio; 95% CI, 95% confidence interval.

for cooking, those who made the switch to clean fuels demonstrated a significant reduction in CF risk (HR: 0.38, 95%CI: 0.16–0.88). A similar association was reported among individuals switching from solid to clean heating fuels in Models 1 and 2. Conversely, 2,174 individuals transformed from clean to solid cooking fuels, and 3,152 made a similar switch for heating, with their CF incidence rates (per 1,000 person-years) estimated to be 6.51 and 5.44, respectively. Compared to those who consistently used clean fuels for cooking, the group that switched from clean to solid fuels had an increased risk of developing CF (HR: 2.45, 95% CI: 1.16–5.19).

Sensitivity analyses

We conducted a series of sensitivity tests to affirm the robustness of our results. Firstly, when central heating was additionally included in the original fuel use, the results remained consistent with previous findings (Supplementary Table S1). Moreover, when analyzing solid fuels (coal and crop residues/wood burning) separately, the results remained stable (Supplementary Tables S2, S3). A similar trend was observed for the use of fuels for heating purposes (HR: 0.21, 95% CI: 0.05–0.86). Finally, stratified analysis revealed variations in how influenced the results (Supplementary Tables S4–S9): despite overall consistency in outcomes when analyzed by stratification, a significant association was found within the group aged 65 and below, but not in those over 65. Similarly, a significant association was observed in groups with lower socioeconomic status, while no such association existed within groups of higher socioeconomic status. Notably, the use of solid fuels was significantly associated with an increased risk of developing CF in both smokers and non-smokers. Concurrently, no statistically significant interactions were observed among participants stratified by age, sex, residence, socioeconomic status, smoking, and drinking (all *P* for interaction >0.05).

Discussion

Our study demonstrates a significant association between the use of indoor solid fuels and an increased risk of CF compared to clean fuels. Both cooking and heating with solid fuels are linked to a higher risk of CF, with the risk being even greater when solid fuels are used for both activities. This suggests that combined exposure to solid fuels for cooking and heating may result in a higher cumulative exposure to harmful pollutants, thereby increasing the risk of CF.

Our study has found a significant link between solid fuel usage and CF among middle-aged and older adult groups, consistent with earlier research findings. Specifically, by examining data from individuals aged 50 and above, three national cohort studies utilized time-dependent Cox regression models and mediation effect analyses (18). These studies provided robust evidence that the use of solid fuels for cooking markedly elevates the risk of CI. Moreover, an extensive analysis of 7,824 individuals in middle age and older from China, evaluating cognitive abilities via standardized surveys, showed that the use of solid fuels for cooking and heating markedly elevated the risk of CI (34). Cao and colleagues conducted a longitudinal study with 4,946 older adult individuals and discovered a positive correlation between the use of solid cooking fuels and the incidence of PF, in line with prior research findings (35). Furthermore, an analysis leveraging prospective data from CHARLS, which included 4,685 participants initially non-frail, identified a positive link between the use of solid fuels and a heightened risk of frailty (36). Additionally, one research conducted on 4,535 older adult individuals from 23 provinces substantiated the link between solid fuel use and a significant increase in the frailty index (37). Taken together, these results substantially reinforce the credibility and strength of our findings, confirming the harmful effects of solid fuel usage on the health of middle-aged and older adults.

To our knowledge, this study represents the inaugural cohort analysis exploring the link between domestic solid fuel consumption

TABLE 3 Incidence rates and adjusted hazard ratios for cognitive frailty in association with switching fuel types.

Exposure	Cases	Number of events	Incidence rate per 1,000 person-years (95% CI)	Model 1[a] HR[d] (95% CI), *p*-value	Model 2[b] HR[d] (95% CI), *p*-value	Model 3[c] HR[d] (95% CI), *P*-value
Cooking						
Solid fuel use	1879	36	6.47 (4.60–9.15)	**1 (Ref.)**	**1 (Ref.)**	**1 (Ref.)**
Solid to clean fuel use	1,045	7	2.24 (0.98–4.84)	0.34 (0.15, 0.77) **0.01**	0.32 (0.14, 0.72) **0.006**	0.38 (0.16, 0.88) **0.02**
Clean fuel use	1720	9	1.75 (0.85, 3.44)	**1 (Ref.)**	**1 (Ref.)**	**1 (Ref.)**
Clean to solid fuel use	2,174	42	6.51 (4.75, 8.87)	3.72 (1.81, 7.66) **<0.001**	3.35 (1.63, 6.90) **0.001**	2.45 (1.16, 5.19) **0.01**
Heating						
Solid fuel use	338	9	8.99 (4.39, 17.65)	**1 (Ref.)**	**1 (Ref.)**	**1 (Ref.)**
Solid to clean fuel use	393	2	1.70 (0.29, 6.83)	0.18 (0.04, 0.87) **0.03**	0.20 (0.04, 0.96) **0.04**	0.25 (0.05, 1.26) 0.09
Clean fuel use	428	1	0.77 (0.04, 5.04)	**1 (Ref.)**	**1 (Ref.)**	**1 (Ref.)**
Clean to solid fuel use	3,152	51	5.44 (4.10, 7.21)	7.00 (0.96, 50.67) 0.053	6.12 (0.84, 44.33) 0.07	4.46 (0.60, 32.82) 0.14

Model 1[a]: no covariates were adjusted; Model 2[b]: adjusted for age and sex; Model 3[c]: age, sex, education level, social activities, marital status, smoking, drinking status, residence, self-reported socioeconomic status, hypertension, diabetes, and stroke; HR[d]: effect value; Bolded P-values indicate statistical significance. HR, hazard ratio; 95% CI, 95% confidence interval.

and CF. However, the exact mechanism of this association is unclear. CF is defined as a coexistence of CI and PF (1). Based on this definition, the potential mechanisms of impact may encompass: Regarding the impact of solid fuels on cognitive function, it was initially found that indoor air pollution, especially resulting from solid fuel combustion, is known to elevate the risk of respiratory and cardiovascular conditions (38, 39), both of which are known risk factors for CI (40). Secondly, pollutants from solid fuel burning can disrupt the regulatory roles of brain capillaries and initiate pro-inflammatory reactions, causing pathological alterations in the central nervous system and additional CI (41). Additionally, toxic pollutants released by the combustion of solid fuels, such as particulate matter, carbon monoxide, and sulfur dioxide (42), might impact protein aggregation through oxidative stress mechanisms, interfering with early biomarkers of neurodegenerative diseases, such as soluble Aβ and α-synuclein, thereby causing cognitive damage (41, 43, 44). Finally, long-term use of solid fuels is associated with reduced insulin levels (45), which could lead to inflammation, abnormal energy metabolism, altered vascular function, and reduced synaptic activity, ultimately resulting in a decline in cognitive function (46). Concerning the effect of solid fuels on PF, studies have shown a strong positive link between solid fuel usage and the incidence of PF in older populations (47). To begin with, PM2.5 particulates generated from solid fuels are closely linked with heightened systemic inflammation, increased platelet activation, and a decrease in erythrocyte antioxidant enzyme activity (48). These factors are key in the progression of PF. Additionally, HAP resulting from solid fuel combustion can hasten the aging process of cells, organs, and systemic functions, ultimately contributing to PF (49). Moreover, prolonged use of solid fuels is found to be directly associated with a heightened risk of arthritis in individuals aged 45 and above (29), a condition frequently identified as an indicator of PF (50). Lastly, long-term exposure to solid fuels correlates with decreased insulin levels, potentially leading to impaired skeletal muscle metabolism and contraction (40) and thereby precipitating the onset of PF (51).

In our stratified analysis, we observed a consistent trend: among smokers, the risk of CF increases regardless of the type of solid fuel used. This finding aligns with previous research, illustrating a broader pattern of risk. For example, population surveys on HAP in Northern China have shown that individuals who smoke and use solid fuels for cooking or heating display lower cognitive abilities. This suggested a compounded effect of smoking and solid fuel use on cognitive health (52). Likewise, analysis of data from rural communities showed a notable rise in CI risk among individuals who smoke and utilize solid fuels, further highlighting the connection between these risk elements and cognitive deterioration (35). A study from India supports this conclusion, showing that smokers generally have diminished cognitive abilities, highlighting the intrinsic risk smoking poses to cognitive well-being (53). The underlying mechanisms for these observations are complex. Harmful chemicals in tobacco smoke may induce neurotoxic effects, leading directly to cognitive deterioration (54). Exposure to smoke can also inhibit neurogenesis and promote glial cell proliferation in the dentate gyrus, which might work in synergy with the decrease in dopaminergic neurons seen with solid fuel use (55). Moreover, tobacco smoke and the free radicals from solid fuel combustion can trigger inflammatory responses, damaging the central nervous system and increasing CI risk (56). Importantly, research has shown that smoking leads to muscle atrophy and reduced resistance to muscle fatigue, potentially impairing physical function (57). Epidemiological evidence indicates that HAP from tobacco and solid fuels can cause various organ damages, accelerate cellular aging, trigger skeletal muscle dysfunction, and heighten the risk of chronic diseases, muscle atrophy, and sarcopenia (58, 59). Furthermore, inhaling smoke from these sources may elevate C-reactive protein levels, correlating with decreased physical function and exacerbating PF (60). Stratified analyses further observe that individuals aged between 45 and 65 are particularly sensitive to the effects of solid fuel use despite the lack of direct evidence. A possible mechanism, according to World Health Organization surveys, is that individuals aged 65 and older often see a decrease in daily activities and an uptick in sedentary behavior. This leads to a lifestyle that becomes more monotonous and potentially less engaging (61). Such a change may result in less frequent use of solid fuels, thereby reducing the risk of cognitive decline associated with their use.

This research possesses several significant strengths. Secondly, it includes a nationally representative cohort with long-term follow-up, enhancing the relevance of our findings for the middle-aged and older demographics in China. What's more, we employed different Cox regression models and referenced past literature, incorporating relevant confounding factors to minimize the potential impact of covariates on our findings. Subsequently, our study primarily centered on CF, an outcome that encompasses cognitive function while also considering the impact of physical health on cognition. This in-depth analysis not only aligns closely with clinical practice but also enhances the thoroughness and depth of our findings. Lastly, by performing multiple sensitivity analyses, we have further validated the consistency and trustworthiness of our outcomes.

However, several limitations warrant attention. Firstly, the dependence on self-reported indoor fuel usage may introduce recall bias, potentially leading to misclassification errors. Concurrently, employing self-reports of cooking and heating with solid fuels as indicators for HAP exposure may not precisely capture the actual exposure levels, given that variations can arise from factors like the effectiveness of ventilation, weather conditions, and humidity levels. Moreover, considering CF encompasses both PF and CI, our analysis did not explore the specific relationships between household solid fuel use and these individual components. Furthermore, while adjustments were made to covariates as comprehensively as possible, based on existing literature, it remains challenging to account for all potential confounders. For example, household ventilation, an influential covariate, was not assessed in the CHARLS. Significantly, the pronounced disparities in the prevalence of conditions such as hypertension, diabetes, and stroke between diagnosed and undiagnosed individuals precluded further stratified analyses for these conditions, aiming to enhance the rigor of our findings. Lastly, the limited sample size led to wide confidence intervals in some stratified analyses. Thus, our findings should be considered with caution. Future research in a large population is essential to validate our initial findings.

Conclusion

This is the first longitudinal study among the Chinese population to explore the association between solid fuel use and CF. Our cohort research reveals a significant link between HAP from solid fuel use and a higher incidence of CF in middle-aged and older adult groups in China. CF is considered a reversible condition. For individuals, our study underscores the importance of personal protection during solid fuel use and early intervention to prevent CF in older adults. At a societal level, the study highlights the harmful effects of solid fuel use and offers a novel perspective on population health, advocating for a transition from solid fuels to clean fuels. Future research should involve larger, population-based cohorts with longer follow-up periods to better characterize fuel composition and individual exposure. Additionally, toxicological studies are needed to provide experimental evidence supporting these findings.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: The data that support the findings of this study are available from the website of China Health and Retirement Longitudinal Study at: http://charls.pku.edu.cn/en.

Ethics statement

The studies involving humans were approved by The data that support the findings of this study are available from the website of China Health and Retirement Longitudinal Study at: http://charls.pku.edu.cn/en. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

M-YT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. G-PW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. S-XZ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. L-HJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing, Writing – original draft.

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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.2025.1444421/full#supplementary-material

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Clinical characteristics of pulmonary embolism at extremely high altitude: a single-center retrospective study

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Background: Exposure to high altitude (HA) has been shown to significantly increase the risk of venous thromboembolism (VTE). However, the clinical characteristics of VTE at extremely high altitudes remain poorly understood. In this single-center retrospective study, we aimed to compare the clinical characteristics and prognoses of pulmonary embolism (PE) patients at extremely high altitudes with those at low altitudes (LA).

Methods: This retrospective analysis focused on PE patients treated at the General Hospital of Xinjiang Military Command between November 1, 2019, and November 1, 2022. The high-altitude group (HA-Group) consisted of patients who sought medical treatment after they had fallen ill into the plateau area, and the low-altitude group (LA-Group) consisted of local residents.

Results: We identified a total of 17 PE patients in the HA-Group and 62 patients in the LA-Group. The average altitude in the HA-Group was 5,041 ± 85.34 m, and 802.1 ± 11.10 m in the LA-Group ($p < 0.0001$). Hematological indicators, including red blood cells, lymphocytes, platelet counts, hemoglobin, PT, APTT, the INR and uric acid, were significantly higher in the HA-Group than in the LA-Group. Kaplan–Meier curve analysis demonstrated that the time to complete resolution of pulmonary thrombosis was significantly shorter in the HA-Group than in the LA-Group (log-rank $p = 0.033$).

Conclusion: This retrospective study revealed the clinical characteristics of PE patients at extremely high altitudes. High-altitude exposure may increase the susceptibility of young people to PE, and abnormal serum uric acid metabolism may be a potential risk factor for PE in high altitude areas.

KEYWORDS

extremely high altitude, venous thromboembolism, pulmonary embolism, uric acid, hypoxia, risk factor

Background

Venous thromboembolism (VTE), which primarily comprises pulmonary embolism (PE) and deep venous thrombosis (DVT) ranks among the top five most common vascular diseases in many countries (1). In China, the age- and sex-adjusted hospitalization rate for VTE is 17.5 per 100,000 people, reflecting a significant increase over the past decade (2). The incidence of VTE in other parts of Asia shows a similar pattern. In the USA and Europe, VTE incidence rates are believed to be higher than those in Asia, with an estimated range of 1–2 cases per 1,000 person-years (3). Naturally, the incidence rates of VTE vary widely across different regions due to variations in age, sex, race, and medical conditions.

PE and DVT are different stages of the same pathological process, and a majority of PE patients experience DVT. Even if DVT is not detected in PE patients, it is possible that the entire thrombus has detached or that it is not detectable by the instrument (4). Numerous mechanisms or pathological processes have been shown to directly or indirectly contribute to venous thrombosis. Depending on the underlying pathological mechanism, risk factors for the development of VTE are often classified as acquired (such as cancer, major surgery, trauma, advanced age, reduced mobility, pregnancy, and postpartum period, etc.) or hereditary (including plasminogen deficiency, antithrombin deficiency, protein S/C deficiency, and prothrombin gene mutation, etc.) (4). In epidemiological studies, events that contribute to VTE are categorized as provoked or unprovoked. The former refers to events occurring within 3 months of specific triggering factors (such as infection, surgery, trauma, fracture, injuries, etc.), while the latter occurs in the absence of these conditions (5).

High altitude areas, as unique geographical environments, have attracted significant amounts of attention because of their role in thrombotic diseases. The incidence of VTE caused by hypoxia, which is the primary trigger, is significantly greater in high altitude regions than in lower altitudes (6–10). The high altitude environment can contribute to disturbances in coagulation and increase the risk of thrombosis, either as an acquired or provoked factor within the body's internal environment. Detecting and diagnosing venous thrombotic diseases in high altitude areas presents certain challenges due to the nonspecific symptoms these diseases present and their similarity to altitude-related ailments (11).

To address this issue, the present study utilized data from a single center to assess the clinical characteristics, hematological status, prognosis, and other pertinent factors of PE patients residing in both extremely high-altitude regions and plains. The focus of the study was to observe trends in characteristic indicators throughout the progression of the disease in PE patients from both regions. The results obtained from this research endeavor are expected to increase awareness of the occurrence of venous thrombotic diseases in high altitude areas.

Abbreviations: VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep venous thrombosis; HAPE, high altitude pulmonary edema; HA, high altitude; LA, low altitude; CVST, cerebral venous sinus thrombosis; WBC, white blood cell; RBC, red blood cell; PT, prothrombin time; TT, thrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio.

Methods

Patients

This retrospective cohort study included patients from the General Hospital of Xinjiang Military Command (Urumqi, China, 800 m) between November 1, 2019, and November 1, 2022. The inclusion criteria were as follows: (1) patients diagnosed according to the International Classification of Diseases (ICD-9/10) standards; (2) diagnosis of pulmonary embolism (PE) confirmed by computed tomography pulmonary angiography (CTPA) showing pulmonary artery filling defects; (3) age older than 18 years; (4) the HA-Group patients had a clear history of high-altitude exposure and could provide relevant information about their history of high-altitude exposure (such as duration of exposure and history of acute or chronic high-altitude illness). Exclusion criteria: (1) incomplete CTPA examination during hospitalization. (2) Age younger than 18 years. (3) Patients were already diagnosed with PE before November 1, 2019. (4) Information on the altitude at the time of onset could not be provided. All the data were collected jointly by two researchers, and if there was any disagreement, a third researcher was consulted.

Grouping and laboratory examination

Patients who developed PE in high altitude areas were classified as the HA-Group; otherwise, they were classified as the LA-Group. Given that the average age of the HA-Group was significantly younger than that of the LA-Group, patients aged younger than 60 years in the LA-Group were defined as the LA-Y-Group to reduce the heterogeneity caused by age. To avoid errors caused by the use of therapeutic drugs, the preferred approach for collecting hematological examination results is to use samples collected before treatment or blood samples obtained during the initial stage of the disease course. As most patients in the HA-Group develop the disease in high-altitude areas and are referred to our hospital from other hospitals, some of the test results were obtained from other medical institutions.

Follow-up and prognosis

The end point of follow-up observation for pulmonary thromboembolism was set at 1 year after diagnosis in this study. The diagnosis of thrombus resorption relies on CTPA. If there was no follow-up record for the patient at our hospital, a telephone follow-up was conducted. Patients for whom follow-up records could not be obtained even after further telephone follow-up were considered lost to follow-up.

Statistical analysis

The data analysis was performed using Prism 6.0c software (GraphPad). Continuous data are presented as the mean ± standard deviation (SD) and were compared using a t test for normally distributed continuous variables. Nonparametric analyses, including the Mann–Whitney *U* test and Kruskal–Wallis test, were used when appropriate. Categorical variables are presented as *n* (%), and the normality of the data was assessed using the Shapiro–Wilk test. Comparisons of categorical data were conducted using the chi-square test or Fisher's exact test. Survival curves for thrombolysis were generated using the Kaplan–Meier method, and differences were compared using the log-rank test. $p < 0.05$ were considered significant (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$); $p > 0.05$: no significant (ns).

Results

Patient demographics

Initially, 161 patients diagnosed with PE were identified. After applying the exclusion criteria, 79 patients were included in the study (Figure 1). The HA-Group comprised 17 individuals with a mean age of 24.35 ± 0.88 years, all of whom were males who had migrated from the plains to high-altitude regions (Qinghai-Xizang plateau). Due to the harsh environmental conditions, large-scale migration to extremely high-altitude regions (>5,000 m) is rare except for specific situations. The patients in the HA group were all from a population that migrated from low-altitude areas to extremely high-altitude regions for training missions, and the majority of this group were male. The average duration from arrival at high altitude to onset of symptoms was 125.1 ± 28.26 days, and the average altitude at the time of onset was 5,041 ± 85.34 m. The LA-Group consisted of 62 individuals, including 40 males, with an average age of 60.39 ± 2.35 years and an average altitude of 802.1 ± 11.10 m (Table 1).

Due to the younger age of the HA-Group, there were significantly fewer underlying diseases, with only one patient having a history of lower extremity venous thrombosis. In contrast, the LA-Group had a significantly greater proportion of patients with underlying disease, such as hypertension, coronary heart disease. In terms of the average duration from symptom onset to definitive diagnosis, the HA-Group was significantly longer than the LA-Group.

Clinical characteristics of patients

In terms of clinical symptoms, there was a statistically significant difference in the proportion of patients with only hemoptysis between the two groups, while the proportions of patients with other symptoms were not significantly different. However, in terms of the frequency of symptom occurrence, common symptoms in the HA-Group included chest pain, panting, pain and swelling in the lower limb and hemoptysis. In the LA-Group, common symptoms included chest pain, panting, and cough. Moreover, there was no statistically significant difference between the two groups in terms of the incidence of respiratory failure, pulmonary embolism, or mortality due to PE. Notably, in the HA-Group, seven individuals had concomitant high altitude pulmonary edema (HAPE) (Table 2).

According to the initial hematological examination results, there were significant differences in several parameters between the two groups. Hematological indicators such as red blood cell counts, lymphocyte counts, platelet counts, hemoglobin levels, clotting-related indices such as PT, APTT, the INR, and uric acid levels were significantly higher in the HA-Group than in the LA-Group. However, there were no significant differences in the triglyceride levels, total white blood cell count, and D-dimer level. A similar trend was also observed in the HA-Group and LA-Y-Group (Table 3; scatter diagram is shown in Figure 2).

Prognostic

Seventeen patients in the HA-Group and 62 patients in the LA-Group were included in the follow-up process, with 3 and 10 individuals lost to follow-up in each group, respectively (Figure 3a). One year after the first definitive diagnosis of PE, CTPA indicated complete resorption of pulmonary thromboemboli in 10 patients in the HA-Group and 23 patients in

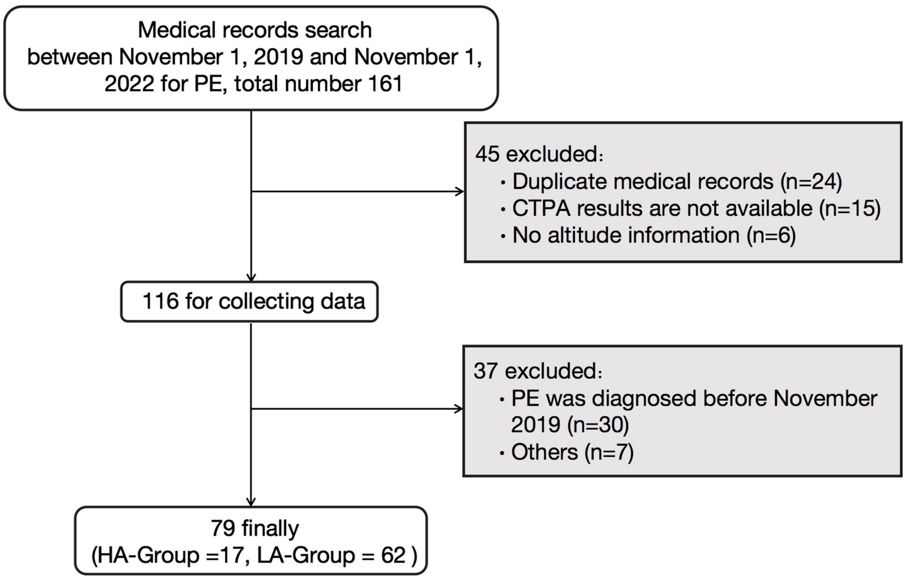

FIGURE 1
Flowchart of the study. PE, pulmonary embolism; CTPA, computer tomography pulmonary angiography; HA-Group, high altitude group; LA-Group, low altitude group.

TABLE 1 Basic characteristics of patients.

Variables	HA-Group (n = 17)	LA-Group (n = 62)	p-value	χ^2
Male (%)	17 (100%)	40 (64.5%)		
Age	24.35 ± 0.88	60.39 ± 2.35	<0.0001	
Male (years, mean ± SD)	24.35 ± 0.88	55.73 ± 3.05	<0.0001	
Female (years, mean ± SD)		68.86 ± 2.88		
Altitude (m, mean ± SD)	5,041 ± 85.34	802.1 ± 11.10	<0.0001	
Time at HA (days, mean ± SD)	125.1 ± 28.26			
Ethnicity				
Han [n (%)]	14 (82.4%)	49 (79%)	0.091	0.763
Smoking [n (%)]	9 (52.9%)	25 (40.3%)	0.418	0.655
Alcohol consumption [n (%)]	1 (5.9%)	14 (22.6%)	0.228	1.455
Long-term bedridden [n (%)]	0	9 (14.5%)		
Long-term administration of glucocorticoid [n (%)]	0	3 (4.8%)		
Long-term administration of anticoagulant [n (%)]*	1 (5.9%)	11 (17.7%)	0.409	0.681
Surgical history within 2 years [n (%)]	0	9 (14.2%)		
The average time from onset of symptoms to diagnosis (days, mean ± SD)	19.59 ± 4.68	7.48 ± 0.9	<0.0001	
Underlying diseases [n (%)]				
Hypertension	0	26 (41.9%)		
Coronary heart disease	0	12 (19.4%)		
Lower limb varicosity	0	9 (14.51%)		
Diabetes	0	8 (12.9%)		
Chronic bronchiti	0	7 (11.3%)		
Cerebral infarction	0	6 (9.7%)		
Lower limb venous thrombosis	1 (5.9%)	6 (9.7%)	0.995	0
Malignant tumor	0	5 (8.1%)		
Chronic obstructive pulmonary disease	0	4 (6.5%)		
Chronic heart failure	0	4 (6.5%)		
Atrial fibrillation	0	5 (8.1%)		

HA-Group, high altitude group; LA-Group, low altitude group; HA, high altitude. *The use of anticoagulants before the onset of the disease is for the treatment of lower extremity venous thrombosis and the prevention of atrial fibrillation.

LA-Group. Kaplan–Meier curve analysis demonstrated that the time to complete resolution of pulmonary embolism was significantly shorter in the HA-Group (log-rank $p = 0.033$; Figure 3b).

Discussion

The epidemiology and pathogenesis of VTE in high-altitude regions have been prominent topics in high-altitude medicine in recent years. Exposure to high altitudes is increasingly recognized as a significant risk factor for VTE, regardless of whether individuals are in normal or diseased physiological states (12–15). This study compared the clinical data of PE patients at different altitudes in the years from 2019 to 2022. The main highlight of the study is that it focused on PE patients in extremely high altitude areas, and the participants were not native residents but migrants from plain areas. Additionally, the altitude of this study was above 5,000 m, emphasizing the uniqueness of the clinical data. This study also identified the particular features of the epidemiology of PE in extremely high-altitude areas, providing new insights into the occurrence and development of such diseases.

Advanced age is a clear risk factor for VTE, and the risk increases with age, especially after 40 years (4). As age increases, abnormalities in coagulation function and the induction of underlying disease may lead to an increased incidence of VTE. In this study, the distribution of different age groups among LA-Group patients followed this pattern (Figure 4). In contrast, the HA-Group patients were all young individuals, with the oldest being 31 years old, and they had significantly fewer underlying disease than did the LA-Group. This could be due to a difference in the age distribution between the population residing in high-altitude areas and the general population, with a significant reduction in the proportion of older adult individuals, resulting in a predominantly young population affected

TABLE 2 Clinical features of patients.

Variables	HA-Group Total number = 17 [*n* (%)]	LA-Group Total number = 62 [*n* (%)]	*p*-value	χ^2
Death	1 (5.9%)	6 (9.7%)	0.995	0
Death caused by PE directly	1 (5.9%)	1 (1.6%)	0.903	0.015
Respiratory failure	2 (11.8%)	17 (27.4%)	0.256	1.290
Pulmonary infarction	5 (29.4%)	10 (16.1%)	0.375	0.789
Comorbidities				
DVT	10 (58.8%)	33 (53.2%)	0.955	0.003
CVST	2 (11.8%)	1 (1.6%)	0.221	1.498
Renal venous thrombosis	1 (5.9%)	0		
HAPE	7 (41.2%)	0		
Symptoms				
Chest pain	7 (41.2%)	20 (32.2%)	0.492	0.472
Panting	6 (35.3%)	26 (41.9%)	0.621	0.244
Cough	5 (29.4%)	18 (29%)	1	0.026
Expectoration	4 (23.5%)	13 (21%)	1	0
Dyspnea	2 (11.8%)	6 (9.7%)	1	0
Pain and swelling in the lower limb	6 (35.3%)	6 (9.7%)	0.026	4.953
Nausea	3 (17.6%)	6 (9.7%)	0.267	0.236
Vomiting	3 (17.6%)	3 (4.8%)	0.212	1.561
Hemoptysis	6 (35.3%)	4 (6.5%)	0.006	7.600
Intravenous thrombolytic therapy	1 (5.9%)	2 (3.2%)	0.609	0.262
Treatment options outside the hospital				
Warfarin (oral)	8/16 (50%)	14/56 (25%)		
Rivaroxaban (oral)	7/16 (43.8%)	40/56 (71.4%)		
Dabigatran (oral)	0	1/56 (1.8%)		
No anticoagulant therapy	0	1/56 (1.8%)		

HA-Group, high altitude group; LA-Group, low altitude group; PE, pulmonary embolism; HAPE, High altitude pulmonary edema; DVT, deep venous thrombosis; CVST, cerebral venous sinus thrombosis.

by the disease. Although this study cannot determine the exact age distribution of the baseline population in the HA-Group, investigations conducted by the research team have revealed that there is also a certain number of older adult individuals, albeit in a relatively smaller proportion. These findings suggest that the low-risk group of young individuals, who normally have a lower incidence of PE, may experience a significantly higher incidence of PE after relocating to high-altitude regions, which is distinctly different from what occurs in the plain areas. As for the specific reasons causing this manifestation, further exploration is still needed.

There were no significant differences in clinical symptoms between the two groups, and only the frequency of occurrence of individual symptoms was different. However, in high-altitude areas, the diagnosis of PE is easily confused with that of altitude-related diseases, such as HAPE (11, 16, 17). Misdiagnosis caused by nonspecific symptoms can delay diagnosis, and the treatment of acute high altitude diseases such as dehydration and diuresis may further promote or worsen venous thrombus formation due to nonspecific symptoms.

In this study, a comparison of laboratory examination data between the two groups revealed that the HA-Group had significantly greater prothrombin time (PT), thrombin time (TT), and activated partial thromboplastin time (APTT) than did the LA-Group. Previous studies have suggested that exposure to high altitudes can lead to hypocoagulable and fibrinolytic system disorders (18–20). However, due to the influence of factors such as different altitudes, the length of time of entering and staying in the plateau, the study population, and exercise load, different studies yield somewhat inconsistent results (21). Currently, there is no unified consensus regarding the impact of hypoxia on the coagulation and fibrinolysis systems. Based on the data of this study, We propose a possible mechanism hypothesis that factors such as the damage to vascular endothelium caused by continuous hypoxic stimulation activate the coagulation and fibrinolysis systems. Nevertheless, the degree of such activation is insufficient to trigger thrombus formation. It is precisely the continuous and low-level activation of both the positive and negative regulatory systems during this ongoing thrombus-formation process that leads to the consumption of coagulation factors and insufficient

TABLE 3 Biochemical index profiles of patients.

Variables	HA-Group Total number = 17 [mean ± SD (*n*)]	LA-Group Total number = 62 [mean ± SD (*n*)]	*p*-value
WBC count (×10⁹/L)	9.60 ± 0.88 (*n* = 17)	8.33 ± 0.41 (*n* = 61)	0.157
Neutrophil count (×10⁹/L)	5.81 ± 0.84 (*n* = 14)	6.26 ± 0.42 (*n* = 61)	0.65
Lymphocyte count (×10⁹/L)	2.30 ± 0.15 (*n* = 15)	1.67 ± 0.10 (*n* = 60)	<0.01
Monocyte count (×10⁹/L)	0.58 ± 0.06 (*n* = 14)	0.55 ± 0.03 (*n* = 61)	0.941
RBC count (×10¹²/L)	5.80 ± 0.22 (*n* = 17)	4.51 ± 0.09 (*n* = 61)	<0.0001
Hemoglobin (g/L)	167.1 ± 6.05 (*n* = 16)	133.9 ± 2.68 (*n* = 62)	<0.0001
Platelet count (10⁹/L)	252.9 ± 22.75 (*n* = 16)	194.5 ± 8.20 (*n* = 61)	<0.01
Fibrinogen (g/L)	3.94 ± 0.51 (*n* = 16)	3.74 ± 0.16 (*n* = 62)	0.622
PT (sec)	13.33 ± 0.57 (*n* = 17)	12.09 ± 0.17 (*n* = 62)	<0.01
TT (sec)	18.28 ± 1.22 (*n* = 15)	16.97 ± 0.20 (*n* = 62)	0.067
APTT (sec)	33.04 ± 1.698 (*n* = 15)	28.04 ± 0.5131 (*n* = 62)	<0.001
INR	1.14 ± 0.052 (*n* = 15)	1.01 ± 0.01 (*n* = 62)	<0.0001
D dimer (mg/L)	3.94 ± 0.97 (*n* = 17)	5.55 ± 0.60 (*n* = 62)	0.201
Uric acid (μmol/L)	448.1 ± 36.41 (*n* = 15)	319.2 ± 11.61 (*n* = 61)	<0.0001
Triglyceride (mmol/L)	1.10 ± 0.12 (*n* = 15)	1.19 ± 0.08 (*n* = 57)	0.544

HA-Group, high altitude group; LA-Group, low altitude group; WBC, white blood cell; RBC, red blood cell; PT, prothrombin time; TT, thrombin time; APTT, activated partial thromboplastin time; INR, international normalized ratio.

synthesis in the body (in the plateau area, there are issues like a single-food structure and a decline in gastrointestinal function). Consequently, APTT and PT show an increasing trend. Generally speaking, the body's stress regulation in response to exposure to a plateau environment is complex and variable. In particular, field studies on human populations are affected by numerous factors.

Notably, the uric acid levels in the HA-Group were significantly higher than those in the LA-Group. Research has confirmed that high-altitude exposure can lead to abnormalities in uric acid production and excretion, resulting in increased serum uric acid levels (22, 23). A study focusing on the East Asian region suggested that elevated serum uric acid is a risk factor for venous thrombosis (24), and other related research has also indicated a positive correlation between increased serum uric acid levels and the risk of venous thrombotic diseases (25–27). Elevated serum uric acid levels can lead to enhanced oxidative stress, causing an increase in reactive oxygen species (ROS), which in turn results in damage to and dysfunction of the vascular endothelium, and further activates platelets and the coagulation cascade (28, 29). Uric acid crystals can also activate the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-6 (IL-6), activating the expression of tissue factor and promoting thrombus formation (28).

In this study, the HA-Group consisted of young individuals who moved from plains to high altitudes, which transformed a low-risk population for venous thrombotic diseases into a susceptible group. Could the underlying mechanism be that hypoxia exposure leads to an increase in serum uric acid levels, thereby increasing the risk of venous thrombosis? This potential mechanism is worth further exploration.

The time from the onset of symptoms to a definite diagnosis in the HA-Group was significantly greater than that in the LA-Group. Factors such as inadequate allocation of medical resources, lack of disease recognition ability among medical personnel, and transportation inconvenience may contribute to these results. Both groups of patients primarily received oral anticoagulant therapy (including warfarin, dabigatran and rivaroxaban) outside the hospital. Survival curve analysis revealed a significant difference in the incidence of complete pulmonary artery thrombosis between the HA-Group and LA-Group, suggesting a better overall prognosis for patients in the HA-Group. This may be because the coagulation dysfunction caused by hypoxia is quickly corrected after the patient leaves the high-altitude environment, without further maintenance or exacerbation of thrombus formation. This assumption, of course, is based on the premise that there is no underlying disease that can cause coagulation dysfunction. In contrast, older adult patients have some underlying conditions that lead to a hypercoagulable state (such as tumors, long-term immobilization, advanced age, infections, etc.), and after anticoagulant therapy, they are still unable to rapidly restore normal coagulation mechanisms. Therefore, compared with young people, the older adult population has a relatively delayed resorption rate of blood clots. The above conclusions are based only on this phenomenon, and further research is needed to clarify the specific underlying mechanism involved.

This study has several limitations. First, this was a retrospective single-center observational study in which the medical records of existing patients were evaluated. Therefore, after filtering the case data, the sample size was relatively small, especially in the HA-Group. This is due to the scarcity of people who have migrated to extremely high altitude areas (>5,000 m), which made it valuable to obtain such a sample size. Second, there is a lack of testing for genetic or endogenous factors (such as plasminogen deficiency, protein S/C and variations in related genes) related to PE in patients' hematological samples. If relevant data could be obtained, they could provide a better evaluation of the risk of developing PE in these two regions.

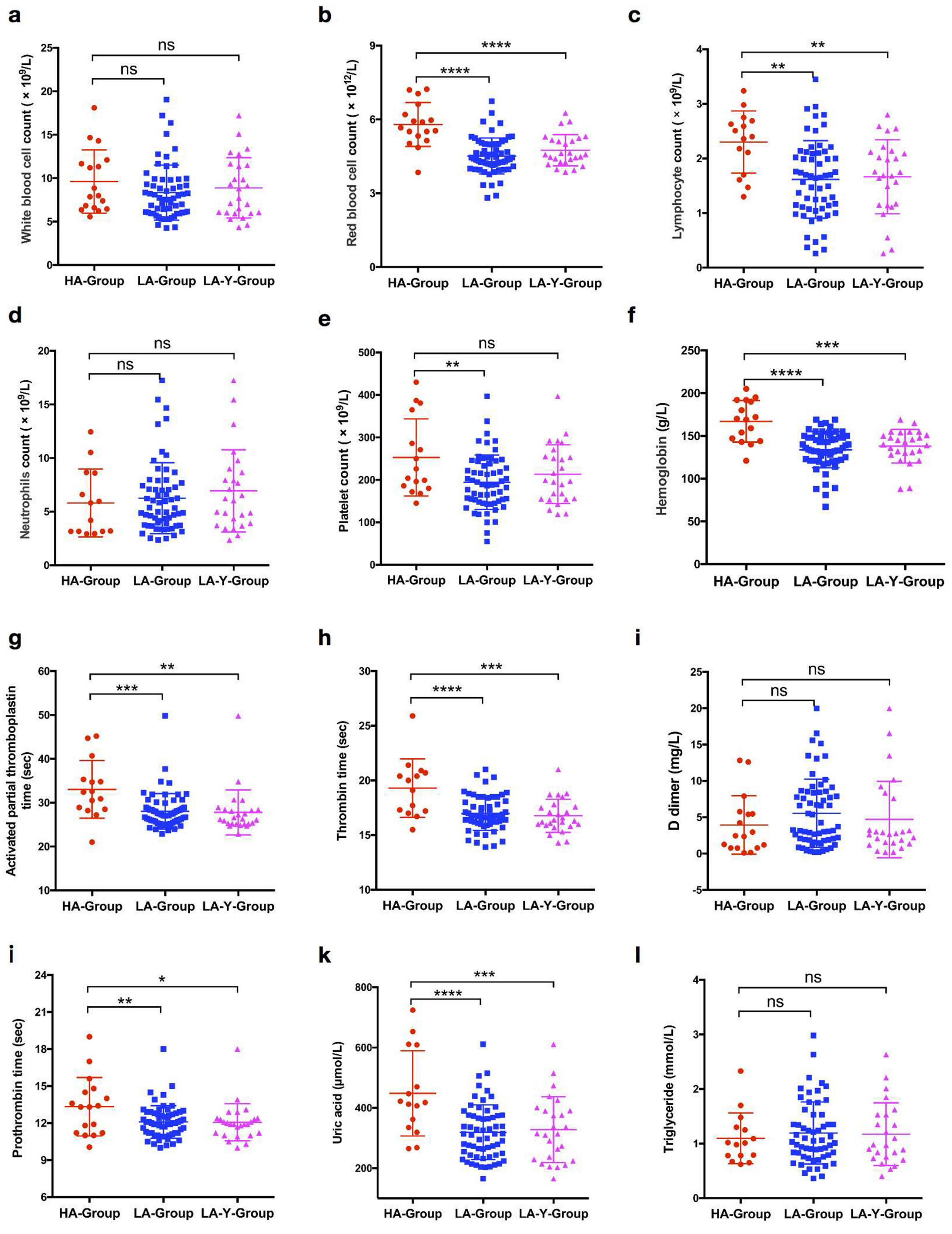

FIGURE 2
Comparison of biochemical indexes expression levels in patients between HA-Group, LA-Group, and LA-Y-Group. **(a)** White blood cell counts in HA-Group (n = 17), LA-Group (n = 61), and LA-Y-Group (n = 26). **(b)** Red blood cell counts in HA-Group (n = 17) and LA-Group (n = 61). **(c)** Lymphocyte counts in HA-Group (n = 15), LA-Group (n = 60), and LA-Y-Group (n = 26). **(d)** Neutrophils counts in HA-Group (n = 14), LA-Group (n = 61), and LA-Y-Group (n = 26). **(e)** Platelet counts in HA-Group (n = 16), LA-Group (n = 61), and LA-Y-Group (n = 26). **(f)** Hemoglobin expression level in HA-Group (n = 16), LA-Group (n = 62), and LA-Y-Group (n = 26). **(g)** Activated partial thromboplastin time in HA-Group (n = 15), LA-Group (n = 62), and LA-Y-Group (n = 26). **(h)** Thrombin time in HA-Group (n = 15), LA-Group (n = 62), and LA-Y-Group (n = 26). **(i)** D dimer in HA-Group (n = 17), LA-Group (n = 62), and LA-Y-Group (n = 26). **(j)** Prothrombin time in HA-Group (n = 17), LA-Group (n = 62), and LA-Y-Group (n = 26). **(k)** Uric acid expression level in HA-Group (n = 15), LA-Group (n = 61), and LA-Y-Group (n = 26). **(l)** Triglyceride expression level in HA-Group (n = 15), LA-Group (n = 57), and LA-Y-Group (n = 24).

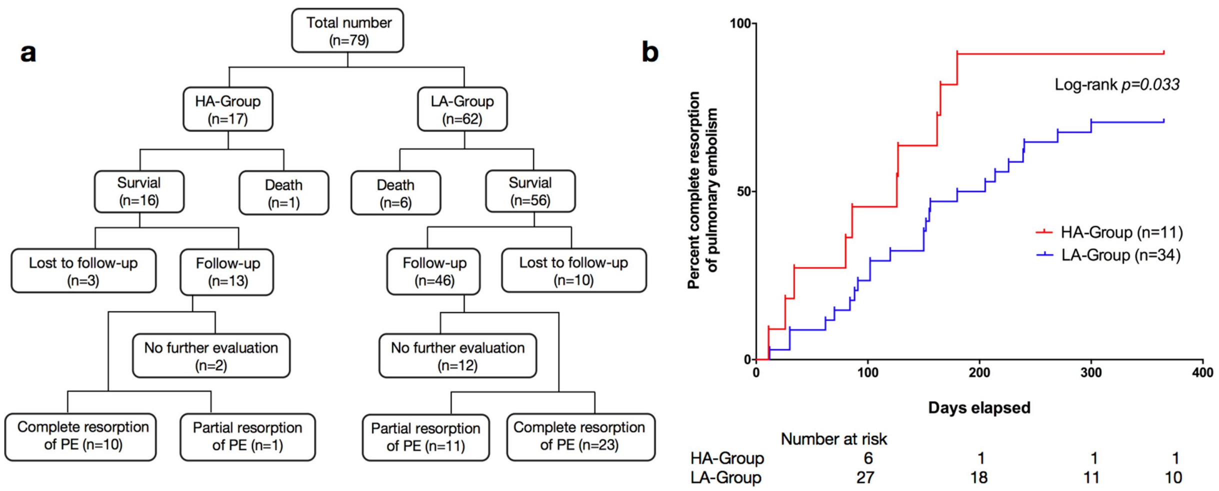

FIGURE 3
(a) Research flow diagram. The flow diagrams illustrate the trial profiles and research design. **(b)** Kaplan–Meier survival curves of pulmonary embolism patients: HA-Group (n = 11) vs. LA-Group (n = 34).

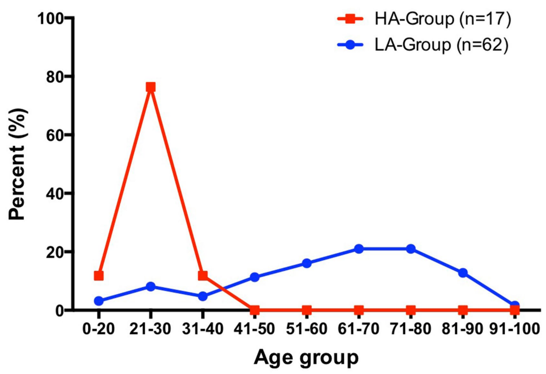

FIGURE 4
Percentage distribution of patients in HA-Group (total number = 17) and LA-Group (total number = 62) by age interval.

Conclusion

In this retrospective study, we included patients with PE from high-altitude and low-altitude areas and analyzed demographic, clinical laboratory, and prognostic data. The results suggest that high-altitude exposure increases the susceptibility of young individuals to PE, while anticoagulant therapy leads to a better prognosis. Abnormal serum uric acid metabolism may be a potential triggering factor for the increased incidence of PE in high-altitude areas, but additional research is needed.

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 authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the General Hospital of Xinjiang Military Command (no. 2023RR0207). The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/Institutional Review Board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this was a retrospective study, and all patient information in this manuscript is anonymous, it does not involve the personal privacy of patients.

Author contributions

JW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. JZ: Data curation, Writing – original draft, Writing – review & editing. RW: Data curation, Writing – original draft, Writing – review & editing. XH: Data curation, Validation, Writing – review & editing. WW: Data curation, Writing – review & editing. QC: Data curation, Writing – review & editing. YG: Data curation, Writing – review & editing. MW: Data curation, Writing – review & editing. PJ: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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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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Knowledge, attitudes, and practices of people living in artisanal mining areas on water pollution in Siguiri, Guinea, 2023

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Introduction: Water pollution is a major public health issue, especially in mining areas where artisanal mining activities are prevalent. The objective of this study was to analyze the knowledge, attitudes, and practices (KAP) of the population regarding water pollution in the mining areas of Siguiri, Guinea.

Methods: A cross-sectional study was conducted from May 15 to June 15, 2023, on the population of Doko, Siguiri. Data were collected using a structured questionnaire that assessed knowledge, attitudes, and practices related to water pollution in artisanal mining areas. Logistic regression was used to analyze factors associated with KAP.

Results: The survey included 501 respondents. Good knowledge of water pollution was observed in 53% of respondents, while 52% exhibited a positive attitude towards water pollution in artisanal mining area. Good practices were reported by 81% of respondents. The multivariate analysis showed that being educated (ORa: 2.13; 95% CI: 1.39; 3.29) and being a foreigner (ORa: 1.88; 95% CI: 1.04; 3.51) significantly associated with positive attitudes towards water pollution in artisanal mining area. Indeed, being single (aOR: 1.84; 95% CI: 1.10; 3.14), having good knowledge of water pollution (aOR: 2.51; 95% CI: 1.47; 4.36) and lack of lifestyle (tobacco and alcohol) (aOR: 2.51; 95% CI: 1.02; 5.97) were significantly associated with good practices.

Conclusion: This study revealed moderate knowledge, positive attitudes and adequate practices regarding water pollution in Siguiri's artisanal mining areas. However, significant gaps remain, including a lack of awareness of the risks associated with prolonged exposure to heavy metals. She advocates an integrated approach combining education, awareness-raising and technical support, accompanied by concrete solutions such as water treatment and the strengthening of community initiatives, in order to convert this knowledge into sustainable behavior.

KEYWORDS

attitude, artisanal mining, knowledge, practice, Siguiri, water pollution

1 Introduction

Water plays an essential role in the survival and health of living beings, as well as in the socio-economic development of communities. When it is intended for consumption, it must be free from any contamination, whether of chemical or biological origin, likely to be harmful to human health (1). Water pollution is therefore a major public health problem. A number of factors, both natural and man-made, are known to have a negative impact on water quality. These include agricultural activities, the production of industrial and municipal waste, construction, and mining operations (2).

Artisanal and small-scale gold mining is a growing activity in many countries around the world (3). It is practiced by more than 40 million people in 120 countries, providing a livelihood for between 80 and 150 million people in low- and middle-income countries (4). Despite its important role in developing the informal economy within communities, artisanal mining also has environmental disadvantages. It generates environmental stress that poses a serious threat to water resources and human health (5).

In mining, water is of vital importance not only for the mining activity but also for the consumption and hygiene of the community (6). However, water bodies are particularly vulnerable to contamination by heavy metals and micro-organisms because of the poor hygiene often observed in these areas (7, 8).

In Guinea, artisanal mining has been practiced for over a century in regions rich in gold and diamond (9). It is carried out in several prefectures, and the miners involved are estimated at over 200,000, with 15% of these miners coming from neighboring ECOWAS countries. For local residents, this is a seasonal activity, carried out at the end of the agricultural season (10).

The prefecture of Siguiri is an area where small-scale gold mining is carried out industrially by the Société Aurifère de Guinee (SAG) and artisanally by the local population. Mining is carried out through a dense network of shafts built along watercourses and in forest galleries (11). On the other hand, access to drinking water is a major public health and development issue worldwide. That's why water pollution is a priority in the Sustainable Development Goals (SDGs), particularly SDG 6, which aims to guarantee access to drinking water for all (12). According to the 2018 Guinea Demographic and Health Survey (EDS V) (13), 79% of households consume water from improved sources, compared with 30% of the rural population who use unimproved sources, and 71% of the population who do not use any water treatment.

Inadequate knowledge, attitudes and practices regarding the management of water bodies can have a negative impact on water quality from the source to the place of use (14, 15). Several studies have shown the positive effects of good knowledge of water pollution and its consequences for good practice in preventing the phenomenon in sub-Saharan Africa (6, 16, 17). However, few studies have looked at people's knowledge, attitudes and practices regarding water pollution in artisanal mining areas.

In Guinea, several studies have been carried out on artisanal mining (7, 11, 18, 19). However, none of these studies has assessed the knowledge, attitudes and practices of the population in relation to water pollution.

The findings of this study will help to raise public awareness of water pollution, support the design of water pollution prevention projects, and raise awareness in artisanal mining areas. These efforts are also part of a global perspective, supporting international initiatives to reduce water pollution and protect vulnerable ecosystems, while promoting sustainable practices in artisanal mining areas.

The aim of this study was to assess the population's knowledge, attitudes and practices in relation to water pollution at artisanal mining sites in Siguiri.

2 Methods

2.1 Study design and period

This was a cross-sectional study conducted from 15 May to 15 June 2023 among communities living in the gold mining areas of the Doko sub-prefecture in the Siguiri health district in Guinea.

2.2 Study area

The Republic of Guinea is a West African country with a surface area of 245,857 km^2 with an estimated 14 million inhabitants in 2022. Around 76% of the population lived in rural areas in 2017 and the literacy rate was 40% in 2018 (20). It has significant mining potential, with reserves of bauxite, iron, gold, diamonds, etc. …. The mining sector is a pillar of the Guinean economy, accounting for more than 85% of exports and providing around 35% of gross domestic product (GDP) in 2020. In 2019, 44% of Guineans were living below the national poverty line and the economy was largely informal (21).

Siguiri is a prefecture located in the extreme north-east of the Republic of Guinea (Figure 1), about 850 km by road from the capital Conakry (11). It has numerous artisanal gold mining sites, particularly in almost all the localities in the prefecture. The region's reputation for gold mining is recognised worldwide, and the mining and trade of the mineral have gone on for several centuries, even if modern techniques have transformed it considerably (22). This study was carried out in three sub-prefectures with artisanal gold mining sites (Oudoula Damafè, Doko centre, Kodiarani 1) due to the high number of mine workers according to the National Action Plan for Artisanal and Small-scale Gold Mining (EMAPE) (10).

2.3 Study population

The study population consisted of all people aged 18 and over who consented to participate in the study without any inducments.

2.4 Sample size and sampling

The minimum sample size was calculated using the Schwartz formula (23). The prevalence used was the proportion of Guinean households utilizing at least one basic drinking water service (access to an improved source) in rural areas (p = 48.7%) (12). The sample size obtained was 357; after correcting for a non-response rate of 10%, we obtained 501.

Sampling was conducted using random sampling technique in order to obtain a representative sample of the population. Households were selected from the Siguiri household enumeration database. In each household selected, we counted all the people eligible for our study.

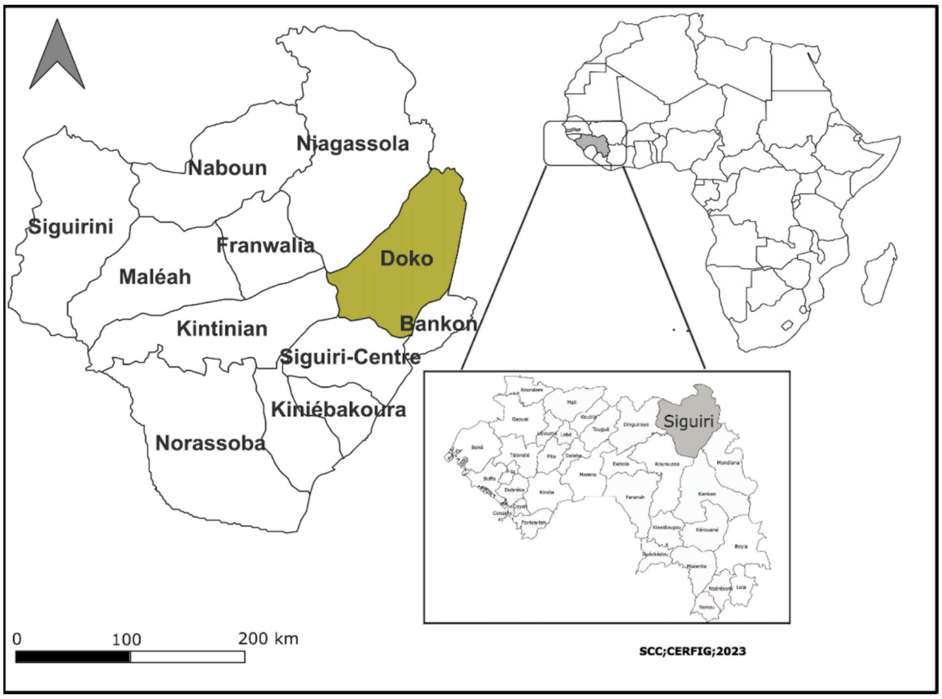

FIGURE 1
Map of the Siguiri prefecture and its sub-prefectures.

We then interviewed the head of the household or his/her spouse if he or she was unavailable. If both were absent or unavailable, we interviewed the oldest resident present. If the selected household was locked or if no eligible participant was present at the time of the visit, the household was revisited the following day. If no member was available, then another household was selected to replace it from a replacement list that was drawn up. All the interviews were conducted during the day.

2.5 Data collection method

Individual face-to-face interviews were conducted using an anonymous, standardized questionnaire. The questionnaire was entered into the Kobo collect software and then loaded onto tablets to facilitate data entry. It was pre-tested and validated before data collection began. Data collectors were recruited and trained on the purpose and methods of the study to ensure consistency and reliability of data collection. The principal investigator supervised the entire data collection and management.

2.6 Study variables

2.6.1 Outcome variable

2.6.1.1 Attitudes

Practices were defined on the basis of 4 close-ended questions on the source of drinking water, the treatment of drinking water at home, the type of container used for storing water at home and the use of latrines. For each question, a response was considered 'correct' if it aligned with scientifically validated practices or demonstrated a positive attitude toward recommended behaviors (e.g., agreeing that boiling water eliminates harmful pathogens). Each correct answer had a value of "1" and the wrong answer or do not know had a value of "0." Scores were added together to give a total score ranging from 0 to 4 points. Participants with a score equal to the total score were considered to have good practice. Those with a score below the total score were considered to have poor practice.

2.6.1.2 Practices

Practices were defined on the basis of 4 close-ended questions on the source of drinking water, the treatment of drinking water at home, the type of container used for storing water at home and the use of latrines. Each correct answer had a value of "1" and the wrong answer or do not know had a value of "0." Scores were added together to give a total score ranging from 0 to 4 points. Participants with a score equal to the total score were considered to have good practice. Those with a score below the total score were considered to have poor practice.

2.6.2 Independent variables

2.6.2.1 Knowledge

Knowledge was evaluated on the basis of 21 close-ended questions with sub-questions on contamination of drinking water by metals and microorganisms, health problems encountered, having information/education on drinking water quality, the reason for boiling water in a covered container, and having a latrine. Each correct answer had a value of "1" and the wrong answer or do not know had a value of "0." Scores were added together to give a total score ranging from 0 to 21 points. Participants with a score above the mean score were considered to have good knowledge. Those with a score below or equal to the average score were considered to have poor knowledge.

Socio-demographic characteristics included: sex (male and female), age group (< 30; 30–45; >45 years), marital status (married and single), occupation (mining worker and non-mining worker), instruction level (unschooled and schooled), origin (foreigner and Guinean), lifestyle (tobacco and alcohol), religion (christian, fetishist and muslim).

2.7 Analysis

The data collected were analyzed using R Studio software (4.2.3). Descriptive statistics were produced. Qualitative variables were presented as frequencies and percentages, and quantitative variables as means and standard deviations. For comparison of categorical variables, a chi 2 test was performed. Factors associated with participants' attitudes and practices were then analyzed using logistic regression. Variables were included in the final model after assessing for collinearity between independent variables. A mean–variance inflation factor (VIF) score of less than four is tolerated. The measures of association were estimated by odds ratios (ORs) with their 95% confidence intervals (CIs). All *p*-value values <0.05 were considered statistically significant.

3 Results

Overall, 501 individuals participated in the survey. The mean age of participants was 32.20 ± 10.28 years, and people aged below 30 years represented more than half of the sample (n = 259; 52%). Almost 74% were men, and 63% were married at the time of the survey. At least two out of three participants (68%) were not in school, and 42% reported being mineworkers (Table 1).

Table 2 shows respondents' level of knowledge about water pollution in artisanal mining areas. Overall, 53% of respondents had a good knowledge of water pollution. The majority (n = 476; 95%) knew that artisanal mining was a source of water pollution. Exposure to heavy metals and microbial germs could also occur via drinking water, according to 78 and 77% of respondents, respectively. About 96% said that ingesting germs could lead to diarrheal diseases. However, more than two-thirds of respondents (n = 334; 67%) did not know that ingesting large quantities of heavy metals could lead to cancer.

Table 3 summarizes respondents' attitudes toward water pollution. Over half (n = 263; 52%) of respondents had a positive attitude about measures to prevent water pollution. Most of them (77%) said that defecating near a water source can cause contamination, and that households are obliged to build their own latrines (99%). All participants (99%) stated that boiling water can eliminate bacteria.

Table 4 shows respondents' practices regarding water pollution. The majority (n = 453; 90%) used protected water sources for domestic activities and eight out of ten respondents treated drinking water at home. Nearly three quarters (73%) used an iron container to store water. All respondents (98%) said they used latrines. Providers who gave positive answers to these four (4) questions were classified as demonstrating good practices (*n* = 404; 81%) regarding water pollution.

The bivariate analysis in Table 5 showed statistically significant associations between positive attitudes to water pollution in artisanal mining area and the variables age, occupation, and level of education.

TABLE 1 Socio-demographic characteristics of respondents in the Doko mining area, Siguiri district, Guinea, June 2023 (*n* = 501).

Variables	Frequency	Percentage
Sex		
Female	129	26
Male	372	74
Age mean (SD) (years)	32 (±10)	
Age_group		
<30	259	52
30–45	194	39
>45	48	19
Marital status		
Married	317	63
Single	184	37
Occupation		
Mining worker	210	42
Non-mining worker	291	58
Education level		
Unschooled	339	68
Schooled	162	32
Origin		
Foreigner	55	11
Guinean	446	89
Lifestyle		
Alcohol	37	7
None	310	62
Tobacco	154	31
Religion		
Christian	24	5
Others	9	2
Muslim	468	93

However, after adjustment by logistic regression, only level of education and origin were statistically significantly associated with positive attitudes toward water pollution in artisanal mining area. Compared to those without education, educated respondents were twice as likely to have positive attitudes towards water pollution (ORa: 2.13; 95% CI: 1.39; 3.29). In addition, being a foreigner was almost twice as likely to have positive attitudes compare to not being a foreigner (ORa: 1.88; 95% CI: 1.04; 3.51).

Table 6 shows the factors associated with good practices toward water pollution in the artisanal mining areas. The bivariate analysis showed statistically significant associations with the following variables: level of education, lifestyle, knowledge, and attitudes.

In the multivariate analysis, marital status, level of education, lifestyle and having good knowledge were statistically significantly associated with good practices toward water pollution. Being single (ORa: 1.84; 95% CI: 1.10; 3.14) and having good knowledge of water pollution (ORa: 2.51; 95% CI: 1.47; 4.36) increased the odds of having good practices regarding water pollution by almost two. However, having attended school (ORa: 0.37; 95% CI: 0.21; 0.63) was 63% less

TABLE 2 Respondents' knowledge of water pollution, Siguiri mining areas, Guinea, June 2023 (*n* = 501).

Variables	Frequency	Percent
Can water be contaminated?		
No/Do not know	15	5
Yes	476	95
Is household waste a source of pollution?		
No/Do not know	183	36
Yes	318	63
Are you aware that artisanal mining is a source of pollution?		
No/Do not know	25	5
Yes	476	95
Is leakage of heavy metals a source of pollution?		
No/Do not know	68	14
Yes	433	86
Did you know that excrement in nature is a source of pollution?		
No Do not know	56	11
Yes	445	89
Did you know that connecting latrines to the water supply is a source of pollution?		
No/Do not know	106	21
Yes	395	79
Does drinking water contain contaminants such as heavy metals?		
No/Do not know	101	21
Yes	400	79
Does drinking water contain contaminants such as germs?		
No/Do not know	107	21
Yes	396	79
Can exposure to heavy metals occur via drinking water?		
No/Do not know	111	22
Yes	390	78
Can exposure to microbial germs occur via drinking water?		
No/Do not know	115	23
Yes	386	77
Can heavy metals build up in the body?		
No/Do not know	111	22
Yes	390	78
Can ingesting a large amount of metals lead to cancer?		
No/Do not know	85	17
Yes	416	83
Can germs accumulate in the body?		
No/Do not know	334	67
Yes	167	33
Can the ingestion of many germs lead to diarrheal disease?		
No/Do not know	22	4
Yes	479	96
Did you know that polluted water is not good for drinking?		
No/Do not know	31	7
Yes	468	93
Does water from rivers, wells or boreholes need to be treated before drinking?		
No/Do not know	47	35
Yes	325	65
What are the consequences of liquid waste?		
Exposure to disease	396	79
Does not expose to disease	105	21
Can unsafe water cause diarrheal disease?		
No/Do not know	21	5
Yes	475	95
Have you ever received education/information about drinking water quality?		
No	249	50
Yes	252	50
The purpose of using a covered container to boil drinking water is to:		
Reduce contamination	463	92
Reduce boiling time	26	5
Both	12	3
Are latrines essential and compulsory for every household?		
No	160	32
Yes	341	68
Total average score (SD)	14,47 (± 1,21)	
Poor knowledge (≤14 points)	235	47
Good knowledge (>14 points)	266	53

likely having a good practice towards water pollution in artisanal mining area. Compared with respondents who consumed tobacco and alcohol, those with no lifestyle (ORa: 2.51; 95% CI: 1.02; 5.97) had almost three times higher odds of having a good practice.

4 Discussion

The aim of this study was to assess the knowledge, attitudes and practices of the population in relation to water pollution in the artisanal mining areas of Siguiri, as well as the associated factors. The results highlighted average knowledge, positive attitudes and adequate practices in this population. Access to safe, available and accessible drinking water is essential for every individual (24).

A good knowledge of water pollution was observed in half of the respondents. Although the majority of respondents were aware that artisanal mining contaminates water sources with heavy metals and micro-organisms, significant gaps remained in understanding the specific risks associated with long-term exposure to heavy metals. A third of participants were unaware of the link between heavy metal ingestion and the development of cancers, a proven risk according to the scientific literature (25–27). This result may be attributed to the low level of education of the population in this region, where more than half of respondents have no formal education. It may also reflect the absence of targeted awareness campaigns on the environmental

TABLE 3 Respondents' attitudes toward water pollution, Siguiri mining areas, Guinea, June 2023 (n = 501).

Variables	Frequency	Percentage
Is drinking water only good when you are ill?		
No	60	12
Yes/Do not know	441	88
Can drinking enough clean water prevent diarrheal disease?		
No/Do not know	16	3
Yes	485	97
Can defecating near a water source cause contamination?		
No/Do not know	114	32
Yes	387	77
Does boiling water before drinking help to eliminate pathogenic micro-organisms?		
No/Do not know	16	4
Yes	479	96
Do you think boiling water can remove the smell?		
No	228	46
Yes	273	54
Do you think boiling water can eliminate contaminants?		
No	12	2
Yes	489	98
Do you think boiling water removes chlorine?		
No	243	49
Yes	258	51
Do you think boiling water can eliminate bacteria?		
No	5	1
Yes	496	99
Do you think boiling water adds minerals?		
No	112	22
Yes	389	78
Are households obliged to build their own latrines?		
No/Do not know	4	1
Yes	495	99
Do households have to possess hand-washing facilities?		
No/Do not know	68	19
Yes	408	81
Total mean score (SD)	7,75 (± 1,21)	
Negative attitude (<8 points)	238	48
Positive attitude (≥8 points)	263	52

TABLE 4 Respondents' practices of water pollution, Siguiri mining areas, Guinea, June 2023 (n = 501).

Variables	Frequency	Percentage
How is your source of water supply?		
Unprotected (well/ river/ swamp)	48	10
Protected (mineral water/ pump/ borehole)	453	90
Do you treat drinking water at home?		
No	80	16
Yes	421	84
What type of storage container do you use?		
Iron container	368	73
Plastic container	135	27
Do you use latrines?		
No	8	2
Yes	493	98
Total Score	4	
Poor practice (<4 points)	97	19
Good practice (=4 points)	404	81

and health impacts of artisanal mining. A study of the impacts of artisanal gold mining in the Republic of Guinea revealed that ineffective enforcement of mining laws and a lack of environmental education contribute to an incomplete perception of the dangers associated with artisanal mining (22). This lack of awareness underlines the importance of targeted information campaigns on the specific dangers associated with heavy metal pollution in mining areas. Campaigns must include clear information on the sources of water pollution, health risks and accessible preventive measures. A study by Ab Razak et al. (28) in Malaysia on knowledge, attitudes, and practices concerning water pollution by metals reported that 80% of respondents were aware of heavy metal contamination in drinking water, and 70% knew they could be exposed to it. In another study, Berhe et al. (16) in Ethiopia found that 78.1% of adults knew about water safety, sanitation and hygiene, and that (82 to 98%) of participants recognized that unsafe drinking water can lead to diarrhea and other illnesses. Most respondents emphasized that ingesting germs could cause diarrheal diseases, which explains why eight out of ten respondents consider the presence of feces in nature to be a source of pollution. Consequently, the use of latrines is seen as essential and mandatory for every household.

Our results showed that around half the respondents have a positive attitude towards water pollution. Residents of artisanal mining areas are frequently confronted with the tangible consequences of this pollution, such as water-borne diseases, degraded water quality and limited access to clean water sources. These personal experiences can reinforce their awareness of the importance of protecting water resources. What's more, in rural communities, water management is often seen as a collective responsibility, which can also foster positive attitudes in this regard. According to Ab Razak et al. (28), eight out of ten respondents have a positive attitude, as 59 % of participants had an intermediate level of education. Factors associated with a positive attitude in our study were respondents' level of education and origin. Individuals with formal education were more likely to recognize the importance of water quality and to adopt environmental behaviors (29). This finding confirms that formal education is an essential lever for influencing behavior. Indeed, foreign respondents, who display more positive attitudes, have probably been exposed to better-regulated water management systems in the past. By reinforcing messages on the importance of water management, while taking into account local realities and traditional knowledge, it would be possible to broaden these favorable attitudes and transform them into sustainable behaviors.

TABLE 5 Factors associated with positive attitudes regarding water pollution in the mining areas of Siguiri, Guinea, June 2023 (*n* = 501).

Characteristic	ORb	95% CI		*p*-value	ORa	95% CI		*p*-value
		Lower	Upper			Lower	Upper	
Sex								
Female	Ref				Ref			
Male	0.77	0.51	1.15	0.199	0.73	0.47	1.14	0.169
Age_group								
<30	Ref				Ref			
30–45	0.73	0.51	1.07	0.106	0.78	0.53	1.15	0.205
>75	0.49	0.26	0.92	0.027	0.56	0.29	1.06	0.078
Marital status								
Married	Ref							
Single	1.16	0.81	1.68	0.413				
Occupation								
Mining worker	Ref				Ref			
Non-mining worker	1.45	1.01	2.07	0.042	1.33	0.91	1.95	0.143
Instruction level								
Unschooled	Ref				Ref			
Schooled	1.81	1.24	2.66	0.002	2.13	1.39	3.29	<0.001
Origin								
Foreigner	1.67	0.95	3.04	0.082	1.88	1.04	3.51	0.041
Guinean	Ref				Ref			
Life style								
Alcohol	Ref							
None	0.89	0.44	1.76	0.739				
Tobacco	0.72	0.35	1.49	0.380				
Religion								
Christian	Ref							
Fetishist	1.17	0.31	4.77	0.819				
Muslim	1.87	0.81	4.68	0.158				
Knowledge class								
Poor knowledge (= < 14 points)	Ref							
Good knowledge (>14 points)	0.76	0.53	1.08	0.122				

ORb, Odds Ratio brut; ORa, Odds Ratio ajusté; CI, Confidence Interval.

In our study, the majority of respondents adopted good water management practices. This finding can be attributed to socio-economic conditions that influence behavior in the face of water pollution. In a context of limited resources, populations are often encouraged to adopt practices designed to protect their health and that of their families. Among these practices, we note in our study the preference for borehole water and sachet water over river or well water as the main sources of supply. The 2017 WHO/UNICEF survey (24) indicates that 48.7% of rural households in Guinea used at least one basic water supply service, reflecting increasing access to improved water sources. In addition, respondents in our study commonly adopted water treatment methods such as boiling and filtration (30, 31). This demonstrates a desire to reduce the risks associated with contamination and ensure safer water consumption (32).

Factors associated with the adoption of good practices include marital status, level of education, adequate knowledge and lifestyle. Respondents living alone may have more time and availability to inform themselves and implement preventive measures (33). However, it is paradoxical that the most educated individuals seem less inclined to follow traditional water pollution prevention practices. This may be because formal education does not sufficiently address local environmental issues, limiting specific awareness of water pollution. Although the knowledge acquired is supposed to translate into good practices, and almost all respondents reported the use of latrines, we found the presence of excrement in the environment. This highlights the gap between knowledge and action to prevent pollution (34). What's more, people who do not have a lifestyle associated with tobacco and alcohol consumption may be more attentive to their overall health, and may be more inclined to

TABLE 6 Factors associated with good practices regarding water pollution in the mining areas of Siguiri, Guinea, June 2023 (n = 501).

Characteristic	ORb	95% CI		p-value	ORa	95% CI		p-value
		Lower	Upper			Lower	Upper	
Sex								
Male	Ref							
Female	1.00	0.59	1.64	0.995				
Age group								
<30	Ref							
30–45	0.97	0.61	1.56	0.913				
>45	1.44	0.64	3.66	0.408				
Marital status								
Married	Ref				Ref			
Single	1.38	0.86	2.24	0.188	1.84	1.10	3.14	0.022
Occupation								
Mining worker	Ref							
Non-mining worker	0.87	0.55	1.36	0.543				
Instruction level								
Unschooled	Ref				Ref			
Schooled	0.50	0.32	0.78	0.003	0.37	0.21	0.63	<0.001
Origin								
Guinean	Ref				Ref			
Foreigner	0.60	0.32	1.17	0.119	0.73	0.35	1.55	0.391
Life style								
Alcohol	Ref				Ref			
None	2.25	1.01	4.76	0.038	2.51	1.02	5.97	0.039
Tobacco	1.34	0.59	2.91	0.474	1.21	0.48	2.94	0.674
Religion								
Muslim	Ref							
Fetishist	1.98	0.36	37.0	0.521				
Christian	1.74	0.58	7.46	0.380				
Knowledge class								
Poor knowledge(= < 14 points)	Ref				Ref			
Good knowledge (>14 points)	1.72	1.10	2.70	0.018	2.51	1.47	4.36	<0.001

ORb, Odds Ratio brut; ORa, Odds Ratio ajusté; CI, Confidence Interval.

adopt proactive behaviors, such as water treatment, to avoid water-borne illnesses. This observation could indicate greater awareness of healthy behaviors and the need to prevent water pollution.

To our knowledge, this is the first study conducted in Guinea, and possibly in Africa, to assess the knowledge, attitudes, and practices of local populations regarding water pollution in artisanal mining areas. It provides essential information to guide future interventions, improve awareness strategies, and promote sustainable behaviors through tailored educational programs. The findings support the development of public policies aimed at mitigating the negative impacts of artisanal mining, complemented by awareness programs focused on water management, a vital resource. They also contribute to strengthening local capacities while aligning with Sustainable Development Goal 6, which seeks universal access to clean and safely managed water. Moreover, this study offers an analytical framework applicable to similar contexts in sub-Saharan Africa, representing a significant step forward in addressing water pollution in mining regions. Despite these strengths, the study has certain limitations. First, as a cross-sectional study, its findings may not be generalizable and do not establish causal relationships between independent variables and the outcomes observed. Second, the reliance on self-reported data introduces the potential for response biases. Third, the study did not include qualitative data collection, which could have provided more in-depth insights from the respondents.

5 Conclusion

This study revealed moderate knowledge, generally positive attitudes, and largely adequate practices regarding water pollution in the artisanal mining areas of Siguiri. However, significant gaps remain, including a lack of awareness about the risks of prolonged exposure to heavy metals, disparities in attitudes, and inconsistencies in the implementation of optimal practices. To remedy these shortcomings, it is essential to enhance local community knowledge through targeted campaigns on the dangers of heavy metals and educational programs tailored to the cultural and environmental realities. Transforming this knowledge into sustainable attitudes and practices is essential for promoting concrete solutions, such as adopting water treatment technologies and strengthening community initiatives. These actions would directly contribute to public health and the protection of water resources in artisanal mining areas. Establishing a strategic partnership between the government, political actors, and stakeholders is also critical to consolidating progress and addressing persistent challenges. Furthermore, future research should delve deeper into the underlying mechanisms influencing knowledge, attitudes, and practices, using a mixed-methods approach that combines quantitative and qualitative methodologies.

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 humans were approved by Comité National D'Ethique pour la Recherche en Santé. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Writing – original draft, Writing – review & editing, Project administration. MarD: Writing – original draft, Writing – review & editing, Investigation, Methodology, Project administration, Conceptualization, Funding acquisition, Data curation, Resources, Validation. SS: Writing – review & editing, Investigation, Methodology, Conceptualization, Formal analysis, Writing – original draft, Data curation, Validation. SB: Methodology, Writing – review & editing, Formal analysis. FG: Methodology, Writing – review & editing, Formal analysis. MalD: Writing – review & editing, Investigation. MB: Writing – review & editing, Investigation. YY: Writing – review & editing, Investigation. MK: Writing – review & editing, Funding acquisition. AD: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing, Investigation, Resources.

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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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Global, regional, and national burden of IHD attributable to PM pollution aged 70 and above: an age-period-cohort modeling and frontiers analysis study

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Background: Particulate matter (PM) pollution is a significant risk factor for ischemic heart disease (IHD). This study evaluates the global, regional, and national burden of IHD attributable to PM pollution from 1990 to 2021, quantifies key contributing factors, and projects trends to 2044, with a focus on regional disparities and population aging.

Methods: Using data from the Global Burden of Disease (GBD) 2021 study, we analyzed trends in IHD-related disability-adjusted life years (DALYs) and mortality attributable to PM pollution. Joinpoint regression assessed long-term trends, Age-Period-Cohort modeling evaluated demographic drivers, and decomposition analysis identified the contributions of population growth, aging, and epidemiological changes. Frontier analysis compared observed DALY rates with the lowest achievable rates based on socio-demographic index (SDI). Future trends were projected using the Nordpred model.

Results: From 1990 to 2021, global age-standardized DALY rates for IHD attributable to PM pollution decreased by −1.51% annually, but absolute DALYs increased due to population aging and growth. High SDI regions saw significant declines in DALY rates (−4.75% annually), while Low SDI regions experienced negligible change (0.01%). Population growth contributed to a 183.57% increase in global DALYs, but epidemiological improvements reduced the burden by 89.29%. Frontier analysis revealed substantial unrealized potential for reducing the IHD burden, particularly in Middle SDI regions. Projections to 2044 indicate that while DALY rates will decline, total DALYs will increase among individuals aged over 70, especially in Low and Low-middle SDI regions.

Conclusions: This study highlights substantial progress in reducing the IHD burden attributable to PM pollution, particularly in High SDI regions. However, disparities remain, especially in Low and Low-middle SDI regions, where the aging population and insufficient healthcare infrastructure exacerbate the burden. The rising IHD burden among the older adult underscores the need for targeted interventions, including stricter air quality regulations, enhanced healthcare access, and policies that specifically address vulnerable populations. Strengthening healthcare systems and air pollution controls in these regions is critical to mitigating the growing IHD burden in the coming decades.

KEYWORDS

ischemic heart disease, global burden of disease, particulate matter pollution, disability adjusted life years (DALYs), age-period-cohort, socio-demographic index

1 Introduction

Ischemic heart disease (IHD) is one of the leading causes of death and disability worldwide (1, 2), with its burden increasingly linked to environmental risk factors, including particulate matter (PM) pollution (3). PM pollution, particularly fine particulate matter ($PM_{2.5}$), has been widely recognized as a significant contributor to cardiovascular diseases (4), with numerous studies demonstrating its association with increased morbidity and mortality due to IHD (5–7). The adverse health effects of PM pollution arise from its ability to penetrate the respiratory and circulatory systems (8), triggering systemic inflammation (9), oxidative stress (10), and endothelial dysfunction (11), which collectively accelerate the development of atherosclerosis (12, 13) (a major precursor of IHD). $PM_{2.5}$ refers to particulate matter that is 2.5 μm or smaller in diameter, which can deeply penetrate the lungs and enter the bloodstream, whereas PM_{10} includes particles with a diameter of 10 μm or smaller (14). Both of these particle sizes have been linked to cardiovascular diseases, though their health effects may vary due to differences in their ability to reach the circulatory system. However, $PM_{2.5}$ rarely exists in isolation and often interacts with other pollutants such as PM_{10}, nitrogen dioxide (NO_2), and ozone (O3), further exacerbating the risk of IHD (15). Studies have shown that combined exposure to these pollutants leads to synergistic effects, enhancing the inflammatory response, oxidative stress, and vascular dysfunction. For example, long-term exposure to both $PM_{2.5}$ and O3 in Tehran has been linked to an increased burden of IHD, with $PM_{2.5}$ alone contributing significantly to mortality from IHD, as estimated to account for 19.8–24.1% of IHD-related deaths. Additionally, the combined exposure to $PM_{2.5}$ and O3 was associated with increased mortality rates from cerebrovascular diseases and respiratory conditions (16). This complex interplay of pollutants contributes to a heightened cardiovascular burden, making it crucial to consider the combined exposure to multiple air pollutants in understanding the full extent of the IHD risk attributable to air pollution.

Despite extensive research, critical knowledge gaps persist regarding the global, regional, and national burden of IHD attributable to PM pollution. While short-term exposure to PM pollution has been shown to exacerbate cardiovascular events, the long-term effects of sustained exposure, particularly to fine particulate matter ($PM_{2.5}$), have not been fully understood. Long-term $PM_{2.5}$ exposure has been linked not only to respiratory diseases and cardiovascular issues but also to neurological disorders (17).

The rationale for this study stems from the urgent need to address the unequal distribution of the IHD burden across different socio-demographic index (SDI) regions. Factors such as continued global population growth, aging, and urbanization are likely to exacerbate PM pollution exposure in many parts of the world (18, 19). Furthermore, while high-income regions have made significant progress in reducing air pollution levels and improving cardiovascular health (20), low-income and middle-income countries continue to face severe pollution challenges (20, 21), compounded by weaker healthcare systems and less stringent environmental regulations. Thus, a comprehensive analysis of the global, regional, and national burden of IHD attributable to PM pollution, as well as projections of future trends, is vital for informing public health strategies and policy interventions aimed at reducing this preventable disease burden.

This study aims to provide a comprehensive analysis of the burden of IHD attributable to PM pollution by quantifying global, regional, and national trends in IHD-related disability-adjusted life years (DALYs) and mortality from 1990 to 2021, identifying the contributions of population growth, aging, and epidemiological changes to the observed burden, evaluating the unrealized potential for reducing IHD burden by comparing observed DALY rates with the lowest achievable rates based on SDI using frontier analysis, and forecasting future trends in IHD burden attributable to PM pollution through 2044 to inform targeted public health interventions. By addressing these objectives, this study seeks to fill critical evidence gaps, provide actionable insights for policymakers, and support the development of equitable strategies to mitigate the burden of IHD globally.

2 Materials and methods

2.1 Overview

This study utilized comprehensive data from the Global Burden of Disease (GBD) 2021 study, managed by the Institute for Health Metrics and Evaluation (IHME). The GBD study provides annual updates on global health metrics, including a wide range of diseases, mortality, DALYs, and associated risk factors, covering global, regional, and country-specific trends (22, 23). This study focuses on the burden of IHD attributable to PM pollution, analyzing data from 1990 to 2021 and projecting future trends through 2044.

2.2 Data sources

We extracted data on IHD-related mortality and DALYs from the Global Burden of Disease Collaborative Network and GBD

Study 2021 results, publicly available through the IHME's online data visualization tool (https://vizhub.healthdata.org/gbd-results/). These datasets provide detailed information on age-standardized mortality and DALYs related to IHD, categorized by age group, sex, year, and SDI region. Our analysis specifically focused on IHD attributable to PM pollution from 1990 to 2021, with future projections to 2044. Additionally, country-level data were used to explore regional disparities and trends, enabling us to assess differences in IHD burden across various SDI categories and geographic regions, highlighting areas with the highest and lowest burden.

2.3 Analytical methods

To investigate temporal trends, regional variations, and projections for the future burden of IHD attributable to PM pollution, we employed the following statistical and modeling techniques:

(1) **Joinpoint regression analysis:** This method was used to identify significant changes in the trends of IHD-related DALYs and mortality attributable to PM pollution over time. Joinpoint regression identifies specific points, known as joinpoints, where a significant shift in the annual percent change (APC) occurs, indicating periods of acceleration or deceleration in the burden. The method also calculates the average annual percent change (AAPC) across the entire study period to provide a comprehensive understanding of long-term trends. We applied this analysis both at the global level and across different SDI regions to capture regional disparities in burden growth.

(2) **Age-Period-Cohort (APC) modeling:** This method was utilized to disentangle the distinct contributions of aging, specific time periods, and birth cohorts to trends in IHD incidence and mortality attributable to PM pollution. APC models allow for the separation of three key effects: age effects, which represent the influence of aging on disease risk; period effects, which reflect changes in disease risk over time due to factors such as environmental conditions, healthcare improvements, and societal changes; and cohort effects, which capture variations in risk among individuals born in different time periods. By applying this method globally and across various SDI regions, we were able to evaluate how demographic shifts, healthcare advancements, and environmental factors contributed to changes in IHD burden. This approach provided insight into the temporal and cohort-specific drivers of disease risk.

(3) **Decomposition analysis:** This method was employed to quantify the relative contributions of population growth, aging, and epidemiological changes to the increase in IHD-related DALYs attributable to PM pollution. Epidemiological changes encompass factors such as urbanization and changes in lifestyle. The analysis was conducted globally and further stratified by SDI regions, enabling an examination of how these factors differed across various socio-economic contexts. By disaggregating the contributions, this approach provided insights into the primary drivers behind the increasing IHD burden linked to PM pollution.

(4) **Frontiers analysis:** This method was used to assess the unrealized potential for reducing IHD-related DALYs attributable to PM pollution based on each country's SDI. The frontier represents the lowest achievable DALYs rate for a given SDI, serving as a benchmark for comparison. Countries were plotted based on their actual DALY rates and SDI levels, and the gap between the frontier and a country's observed DALYs rate indicated the potential for improvement. We categorized countries with the largest gaps from the frontier to highlight those with the most significant room for reducing IHD burden. This analysis was applied globally and across SDI regions to evaluate how much a country's IHD burden could be reduced if it achieved frontier performance. Additionally, we identified countries in Low SDI regions that were closest to the frontier, indicating that they were already maximizing their potential given their current socio-economic status, as well as countries in High SDI regions that still had significant room for improvement despite higher development levels.

(5) **Nordpred prediction model:** To forecast the future burden of IHD attributable to PM pollution through the year 2044, we employed Nordpred prediction model. These models utilize historical data to predict future trends, incorporating both current and projected changes in demographic factors such as population aging and growth. In addition, shifts in epidemiological risk factors, such as lifestyle changes and improvements in healthcare, were also accounted for. The projections provide estimates of the future number of DALYs and DALY rates, broken down by age group, sex, and SDI levels. A particular focus was placed on the older adult population (those aged 70 and above), as this group is expected to experience the sharpest increase in IHD burden over time.

2.4 Socio-demographic index (SDI)

The SDI is a composite metric that reflects a region's development level, incorporating income per capita, educational attainment, and fertility rates (24, 25). It is calculated using these three key indicators, allowing countries and regions to be classified into five SDI categories: Low, Low-middle, Middle, High-middle, and High. This classification facilitates comparisons of disease burden and health trends across regions with varying levels of socio-economic development, offering a more precise understanding of global health disparities.

2.5 Statistical analyses

To account for the variability in DALY rates and model predictions, we assumed that these rates followed log-normal distributions. To estimate the uncertainty of the predicted increases in DALYs and mortality rates, we employed bootstrap resampling methods, generating 1,000 draws to calculate 95% confidence intervals (CIs). All statistical analyses were performed using Python version 3.7.3, with a significance threshold set at $p < 0.05$. Details of all of the above methods can be found in Supplementary material 1.

3 Results

3.1 Deaths and DALYs of IHD attributable to PM pollution in 2021

In 2021, the global distribution of deaths related to IHD attributable to PM pollution exhibited significant regional disparities (Figure 1A). Based on death rate, countries were categorized into five groups, ranging from fewer than 136.92 deaths per 100,000 to as high as 2,010.66 deaths per 100,000. Countries with the lowest death rate (<136.92/100,000) included Spain, France, Norway, and Switzerland. Countries with slightly higher but still relatively low death rate (136.92/100,000–389.17/100,000) included Chile, Peru and Mexico. The middle-range death rate category (389.17/100,000–795.87/100,000) encompassed countries such as Poland, Guyana, and Namibia. Higher death rate (795.87/100,000–1,072.91/100,000) was observed in countries like Morocco, China, and Mali, while the highest death rate (1,072.91/100,000–2,010.66/100,000) was found in countries such as Samoa, Cambodia and Gambia.

Similarly, the 2021 distribution of DALYs, which reflect both mortality and morbidity, showed marked regional differences (Figure 1B). Countries with the lowest DALYs (<1,791.34/100,000) included Iceland, France, and Canada. Countries with slightly higher DALYs (1,791.34/100,000–5,458.94/100,000) included Thailand, Poland, and Mexico, while the middle-range category (5,458.94/100,000–12,011.13/100,000) included Fiji, Morocco, and Tonga. Countries with moderately high DALYs (12,011.13/100,000–17,068.27/100,000) included Oman, Nepal, and Burundi. The highest DALYs (17,068.27/100,000–31,384.07/100,000) were observed in Sudan, Cameroon, and Samoa. The specific information of deaths in Supplementary material 2. The specific information of DALYs in Supplementary material 3.

3.2 Trends in DALYs of IHD attributable to PM pollution from 1990 to 2021 across SDI levels

At the global level, there has been a consistent decline in the age-standardized DALY rates due to IHD attributable to PM pollution, with an overall average annual percentage change (AAPC) of −1.51%. Two distinct periods of change can be observed: from 1990 to 2014, the annual percentage change (APC) was −1.10%, followed by a steeper decline from 2014 to 2021, where the APC reached −2.90% (Figure 2A).

In the Low SDI region, the trend was less consistent. The overall AAPC was 0.01%, indicating minimal change across the full-time span. A slight decrease was noted between 1990 and 2010 (APC −0.06%), followed by a sharp increase in the burden between 2010 and 2014 (APC 3.53%), and a subsequent decline from 2014 to 2021 (APC −1.74%; Figure 2B). The Low-middle SDI region exhibited a complex trend with an overall AAPC of −0.18%. The initial period from 1990 to 1997 saw a moderate increase (APC 0.43%), which was followed by a decrease from 1997 to 2000 (APC −1.70%). An increase occurred between 2000 and 2014 (APC 0.45%), followed by another decline in the final period from 2014 to 2021 (APC −1.40%; Figure 2C).

The Middle SDI region experienced a relatively stable trend with an overall AAPC of −0.7%. Between 1990 and 2000, the burden decreased slightly (APC −0.35%) before experiencing a sharp increase between 2000 and 2004 (APC 1.78%). From 2007 to 2014, the trend was largely stable (APC 0.20%), but a notable decrease occurred between 2014 and 2019, with an APC of −3.98% (Figure 2D).

In the High-middle SDI region, the overall burden of IHD attributed to PM pollution steadily declined, with an AAPC of −2.06%. The period from 1994 to 2021 witnessed a continuous decline, with the most substantial reduction occurring between 2014 and 2019 (APC −5.03%). However, a smaller decline was observed in the final years, with an APC of −1.10% from 2019 to 2021 (Figure 2E). The High SDI region showed the most significant and consistent decline in IHD burden attributable to PM pollution, with an overall AAPC of −4.75%. The rate of decline was greatest between 2004 and 2011 (APC −6.18%), and although the trend remained negative throughout the study period, the rate of decline slowed slightly in recent years, with an APC of −0.44% between 2019 and 2021. This consistent downward trend highlights the effectiveness of interventions and policies aimed at reducing air pollution and its associated health impacts in higher-income regions (Figure 2F). The specific information of AAPC in Supplementary material 4. The specific information of APC in Supplementary material 5.

3.3 Net drift in IHD attributable to PM pollution across SDI levels

In 2021, the global net drift in DALYs associated with IHD attributable to PM pollution varied significantly across SDI levels and between genders. Globally, the net drift for IHD-related DALYs was −1.13% (95% CI, −1.27 to −0.98) in males and −1.85% (95% CI, −1.93 to −1.77) in females, indicating a more significant decline in females. Among SDI regions, the Low SDI region showed the highest growth rate in males, at 1.11% (95% CI, 0.67–1.55), while the High SDI region had the steepest decline, at −5.04% (95% CI, −5.14 to −4.94). For females, the highest growth was observed in the Low SDI region at 0.01% (95% CI, −0.22 to 0.25), and the largest decline was in the High SDI region at −5.34% (95% CI, −5.41 to −5.26). Overall, the combined net drift for both genders was 0.55% (95% CI, 0.24–0.86) in the Low SDI region and −5.11% (95% CI, −5.19 to −5.03) in the High SDI region (Figure 3). The specific information of net drift in Supplementary material 6.

3.4 Age, period, and cohort effects on IHD attributable to PM pollution incidence and death rate, 1990–2021

(1) **Age Effect:** The age-specific rates of IHD attributable to PM pollution show a clear increase with advancing age across all SDI regions. Globally, and in the Low and Low-middle SDI

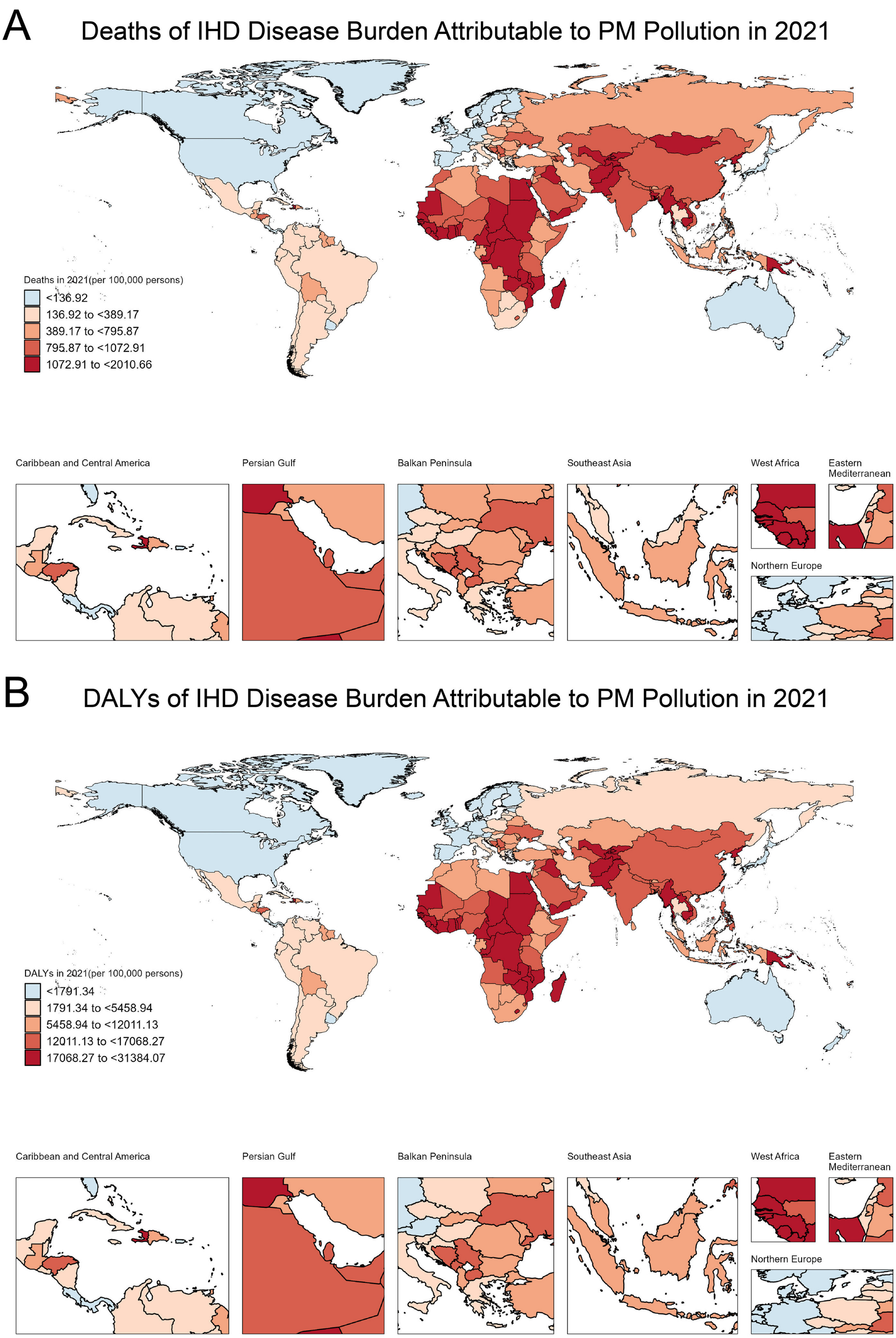

FIGURE 1
Global distribution of deaths and DALYs due to IHD attributable to PM pollution in 2021. **(A)** Deaths of IHD disease burden attributable to PM pollution in 2021 (per 100,000 persons). **(B)** DALYs of IHD disease burden attributable to PM pollution in 2021 (per 100,000 persons).

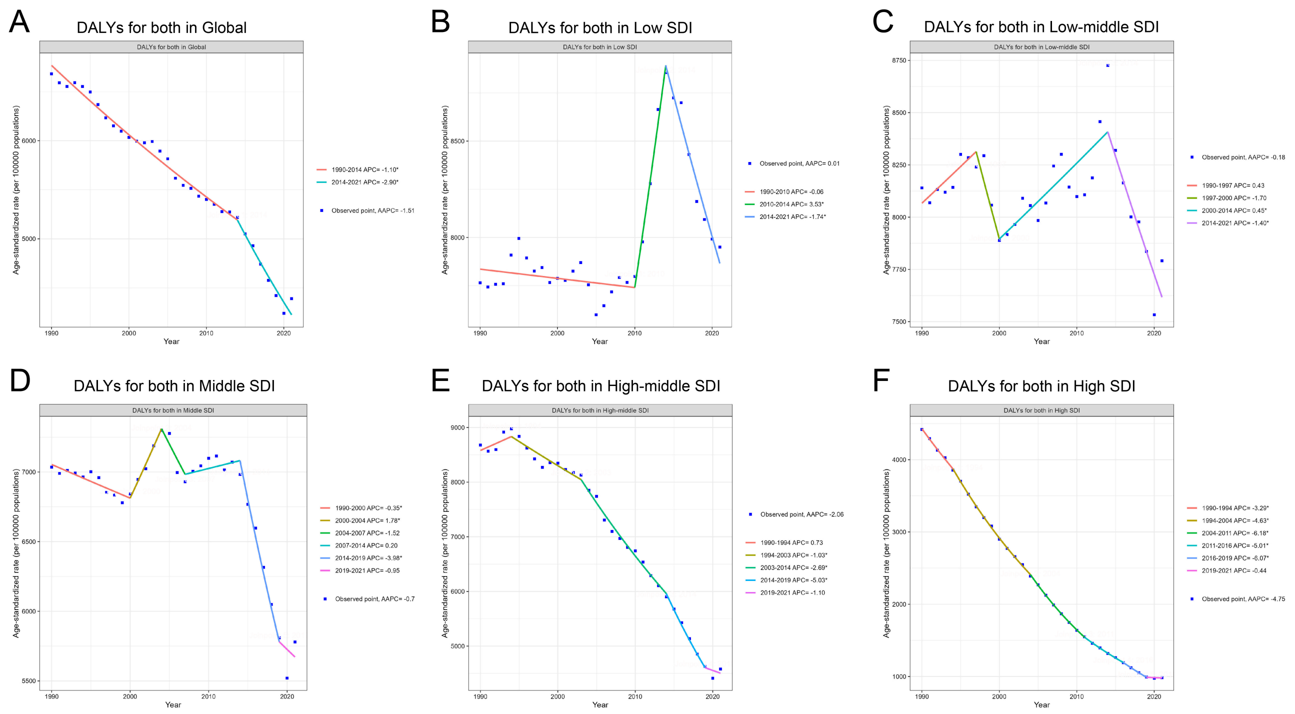

FIGURE 2
Trends in DALYs for IHD attributable to PM pollution from 1990 to 2021 across different SDI levels. **(A)** DALYs for both in Global. **(B)** DALYs for both in Low SDI. **(C)** DALYs for both in Low-middle SDI. **(D)** DALYs for both in Middle SDI. **(E)** DALYs for both in High-middle SDI. **(F)** DALYs for both in High SDI.

regions, IHD rates rise significantly from ages 70 to 95 and older, with males experiencing higher rates than females in all age groups. In these SDI regions, the oldest age groups (90–94 years and 95+ years) display a substantial increase in IHD burden. In contrast, the High SDI regions show a more gradual increase, with a slight peak in the 95+ age group (Figure 4A). Globally, the risk ratio for IHD attributable to PM pollution declines with age. The High and High-middle SDI regions show the sharpest decline in risk ratios with advancing age, indicating a lower relative risk of IHD in older populations in these higher-income regions. However, the risk ratio in Low SDI regions steadily increases with age, especially in males (Figure 4B).

(2) **Period Effect:** The period effect, depicted in Figure 5A, reflects the influence of environmental, healthcare, and social factors on IHD incidence and death rate during specific time periods. Globally, the period effects demonstrate a consistent decline in the rate ratios for IHD attributable to PM pollution from 1990 to 2021. Both males and females exhibit a reduction in rate ratios, with a steeper decline observed after 2016. The High and High-middle SDI regions show the most pronounced decrease, reflecting the impact of improved air quality measures and healthcare advancements over time. The Low SDI region, however, shows an initial period of stability, followed by a slight increase in more recent years, especially among males, suggesting a growing burden in this region.

(3) **Cohort Effect:** The cohort effect, as shown in Figure 5B, captures the influence of birth cohort on the risk of IHD incidence and death rate attributable to PM pollution, representing the evolution of risk in individuals born during specific time periods. Cohort effects show a marked decline in risk ratios for IHD attributable to PM pollution, particularly for cohorts born after 1922–1931 in most SDI regions. Globally and in the High and High-middle SDI regions, there is a consistent downward trend, with more recent birth cohorts (e.g., 1942–1951) exhibiting significantly lower risk ratios compared to earlier cohorts. In the Low and Low-middle SDI regions, the risk ratios show less consistent patterns, with some cohorts (e.g., those born between 1927 and 1936) showing stabilization or slight increases, particularly among males, indicating that risk may persist in these populations.

3.5 Driving factors of IHD attributable to PM pollution, 1990–2021

From 1990 to 2021, there has been a global increase of 8.24 million DALYs attributable to IHD due to PM pollution. Population growth is the largest contributor (183.57%), while aging is also contributing to DALYs (5.73%). In contrast, epidemiological changes have mitigated the burden (−89.29%). In the High SDI region, the IHD burden has decreased by 1.53 million DALYs overall. This decline is primarily driven by epidemiological changes (−232%). In the Low SDI region, the IHD burden increased by 946,343 DALYs. Population growth was the dominant factor (98.64%), while aging added 14,140 DALYs

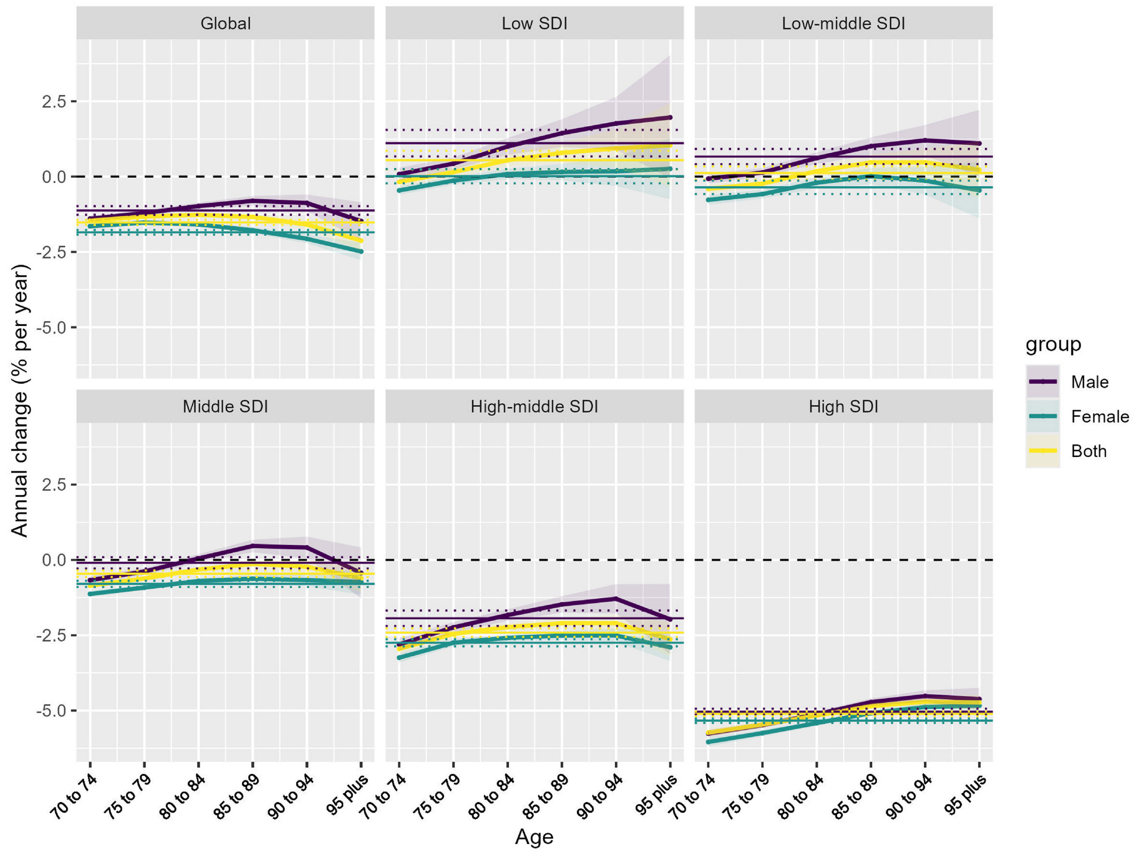

FIGURE 3
Net drift of IHD attributable to PM pollution by SDI regions and age groups. Net annual percentage change (% per year) in IHD attributable to PM pollution across different SDI regions and age groups, stratified by sex (male, female, and both combined).

(1.49%). Epidemiological changes had a negligible effect, reducing only 1,297 DALYs (−0.14%; Figure 6). The specific information of driving factors in Supplementary material 7.

3.6 Frontiers analysis of IHD DALY rates relative to SDI, 1990–2021

Figure 7A illustrates the changes in IHD DALY rates (vertical axis) over time (depicted by a color gradient from dark blue in 1990 to light blue in 2020) at different SDI levels (horizontal axis). As countries experience economic development, DALY rates generally decline over time. The solid black line represents the optimal (frontier) DALY rate achievable at a given SDI level. Countries that deviate further from this line exhibit greater unrealized health gains, indicating that their performance is suboptimal relative to their level of development. In Figure 7B, the frontier is delineated by a solid black line, and countries and territories are represented as dots. The 15 countries with the largest actual differences from the frontier (largest IHD DALYs gap) are labeled in black, including Yemen, Azerbaijan, Iraq, and Sudan. Five countries with Low SDI but closest to the frontier, such as Somalia, Niger, Mozambique, Ethiopia, and the Comoros, are marked in blue, indicating that despite their low level of development, they are achieving the best possible outcomes within their capacity. In contrast, five countries with High SDI but the largest actual distance from the frontier, including Austria, Netherlands, Republic of Korea, Monaco, and Lithuania, are marked in red, signifying that while they have achieved a high level of development, they have not yet realized their potential in reducing DALY rates and should reconsider how to leverage their advanced resources to further lower these rates. Middle and High-middle SDI regions have greater burden improvement potential. The specific information of frontiers analysis in Supplementary material 8.

3.7 Predicted rise in IHD cases and incidence rates from 1990 to 2044

The projections for the DALYs of IHD attributable to PM pollution from 1990 to 2044 show a dramatic rise in the number of DALYs across all age groups over 70 years. After 2020, the number of DALYs is projected to increase significantly. The number of DALYs in the older adult population, particularly those aged over 95, is also expected to rise substantially, although the absolute numbers are smaller compared to younger older adult groups. Both males and females are projected to follow similar patterns of growth in DALY numbers (Figure 8A). In terms of DALY rates, projections

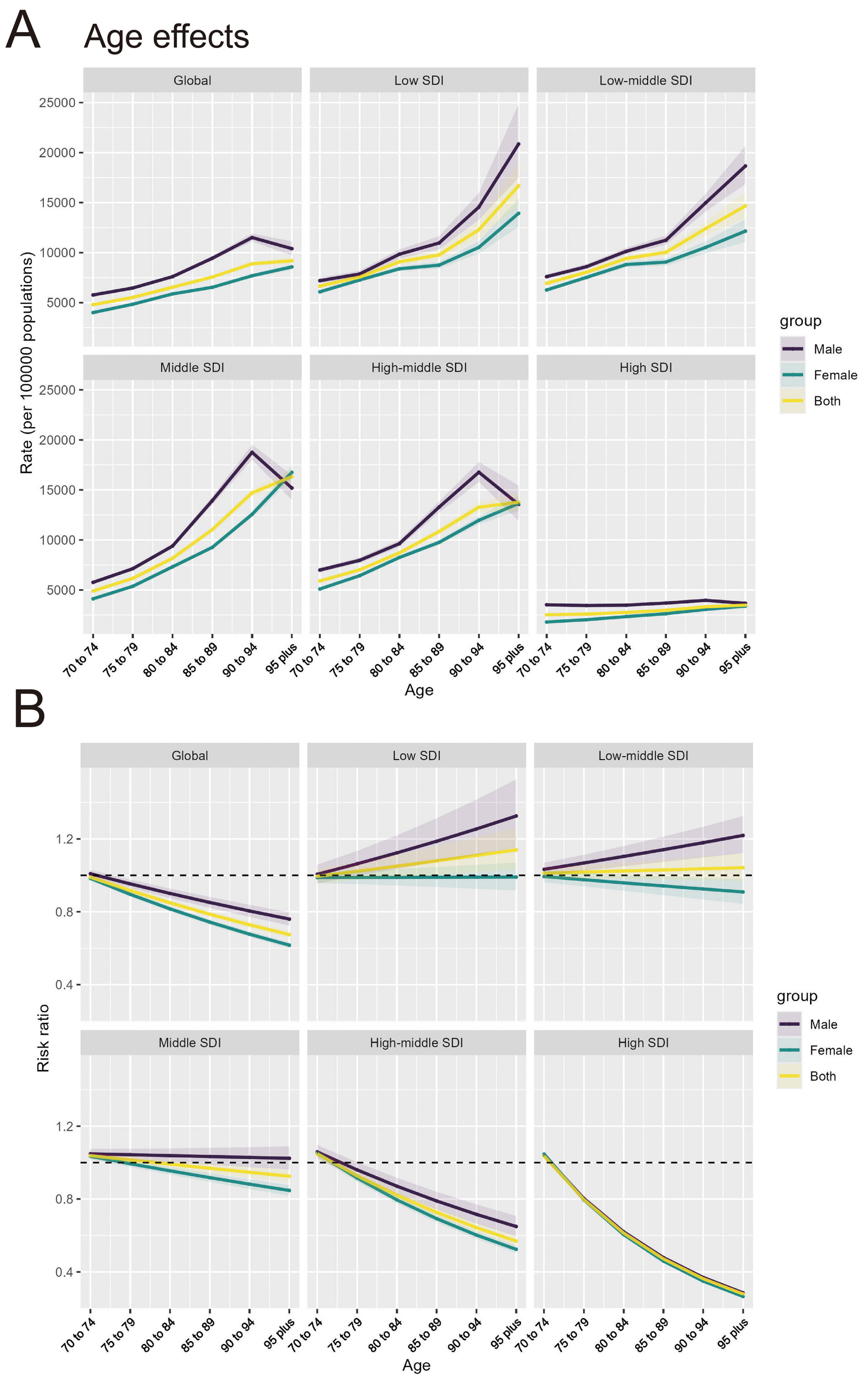

FIGURE 4
Age effects of IHD attributable to PM pollution by SDI regions and age groups. **(A)** Age effects of IHD attributable to PM pollution (rate per 100,000 population) across SDI regions. **(B)** Risk ratio of IHD attributable to PM pollution across SDI regions by age groups.

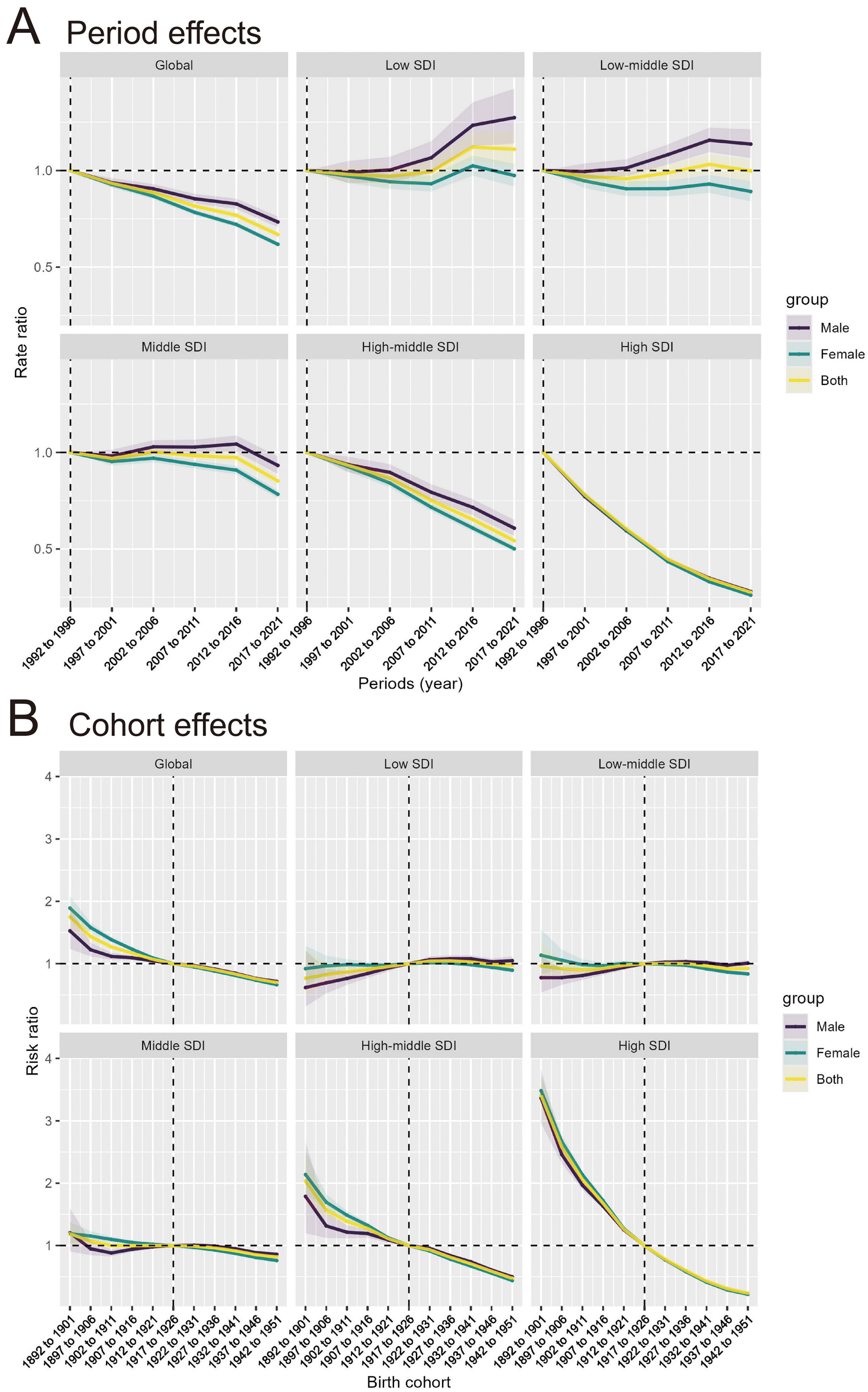

FIGURE 5
Period and cohort effects of IHD attributable to PM pollution by SDI regions. **(A)** Period effects of IHD attributable to PM pollution across SDI regions by periods. **(B)** Cohort effects of IHD attributable to PM pollution across SDI regions by birth cohorts.

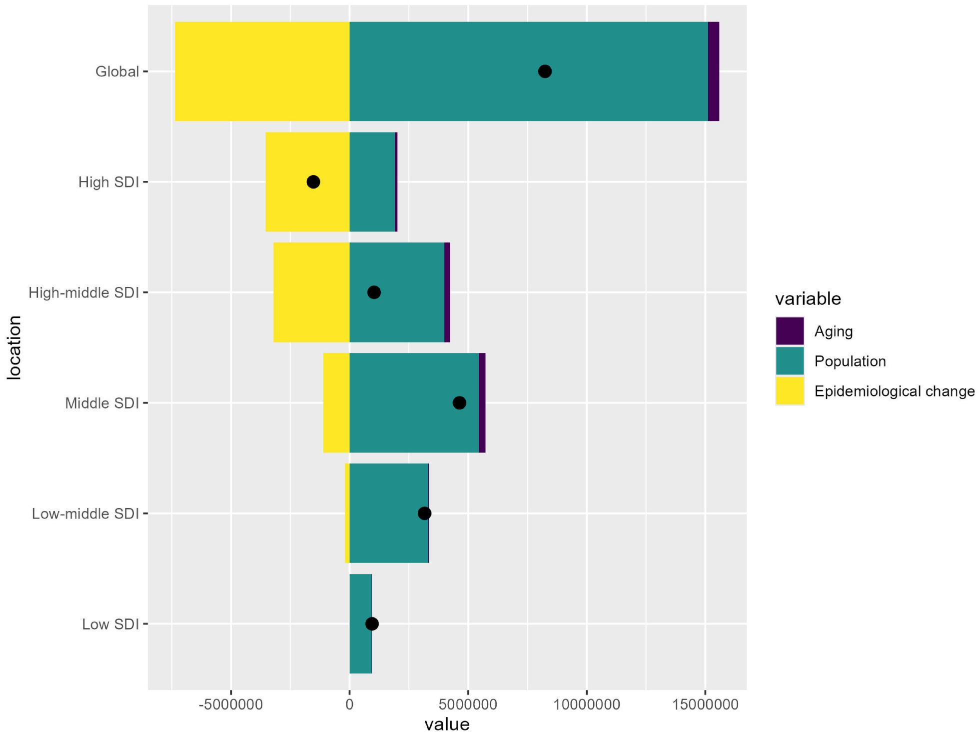

FIGURE 6
Drivers of IHD attributable to PM pollution by SDI regions. The bar chart shows the relative contributions of aging, population growth, and epidemiological change to the overall IHD burden globally and across different SDI levels.

show a steady decline across all age groups after 2020, with the most significant decline expected in the oldest population segment (those over 95 years old; Figure 8B).

4 Discussion

The results of this study highlight several critical insights regarding the global burden of IHD attributable to PM pollution, revealing notable trends and regional disparities that provide a deeper understanding of how socio-economic factors, demographic shifts, and environmental policies interplay in shaping health outcomes. While the overall global decline in IHD-related DALY rates attributable to PM pollution signals progress in managing both air quality and cardiovascular health, the persistence of large disparities across regions underscores the uneven distribution of these improvements and the significant challenges that remain.

4.1 Global decline and regional disparities

The global decline in age-standardized DALY rates for IHD attributable to PM pollution from 1990 to 2021 reflects, in part, the success of international and national efforts to reduce air pollution through stricter environmental regulations and public health interventions (26). This progress is most evident in High and High-middle SDI regions, where significant investments in air quality control, healthcare access, and health education have yielded substantial reductions in the burden of IHD (27). Countries in these regions have benefited from improved healthcare infrastructure, better access to advanced medical treatments for cardiovascular disease, and robust public policies aimed at reducing emissions from industrial activities, transportation, and energy production (28–30). The accelerated decline in High SDI regions, particularly from 2004 to 2011, highlights how coordinated efforts in policy and healthcare can produce marked improvements in public health.

However, the contrasting trends in Low and Low-middle SDI regions reveal a different narrative. In these areas, the overall burden of IHD attributable to PM pollution has been far less responsive to global progress. The slower or inconsistent improvements reflect deep-rooted challenges in these regions, including weaker enforcement of environmental regulations (31), less access to healthcare services (32), and higher exposure to PM pollution, particularly in rapidly urbanizing areas (20). The slight periods of increases in IHD burden during the early 2000s in some of these regions illustrate the detrimental effects of unchecked urbanization and industrialization (33), where economic growth has often occurred without corresponding improvements in air quality management.

4.2 Driving forces: population growth, aging, and epidemiological changes

One of the study's most striking findings is the critical role that population growth play in driving the overall burden of IHD attributable to PM pollution. The decomposition analysis

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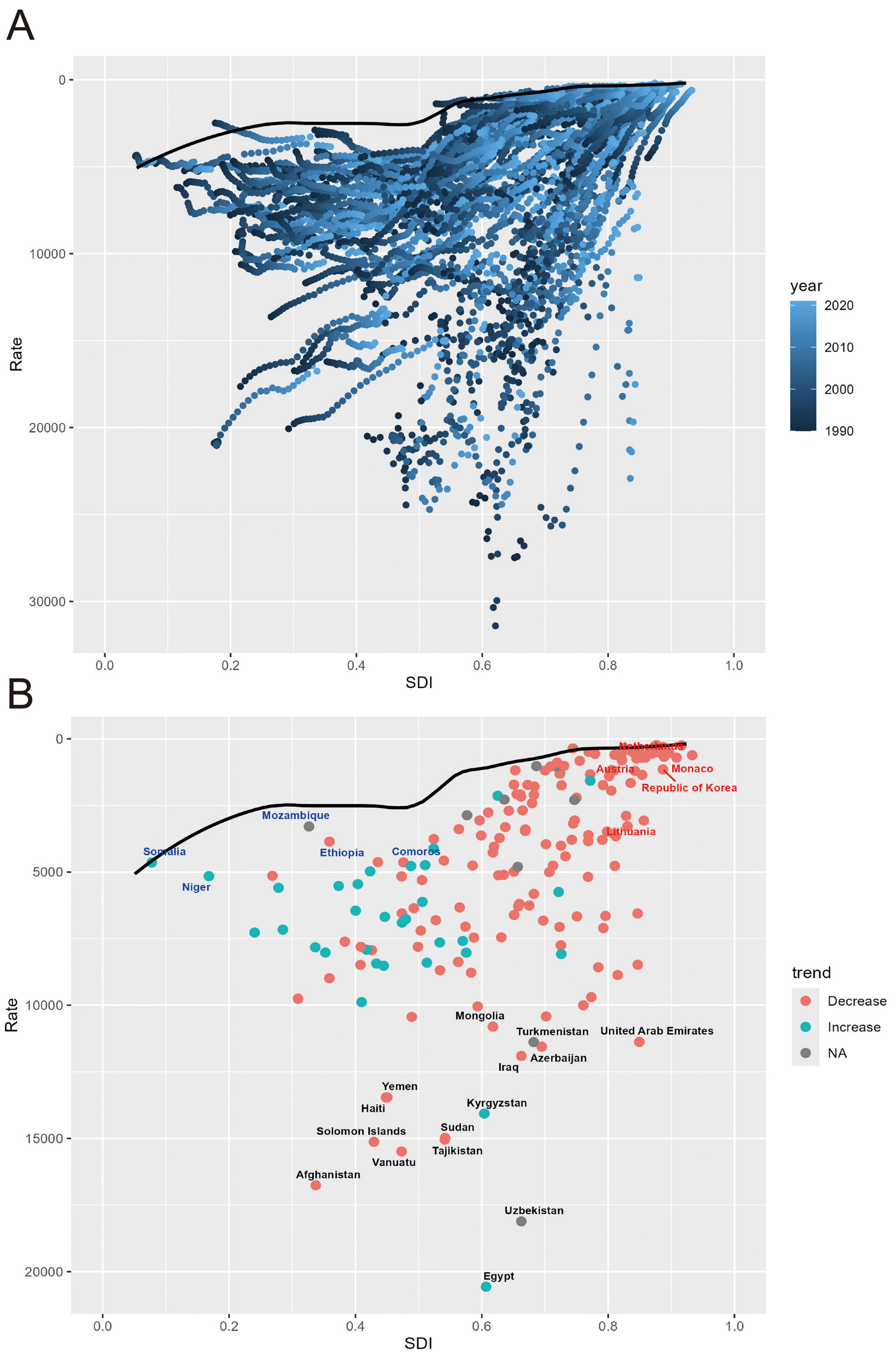

FIGURE 7
Frontier analysis based on SDI and IHD DALYs rate. **(A)** Frontier analysis based on SDI and IHD DALYs rate from 1990 to 2021. **(B)** Frontier analysis based on SDI and IHD DALYs rate in 2021.

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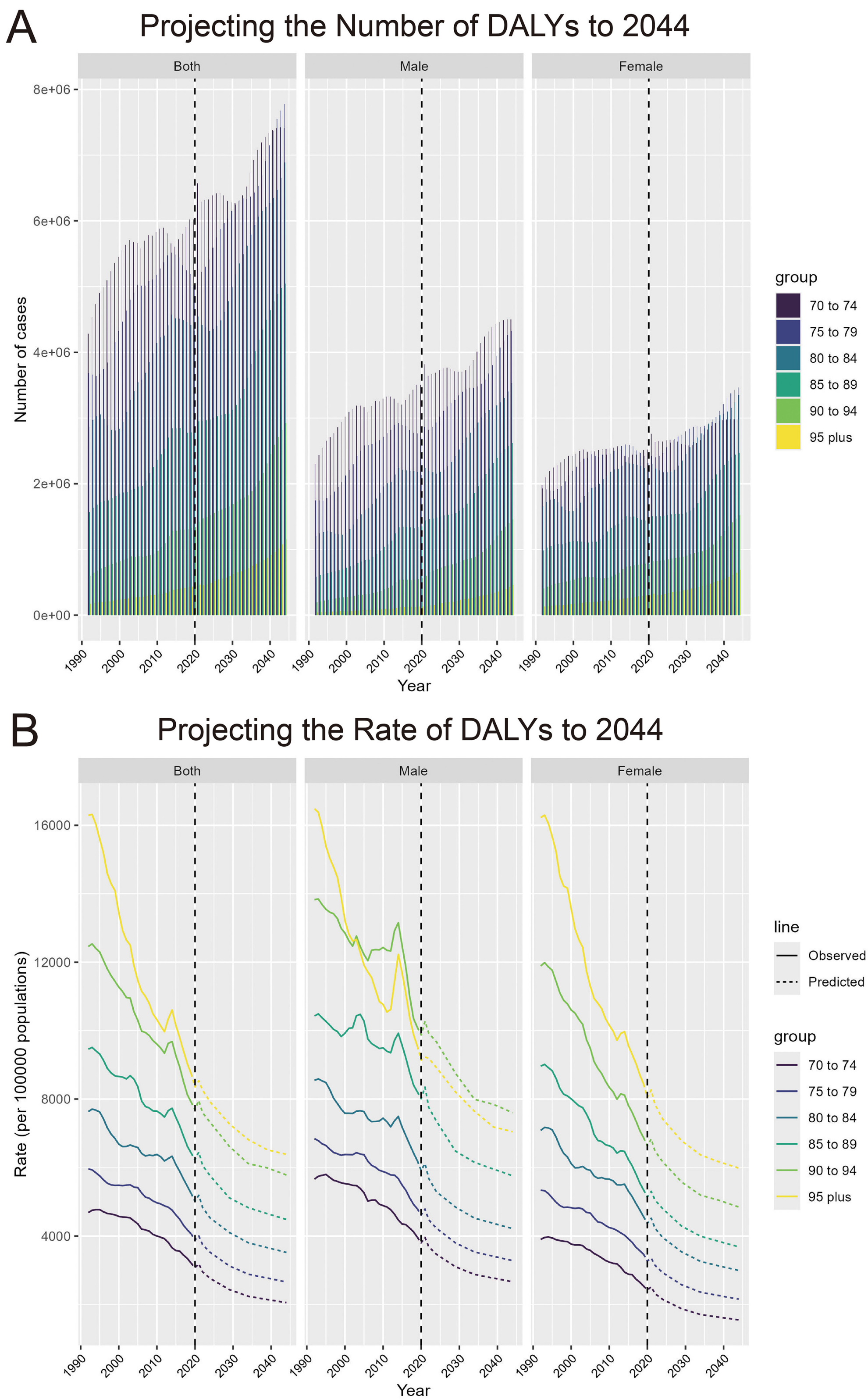

FIGURE 8
Projecting the number and rate of DALYs due to IHD attributable to PM pollution to 2044. **(A)** Projecting the number of DALYs to 2044, by sex and age groups. **(B)** Projecting the rate of DALYs to 2044 (per 100,000 population), by sex and age groups.

reveals that population growth is the largest contributor to the increase in DALYs globally, especially in Low and Low-middle SDI regions, where population growth remains high. As these populations continue to expand, more individuals are exposed to the health risks associated with PM pollution, particularly in densely populated urban areas where pollution levels are typically higher (34, 35).

Aging is also a key factor driving the IHD burden, particularly in Middle SDI regions. As life expectancy increases, the aging population, especially those over 70, experiences heightened susceptibility to cardiovascular diseases (36). The results show that while overall DALY rates have declined, older age groups continue to bear a significant portion of the burden.

In contrast, epidemiological changes, such as better cardiovascular healthcare and reductions in smoking and other risk factors, have played a crucial mitigating role (37, 38), particularly in High SDI regions. These improvements have significantly offset the negative impacts of population growth and aging, contributing to the overall decline in DALY rates in these regions. In Low SDI regions, the lack of significant epidemiological changes means that the rising IHD burden cannot be adequately mitigated, leaving these populations at heightened risk.

4.3 Unrealized potential: frontier analysis and policy gaps

The frontier analysis offers a revealing look at the unrealized potential for reducing IHD-related DALYs attributable to PM pollution, particularly in Middle and High-middle SDI regions. Many countries in these regions, despite their relative economic advancement, have not yet fully leveraged their development potential to reduce IHD burden. For example, the Republic of Korea has experienced rapid development and urbanization due to significant economic growth, which has resulted in severe air pollution (39). However, a study found that the emergency reduction measures (ERMs) implemented in response to high concentrations of particulate matter in Seoul were ineffective, and the existing ERM policies in the Republic of Korea are insufficient to effectively reduce $PM_{2.5}$ levels (31).

The identification of countries operating near their frontier in Low SDI regions, such as Somalia and Mozambique, suggests that these countries are already maximizing their health outcomes given their current socio-economic conditions. This finding emphasizes the need for external support and investment in these regions to bridge the resource gap and provide the necessary infrastructure for further health improvements.

4.4 Future projections and policy implications

The projections through 2044 offer a cautionary outlook. Although DALY rates are expected to continue declining globally, the absolute number of DALYs is projected to rise, driven by population growth. This trend highlights a potential strain on healthcare systems, especially in middle and low-income countries that may lack the capacity to manage the growing older adult population (40). Therefore, it is necessary to implement targeted interventions for the older adult. These interventions, such as regular cardiovascular screenings (41), increased indoor physical activities, and stricter air quality control policies (42), can enhance the older adult's access to preventive healthcare. Policies aimed at reducing PM pollution, such as transitioning to cleaner energy sources (43), promoting sustainable urbanization (44), and enforcing stricter air quality standards, are essential.

4.5 Limitations and future directions

While this study offers a comprehensive analysis of the global burden of IHD attributable to PM pollution, it has several limitations. First, the reliance on large-scale datasets such as the GBD may introduce uncertainties, particularly in regions with limited data availability or reporting inconsistencies. This can affect the accuracy of the DALY estimates and the granularity of regional analyses. Second, the study does not account for the potential impacts of future technological advancements, policy changes, or shifts in energy sources that could alter PM pollution levels and health outcomes. Additionally, the models used for forecasting may not fully capture the complex interactions between demographic shifts, healthcare access, and environmental factors, especially in Low and Low-middle SDI regions.

Future research should focus on improving the accuracy of pollution exposure assessments, particularly in underrepresented regions, and integrating real-time air quality data with health outcomes. There is also a need to explore the long-term effects of emerging pollution sources, such as wildfires and extreme weather events, which could exacerbate IHD risks.

5 Conclusion

This study offers a comprehensive evaluation of the global, regional, and national burden of IHD attributable to PM pollution, emphasizing the crucial role of environmental factors in cardiovascular health outcomes. Our findings highlight significant progress in reducing the IHD burden in high SDI regions, where air pollution control measures and healthcare improvements have led to notable reductions in IHD-related DALYs. However, substantial regional disparities remain, with low and low-middle SDI regions experiencing slower progress. These regions face heightened challenges due to factors such as rapid population growth, aging populations, and insufficient healthcare infrastructure, which exacerbate the burden of IHD. One of the most striking findings of this study is the substantial unrealized potential for further reductions in IHD burden in middle SDI regions. These areas, despite having some economic development, still show considerable room for improvement in both environmental and healthcare policies. Strengthening healthcare systems and implementing stricter air quality regulations are crucial steps toward reducing the future burden of IHD in these regions. Furthermore, the study reveals the potential for more equitable health outcomes globally. By addressing the unique challenges faced by low and low-middle SDI regions—particularly in terms of air pollution control and healthcare accessibility—this research supports the development of policies that aim to reduce the health disparities associated with PM pollution. To achieve meaningful progress, it is critical to prioritize the most vulnerable populations, including those in the older adult age group, and to promote policies that target long-term reductions in air pollution exposure.

Data availability statement

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

Author contributions

K-JH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HW: Data curation, Validation, Writing – original draft. XL: Supervision, Validation, Writing – original draft. RY: Data curation, Writing – original draft. GG: Visualization, Writing – original draft.

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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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

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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.2025.1573599/full#supplementary-material

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Impact of meteorological factors on transmission of respiratory viruses across all age groups in the hot arid climate in Qatar

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Background: The association between meteorological parameters and viral transmission in temperate and subtropical arid climates is not fully understood. The climate in Qatar reaches extremes of heat and humidity but retains a similar pattern of transmission of respiratory viruses as in temperate climates.

Gap statement: The need for a better understanding of the demographic and meteorological factors that drive the transmission of respiratory viruses in the community.

Aim: To evaluate the relationship between meteorological and demographic factors on the transmission of 18 respiratory viruses in the State of Qatar.

Materials and methods: In total, 355,948 nasopharyngeal swabs were tested for respiratory viruses from 31-Dec-2018 to 29-Dec-2019. The study involved 18 viruses, of which only 8 viruses were included in the analysis: ADV, hBoV, Flu-A, Flu-B, hPIV3, hMPV, HRV, and RSV. Respiratory virus prevalence was compared with local meteorological data including outdoor air temperature; dew point; wind speed; atmospheric pressure; relative humidity; solar radiation, and demographic factors, including age, gender, and nationality.

Results: Transmission waves were seen for ADV, hBoV, Flu-A, Flu-B, hMPV, HRV and RSV but not with hPIV-3. Wind speed, air temperature, relative humidity, and solar radiation were significantly associated with Flu-A, Flu-B, hMPV, and RSV, which showed clear seasonality, but not with HRV, hBoV, and ADV, which had atypical seasonality and hPIV-3, which had no seasonality. Incidental associations could not be excluded and would need to be confirmed through multiple seasons. School age was the most significant demographic.

Conclusion: Young children, rather than meteorological factors, served as the primary determinant of viral transmission. The proximity of 3 large viral waves to school reopening after the summer break suggested school transmission is an important contributor. The significant association of meteorological factors with viral transmission increased the risk further, reflecting the period of the year of maximum transmission. This was seen with as viruses with a clear seasonality but not with viruses with atypical or absent seasonality.

KEYWORDS

respiratory viruses, meteorological factors, epidemiology, age, gender, hot and climate

Introduction

Respiratory virus infections often result in hospital admission and inappropriate use of antibiotics, a driver of antibiotic resistance Kabir (1). They are widely associated with acute lower respiratory tract infections (LRTIs), which constitute an important public health problem in both high and low-income countries and a leading cause of death; in 2016 alone LRTIs were linked to nearly 2.38 million deaths globally Collaborators (2). Influenza and respiratory syncytial virus (RSV) produce annual waves of transmission and are linked to over 65% of patients hospitalized with LRTIs, with significant levels of morbidity and mortality Scheltema et al. (3). The seasonal appearance of influenza and other respiratory viruses is well described in temperate climates, and seasonal transmission patterns are mostly associated with increased prevalence in winter. This is thought to be associated with increased indoor and outdoor mixing because of extremes of temperature. Children are more socially connected than adults because of schooling and are more susceptible to viral infections because of less immunity to viral infections than adults. Therefore, epidemics, within a single season or across seasons, likely involve an interplay between children and adults Bansal et al. (4). Meteorological factors may play a role indirectly by encouraging indoor mixing in hot and cold weather or directly through mucosal inflammation D'Amato et al. (5). Inflammation supports microbial adherence to the respiratory tract mucosa, impacting the respiratory microbiome and triggering infection Liu et al. (6).

Temperature also has an important effect on viral survival. The envelope of Flu-A is more stable at lower temperatures, with viability reduced at warmer temperatures Lowen et al. (7). Absolute rather than relative humidity is thought to increase Flu-A viability Pica and Bouvier (8) and Price et al. (9). Liu et al. (6) also showed a significant correlation of transmission with air temperature, atmospheric pressure, rainfall, and relative humidity, but no correlation with sunlight intensity or wind speed. In addition, the rate of lower respiratory tract infection-related hospital admissions was found to decrease with gradual increases in temperature and relative humidity. Understanding these dynamics more fully could help develop strategies to reduce their transmission.

Qatar is a city state bordering the Kingdom of Saudia Arabia with a population of 2.8 million. It is a peninsula protruding into the Persian Gulf with a flat terrain, a long coastal strip, and a significant inland desert. The climate is subtropical and arid, with low annual rainfall. The weather can be broadly grouped into three seasons: (1) warm from October to April; (2) hot from May to July; and (3) hot and humid from August to September. Temperatures range from 14°C to 22°C in the cooler months and from 32°C to 40°C in the hot months, with temperatures occasionally reaching 50C.

The aim of the present study was to examine the impact of meteorological factors on the transmission of respiratory viruses over the 12-month period of 2019. The meteorological factors studied were temperature; relative humidity; wind speed; atmospheric pressure; dew point; solar radiation. The demographic factors analyzed were gender, age and nationality.

Materials and methods

Study design and data collection

The results of respiratory virus testing were available for the period 1-Jan-2019 to 29-Dec-2019 and included results from 355,948 patients (Figure 1). The study population covered all age groups from multiple nationalities. Samples were tested by Real-time Polymerase Chain Reaction (qPCR) for a panel of 18 respiratory viruses and atypical bacteria using the Fast Track Diagnostics Respiratory pathogens 21 assay (***FTD™, Luxembourg***). These included: adenovirus (ADV); influenza A virus (Flu-A); influenza B virus (Flu-B); human rhinovirus (HRV); human coronaviruses (HCoV); 229E; NL63; HKU1; OC43; MERS-CoV; human parainfluenza viruses (hPIV) 1 to 4; human metapneumovirus (hMPV); human bocavirus (hBoV); respiratory syncytial virus (RSV); Parechovirus and *Mycoplasma pneumoniae* (MPN). Out of the 18 viruses, only 8 were further analyzed due to their high number of confirmed infections, based on an arbitrary threshold of 500. Samples tested were received from hospital in-patients, adult and pediatric emergency departments, primary health care centers, and outpatient clinics.

Demographic data and meteorological factors

Data on average monthly outdoor meteorological factors were recorded. These included air temperature in degree Celsius (°C), dew point temperature (°C) (The temperature the air needs to be cooled in order to produce a relative humidity of 100%, which depends on the pressure and water content of the air), wind speed (Kt), atmospheric pressure (VP; hPa), % relative humidity (RH) and solar radiation

(W/m^2) (Energy emitted by the Sun, through electromagnetic waves) were obtained from the Qatar Meteorology Department weather station in Doha, situated 13 m above sea level at a Latitude of

25°16′45″N and Longitude: 51°31′20″E. The daily incidence of each pathogen by qPCR was analyzed for association with climate factors, using average monthly means of the respective meteorological parameters. Multivariate logistic regression analysis of virus, meteorological factors, and demographic are shown (Figure 2).

The study population of 355,948 patients included 150,570 females and 205,378 males divided into eight age groups respectively: < 1 year (infants); 1–4 years (pre-school age); 5–12 years (school age); 13–18 years (adolescence); 19–30 (young); 31–45 (adult); 40–60 years (old); > 60 years (older adult). Qatari nationals comprised 30.7% of the study population, and the remaining 69.3% were mainly nationals from other Arab (Egypt, Syria, Jordan, and GCC countries) and Asian (Indian, Bangladesh, and Philippines) countries, and other countries contributing smaller population sizes.

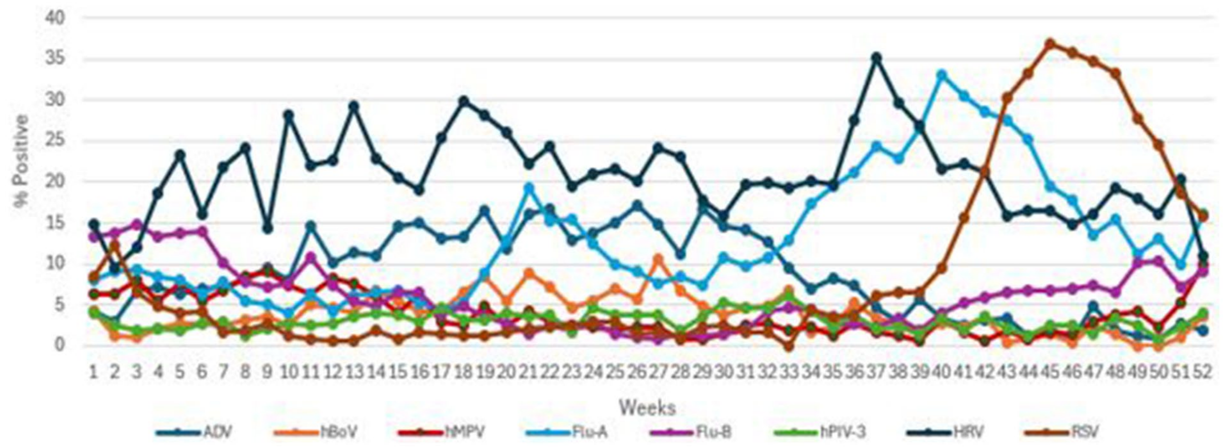

FIGURE 1
The transmission pattern of common viruses (ADV, hBoV, hMPV, Flu A, Flu B, hPIV3, HRV, and RSV) during 2019.

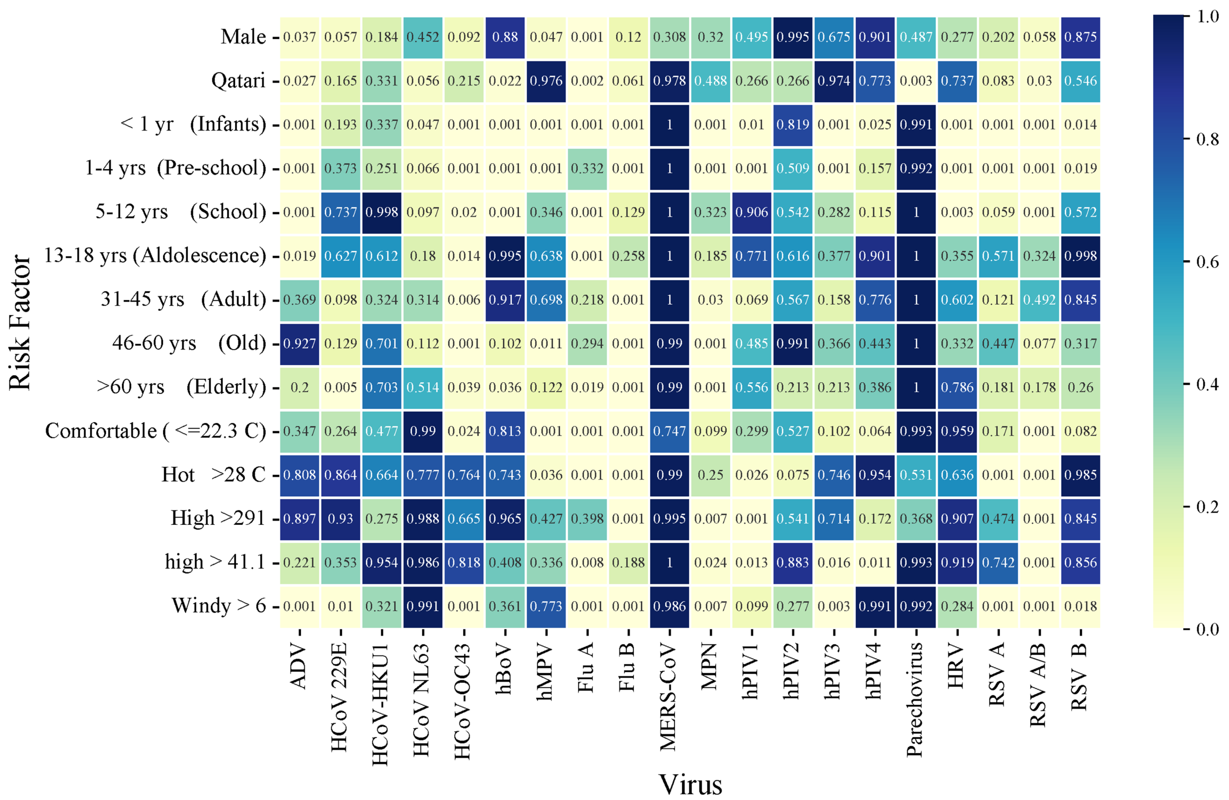

FIGURE 2
Heatmap of multivariate logistic regression analysis of virus-meteorological and virus-demographic associations. Numbers within the figure represent *p* values.

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Meteorological factors were categorized based on their average monthly values throughout the year, using non-linear regression models to convert continuous variables into categorical ones through threshold-based classification. Specifically, Temperature was divided into three categories: "Comfortable" for temperatures ≤ 22.3°C, "Warm" for temperatures between 22.4°C and 27°C, and "Hot" for temperatures ≥ 28°C. Solar Radiation was classified as "High" when it exceeded 291 W/m^2 and "Low" when it was ≤ 291 W/m^2. Atmospheric Pressure was categorized as "High" when it was greater than 1,000 hPa and "Low" when it was ≤ 1,000 hPa. Relative Humidity was classified as "High" when it exceeded 41.1%, and "Low" when it was ≤ 41.1%. Dew Point was categorized as "Medium" when it ranged from 13.56°C to 14.82°C, "Low" when it was ≤ 13.56°C, and "High" when it was > 14.83°C. Finally, Wind Speed was classified as "Windy" when it exceeded 6 kt and "Calm" when it was ≤ 6 kt. These thresholds were established based on Qatar's typical climate, its average weather patterns over the year, and the guidelines for wind speed classification provided by the national weather service and other relevant sources Ku-Mahamud and Khor (10). The information was gathered by the primary investigators at each location from the local Weather Spark website (weatherspark), as well as from the National Weather Service's (weather).

Statistical analysis

Statistical analysis used IBM SPSS 29 software (SPSS, Chicago, IL, United States). All categorical and binary variables were reported as numbers and percentages. The overall incidence of viral infections, gender, age, and meteorological factors was analyzed using Chi-Square analysis on the differences between each virus with positive and negative results. Regression analyses were performed for gender, age, nationality, and meteorological factors associated with positive results of viral infections and were reported as odds ratios (OR) with 95% confidence intervals (CI).

Univariate logistic regression was used to investigate the association of the above-mentioned factors with viral infection. Multiple logistic regression was then performed for significant variables with $p < 0.05$. Dew point and atmospheric pressure were excluded from the multiple logistic regression due to their low detection rates, which could potentially lead to redundancies with the other variables. Multiple logistic regression was then performed adjusting for all the variables. Non-significant variables were retained in the model as they interact synergistically within the same climatic system, contributing significantly to the understanding of seasonality patterns and viral dynamics. The independent risk factors included in the final model were reported as ORs with 95% CIs and statistical significance was defined as $p < 0.05$ (Table 1).

In addition, univariate analysis of continuous variables (mean temperature, dew point, wind speed, atmospheric pressure, relative humidity, and solar radiation) were compared between days where one or more samples were, respectively, positive or negative for a given virus using two-sample *t*-tests (Table 2). Multicollinearity was observed in meteorological factors due to moderate to strong correlations among variables.

An ANOVA, followed by Tukey's post-hoc test, was conducted to determine if there were differences in the mean temperature, dew point, atmospheric pressure, relative humidity, solar radiation, and wind speed associated with the presence of various viruses.

Results

Viral transmission in the study population

Viruses were arbitrarily defined as the main circulating viruses where ≥500 was detected in the 12-month period. These were Flu-A, Flu-B, RSV, ADV, HRV, hMPV, hBoV, and hPIV-3. The remaining viruses and MPN, arbitrarily defined as minor circulating viruses with <500 detected were hPIV-1, OC43-CoV, HKU-COV, hPIV-4, NL63-CoV, hPIV-2, Parechovirus and MPN; 2 cases of MERS-CoV were confirmed. Data analysis was restricted to the main virus groups.

The local Qatari population made up to 34% of those tested. The male to female ratio of the patient cohort was 1.3:1, with 19,671 (5.5%) positives for one or more viruses. A total of 355,948 NPA samples were examined during the study period. Respective transmission patterns of the 8 main viruses are shown in Figure 1, with their detection frequencies in Table 1. Flu-B and hMPV had waves straddling the beginning and end of the year. The first hMPV wave peaked in week 9 and the second in week 52. The first Flu-B wave peaked in week 3 and the second in week 49. hBoV and ADV both had extended waves of 7 months from week 6 to week 40, peaking around week 26. Larger waves were seen with Flu-A, RSV and HRV. A small Flu-A wave peaked in week 21 and the larger one in week 40. RSV peaked in Week 45. HRV showed high prevalence throughout the year with a large wave peaking in week 35. hPIV-3 showed no seasonality.

Meteorological associations

All the main viruses showed significant correlations with all meteorological parameters except Flu-A, which did not reach significance with solar radiation and Flu-B, hPIV-3 and HRV did not reach significance with wind velocity (Table 1; Figure 3).

Wind velocity appeared to enhance the transmission of certain viruses, such as ADV, with an odds ratio (OR) of 2.448, while for other viruses, it appeared to reduce, i.e., hMPV, Flu-A, Flu-B and RSV transmitted at temperatures ≤ 22.3°C and > 28°C, suggesting that temperature did not consistently influence transmission. Relative humidity was significantly linked to Flu-A transmission (OR) of 1.414 but showed no significant association with Flu-B. Solar radiation >291 W/m^2 was positively correlated with an increased probability of RSV transmission as reflected by an odds ratio (OR) of 2.405. In contrast, solar radiation >291 W/m^2 was linked to a lower likelihood of Flu B transmission, with (OR) of 0.508 (Figure 4).

Demographics

There were clear differences in the age associated with individual virus transmission. ADV, HRV and hBoV were significantly associated with transmission in newborn, pre-school, and school-age children with the highest seen, respectively, for ADV and HRV in newborns and for hBoV in pre-school children (Figures 4A,B,D). hPIV3, hMPV and Flu-A were strongly associated with infections in infants and preschool children, while RSV had the strongest association with infants. Flu-B showed negative association with age (Figures 4C,E,F,G). Male gender and Qatari nationality showed significant but differing associations with various viruses.

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TABLE 1 Frequency differences of 17 respiratory viruses and MPN by demographic and meteorological factors over a 12-month period.

Risk factors	ADV		HCoV 229E		HCoV-HKU1		HCoV NL63		HCoV-OC43		hBoV		hMPV	
	n (=1843/ 20205)	*p*-value	*n* (=195/ 16940)	*p*-value	*n* (=170/ 16940)	*p*-value	*n* (=166/ 16940)	*p*-value	*n* (=326/ 16940)	*p*-value	n (=700/ 16226)	*p*-value	*n* (=643/ 16940)	*p*-value
Gender		0.185		0.544		0.257		0.762		0.096		**0.016**		0.081
Female (*n*)	737 (40%)		77 (39.5%)		78 (45.9%)		71 (42.8%)		121 (37.1%)		322 (46%)		289 (44.9%)	
Male (*n*)	1,106 (60%)		118 (60.5%)		92 (45.1%)		95 (57.2%)		205 (62.9%)		378 (54%)		354 (55.1%)	
Nationality		**0.031**		0.469		0.316		0.103		0.263		**0.002**		0.579
Non-Qatari (*n*)	1,259 (68.6%)		140 (72.2%)		112 (66.3%)		124 (75.6%)		236 (72.6%)		451 (64.6%)		453 (70.8%)	
Qatari (*n*)	577 (31.4%)		54 (27.8%)		57 (33.7%)		40 (24.4%)		89 (27.4%)		247 (35.4%)	0.002	187 (29.2%)	0.579
Ageband		**<0.001**		**0.034**		0.251		**<0.001**		**<0.001**		**<0.001**		**<0.001**
<1 yr. (infants)	566 (30.7%)		53 (27.2%)		53 (31.2%)		72 (43.4%)		129 (39.7%)		206 (29.4%)		198 (30.8%)	
1–4 yrs. (Pre-school)	905 (49.1%)		41 (21%)		34 (20%)		45 (27.1%)		91 (28%)		417 (59.6%)		234 (36.4%)	
5–12 yrs. (school)	196 (10.6%)		6 (3.1%)		11 (6.5%)		13 (7.8%)		17 (5.2%)		40 (5.7%)		29 (4.5%)	
13–18 yrs. (adolescence)	16 (0.9%)		3 (1.5%)		1 (0.6%)		2 (1.2%)		4 (1.2%)		2 (0.3%)		5 (0.8%)	
19–30 yrs. (Young)	46 (2.5%)		13 (6.7%)		11 (6.5%)		8 (4.8%)		13 (4.0%)		14 (2.0%)		27 (4.2%)	
31–45 yrs. (adult)	71 (3.9%)		28 (14.4%)		31 (18.2%)		13 (7.8%)		34 (10.5%)		15 (2.1%)		49 (7.6%)	
46–60 yrs. (old)	25 (1.4%)		19 (9.7%)		14 (8.2%)		8 (4.8%)		23 (7.1%)		3 (0.4%)		53 (8.2%)	
>60 yrs. (older adult)	18 (1.0%)		32 (16.4%)		15 (8.8%)		5 (3.0%)		14 (4.3%)		3 (0.4%)		48 (7.5%)	
Temperature		**<0.001**		0.171		**0.035**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Warm (22.4–27°C)	242 (13.1%)		23 (11.8%)		20 (11.8%)		13 (7.8%)		23 (7.1%)		82 (11.7%)		86 (13.4%)	
Comfortable (<=22.3°C)	506 (27.5%)		71 (36.4%)		67 (39.4%)		6 (3.6%)		190 (58.3%)		155 (22.1%)		344 (53.5%)	
Hot >28°C	1,095 (59.4%)		101 (51.8%)		83 (38.8%)		147 (88.6%)		113 (34.7%)		463 (66.1%)		213 (33.1%)	
Solar energy		**<0.001**		**0.012**		0.587		**<0.001**		0.317		**<0.001**		**<0.001**
Dark > 291	1,268 (68.8%)		133 (68.2%)		132 (77.6%)		97 (58.4%)		255 (78.2%)		479 (68.4%)		560 (87.1%)	
Bright <= 291	575 (31.2%)		62 (31.8%)		38 (22.4%)		69 (41.4%)		71 (21.8%)		221 (31.6%)		83 (12.9%)	
Pressure		**<0.001**		**0.012**		0.587		**<0.001**		0.317		**<0.001**		**<0.001**
Low <=1,000	575 (31.2%)		62 (31.8%)		38 (22.4%)		69 (41.6%)		71 (21.8%)		221 (31.6%)		83 (12.9%)	
High > 1,000	1,268 (68.8%)		133 (68.2%)		132 (77.6%)		97 (58.4%)		255 (78.2%)		479 (68.4%)		560 (87.1%)	
Humidity		**<0.001**		**0.003**		0.657		0.946		**<0.001**		**<0.001**		**<0.001**
Low <= 41.1	1,141 (61.9%)		104 (53.3%)		76 (44.7%)		71 (42.8%)		102 (31.3%)		425 (60.7%)		209 (32.5%)	
High > 41.1	702 (38.1%)		91 (46.7%)		94 (55.3%)		95 (57.2%)		224 (68.7%)		275 (39.3%)		434 (67.5%)	
Dew point		**<0.001**		**0.021**		**0.027**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Medium (13.56–14.82)	214 (11.6%)		20 (10.3%)		13 (7.6%)		1 (0.6%)		18 (5.5%)		64 (9.1%)		58 (9.0%)	

(Continued)

TABLE 1 (Continued)

Risk factors	ADV		HCoV 229E		HCoV-HKU1		HCoV NL63		HCoV-OC43		hBoV		hMPV	
	n (=1843/ 20205)	*p*-value	*n* (=195/ 16940)	*p*-value	*n* (=170/ 16940)	*p*-value	*n* (=166/ 16940)	*p*-value	*n* (=326/ 16940)	*p*-value	n (=700/ 16226)	*p*-value	*n* (=643/ 16940)	*p*-value
Low <= 13.56	506 (27.5%)		71 (36.4%)		67 (39.4%)		6 (3.6%)		190 (58.%)		155 (22.1%)		344 (53.5%)	
High > 14.83	1,123 (60.9%)		104 (53.3%)		90 (52.9%)		159 (95.8%)		118 (36.2%)		481 (68.7%)		241 (37.5%)	
Wind speed		**<0.001**		**<0.001**		**<0.001**		**0.049**		**<0.001**		**<0.001**		**<0.001**
Windy > 6	998 (91.5%)		112 (88.9%)		72 (72%)		28 (54.9%)		194 (87.8%)		322 (84.1%)		301 (75.3%)	
Calm <= 6	93 (8.5%)		14 (11.1%)		28 (28%)		23 (45.1%)		27 (12.2%)		61 (15.9%)		99 (24.8%)	

Risk factors	Flu-A		Flu-B		MERS-CoV		MPN		hPIV-1		hPIV-2		hPIV-3	
	n (=5695/ 40539)	*p*-value	*n* (=2741/ 40539)	*p*-value	*n* (=21/ 6073)	*p*-value	*n* (=323/ 16940)	*p*-value	*n* (=340/ 16927)	*p*-value	*n* (=84/ 16940)	*p*-value	*n* (=527/ 16940)	*p*-value
Gender		**<0.001**		0.158		**<0.001**		0.769		0.542		0.370		0.491
Female (*n*)	2,702 (47.4%)		1,168 (42.6%)		17 (81.0%)		137 (42.4%)		147 (43.2%)		39 (46.4%)		227 (43.1%)	
Male (*n*)	2,993 (52.6%)		1,573 (57.4%)		4 (19.0%)		186 (57.6%)		193 (56.8%)		45 (53.6%)		300 (56.9%)	
Nationality		**<0.001**		**0.028**		**<0.001**		0.443		0,105		**0.011**		0.451
Non-Qatari (*n*)	3,670 (64.6%)		1908 (69.8%)		5 (31.3%)		231 (71.7%)		223 (65.8%)		48 (57.1%)		360 (68.3)	
Qatari (*n*)	2012 (35.4%)		825 (30.2%)		11 (68.8%)		91 (28.3%)		116 (34.2%)		36 (42.9%)		167 (31.7%)	0.452
Ageband		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**0.013**		**<0.001**
<1 yr. (infants)	797 (14.0%)		384 (14.0%)		0		42 (13.0%)		122 (35.9%)		26 (31.0%)		215 (40.8%)	
1–4 yrs. (Pre-school)	2034 (35.5%)		755 (27.6%)		0		64 (19.9%)		162 (47.6%)		27 (23.1%)		193 (36.6%)	
5–12 yrs. (school)	678 (11.9%)		426 (15.5%)		5 (23.8%)		58 (18.0%)		12 (3.5%)		11 (13.1%)		13 (2.5%)	
13–18 yrs. (adolescence)	161 (2.8%)		88 (3.2%)		0		8 (2.5%)		4 (1.2%)		2 (2.4%)		3 (0.6%)	
19–30 yrs. (Young)	537 (9.4%)		561 (20.1%)		0		74 (23%)		12 (3.5%)		5 (6.0%)		28 (5.3%)	
31–45 yrs. (adult)	764 (13.4%)		424 (15.5%)		5 (23.8%)		51 (15.8%)		9 (2.6%)		6 (7.1%)		15 (2.8%)	
46–60 yrs. (old)	400 (7.0%)		61 (2.2%)		4 (19.0.%)		18 (5.6%)		9 (2.6%)		5 (6.0%)		27 (5.1%)	
>60 yrs. (older adult)	321 (5.6%)		41 (1.5%)		7 (33.3%)		7 (2.2%)		10 (2.9%)		2 (2.4%)		33 (6.3%)	
Temperature		**<0.001**		**<0.001**		0.320		0.900		**<0.001**		0.985		0.152
Warm (22.4–27°C)	926 (16.3%)		437 (15.9%)		5 (23.8%)		54 (16.7%)		42 (12.4%)		11 (13.1%)		73 (13.9%)	

(Continued)

TABLE 1 (Continued)

Risk factors	Flu-A		Flu-B		MERS-CoV		MPN		hPIV-1		hPIV-2		hPIV-3	
	n (=5695/ 40539)	*p*-value	*n* (=2741/ 40539)	*p*-value	*n* (=21/ 6073)	*p*-value	*n* (=323/ 16940)	*p*-value	*n* (=340/ 16927)	*p*-value	*n* (=84/ 16940)	*p*-value	*n* (=527/ 16940)	*p*-value
Comfortable (<=22.3°C)	1,327 (23.3%)		1,671 (61.0%)		11 (52.4%)		106 (32.8%)		51 (15.0%)		26 (31.0%)		140 (26.6%)	
Hot >28°C	3,442 (60.4%)		633 (23.1%)		5 (23.4%)		163 (50.5%)		247 (72.6%)		47 (56.0%)		314 (59.6%)	
Solar energy		**<0.001**		**<0.001**		0.223		**0.006**				0.485		**0.003**
Dark > 291	4,970 (87.3%)		2,596 (94.7%)		16 (76.2%)		266 (82.4%)		256 (75.3%)		61 (72.6%)		371 (70.4%)	
Bright <= 291	725 (12.7%)		145 (5.3%)		5 (23.8%)		57 (17.6%)		84 (24.7%)		23 (27.4%)		156 (29.6%)	
Pressure		**<0.001**		**<0.001**		0.894		**0.006**		0.807		0.485		**0.003**
Low <=1,000	725 (12.7%)		145 (5.3%)		5 (23.8%)		57 (17.6%)		84 (24.7%)		23 (27.4%)		156 (29.6%)	
High > 1,000	4,970 (87.3%)		2,596 (94.7%)		16 (76.2%)		266 (82.4%)		256 (75.3%)		61 (72.6%)		371 (70.4%)	
Humidity		**<0.001**		**<0.001**		0.223		**<0.001**		**0.008**		0.360		0.000
Low <= 41.1	1,263 (22.2%)		348 (12.7%)		5 (23.8%)		177 (54.8%)		170 (50.0%)		32 (38.1%)		270 (51.2%)	
High > 41.1	4,432 (77.8%)		2,393 (87.3%)		16 (76.2%)		146 (45.2%)		170 (50.0%)		52 (61.9%)		257 (48.8%)	
Dew point		**<0.001**		**<0.001**		0.453		**<0.001**		**<0.001**		0.441		0.072
Medium (13.56–14.82)	118 (2.1%)		106 (3.9%)		NA		47 (14.6%)		33 (9.7%)		3 (3.6%)		47 (8.9%)	
Low <= 13.56	1,327 (23.3%)		1,671 (61.0%)		11 (52.4%)		106 (32.8%)		51 (15.0%)		26 (31.0%)		140 (26.6%)	
High > 14.83	4,250 (74.6%)		964 (35.2%)		10 (47.6%)		170 (52.6%)		256 (75.3%)		55 (65.5%)		340 (64.5%)	
Wind speed		**<0.001**		**<0.001**		0.154		**<0.001**		0.602		0.182		0.354
Windy > 6	818 (26.1%)		644 (41.8%)		5 (31.3%)		157 (84.9%)		98 (65.8%)		39 (76.5%)		201 (70.3%)	
Calm <= 6	2,321 (73.9%)		895 (58.2%)		11 (68.8%)		28 (15.1%)		51 (34.2%)		12 (23.5%)		85 (29.7%)	

Risk factors	hPIV-4		Parechovirus		HRV		RSV A		RSV A/B		RSV B	
	n (=167/16940)	*p*-value	*n* (=64/14596)	*p*-value	*n* (=1109/3980)	*p*-value	*n* (=250/3935)	*p*-value	*n* (=4238/35860)	*p*-value	*n* (=69/3935)	*p*-value
Gender		0.305		0.836		0.375		0.274		**<0.001**		0.142
Female (*n*)	76 (45.5%)		27 (42.2%)		471 (42.5%)		117 (46.8%)		1936 (45.7%)		36 (52.2%)	
Male (*n*)	91 (54.5%)		37 (57.8%)		638 (57.5%)		133 (53.2%)		2,302 (54.3%)		33 (47.8%)	
Nationality		0.792		**<0.001**		0.393		**<0.001**		**<0.001**		**<0.001**
Non-Qatari (*n*)	115 (68.9%)		29 (45.3%)		758 (68.5%)		144 (58.8%)		2,670 (63.2%)		34 (50%)	
Qatari (*n*)	52 (31.1%)		35 (54.7%)		348 (31.5%)		101 (41.2%)		1,552 (36.8%)		34 (50%)	

(Continued)

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TABLE 1 (Continued)

Risk factors	hPIV-4		Parechovirus		HRV		RSV A		RSV A/B		RSV B	
	n (=167/16940)	*p*-value	*n* (=64/14596)	*p*-value	*n* (=1109/3980)	*p*-value	*n* (=250/3935)	*p*-value	*n* (=4238/35860)	*p*-value	*n* (=69/3935)	*p*-value
Ageband		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
<1 yr. (infants)	64 (38.3%)		42 (65.6%)		458 (41.3%)		146 (58.4%)		1960 (46.2%)		33 (47.8%)	
1–4 yrs. (Pre-school)	36 (21.6%)		20 (31.3%)		280 (25.3%)		62 (24.8%)		1867 (44.1%)		20 (29%)	
5–12 yrs. (school)	17 (10.2%)		2 (3.1%)		75 (6.8%)		7 (2.8%)		151 (3.6%)		1 (1.4%)	
13–18 yrs. (adolescence)	4 (2.4%)		0		11 (1.0%)		2 (0.8%)		8 (0.2%)		0	
19–30 yrs. (Young)	9 (5.4%)		0		73 (6.6%)		4 (1.6%)		51 (1.2%)		4 (5.8%)	
31–45 yrs. (adult)	10 (6.0%)		0		96 (8.7%)		13 (5.2%)		74 (1.7%)		2 (2.9%)	
46–60 yrs. (old)	16 (9.6%)		0		49 (4.4%)		5 (2.0%)		64 (1.5%)		4 (5.8%)	
>60 yrs. (older adult)	11 (6.6%)		0		66 (6.0%)		11 (4.4%)		63 (1.5%)		5 (7.2%)	
Temperature		**<0.001**		0.170		**<0.001**		**<0.001**		**<0.001**		0.130
Warm (22.4–27°C)	32 (19.2%)		6 (9.4%)		178 (16.1%)		83 (33.2%)		1,541 (36.4%)		18 (26.1%)	
Comfortable (<=22.3°C)	83 (49.7%)		27 (42.2%)		439 (39.6%)		80 (32.0%)		1,331 (31.4%)		18 (26.1%)	
Hot >28°C	52 (31.1%)		31 (48.4%)		492 (44.4%)		87 (34.8%)		1,366 (32.2%)		33 (47.8%)	
Solar energy		**0.005**		**0.047**		0.477		**<0.001**		**<0.001**		0.152
Dark > 291	142 (85.0%)		54 (84.4%)		940 (84.8%)		243 (97.2%)		4,105 (96.9%)		63 (91.3%)	
Bright <= 291	25 (15.0%)		10 (15.6%)		169 (15.2%)		7 (2.8%)		133 (3.1%)		6 (8.7%)	
Pressure		**0.005**		**0.047**		0.477		**<0.001**		**<0.001**		0.152
Low <=1,000	25 (15.0%)		10 (15.6%)		169 (15.2%)		7 (2.8%)		133 (3.1%)		6 (8.7%)	
High > 1,000	142 (85.0%)		54 (84.4%)		940 (4.8%)		243 (97.2%)		4,105 (96.9%)		63 (91.3%)	

(Continued)

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TABLE 1 (Continued)

Risk factors	hPIV-4		Parechovirus		HRV		RSV A		RSV A/B		RSV B	
	n (=167/16940)	*p*-value	*n* (=64/14596)	*p*-value	*n* (=1109/3980)	*p*-value	*n* (=250/3935)	*p*-value	*n* (=4238/35860)	*p*-value	*n* (=69/3935)	*p*-value
Humidity		0.446		0.255		0.138		**<0.001**		**<0.001**		**0.008**
Low <= 41.1	67 (40.1%)		26 (40.6%)		296 (26.7%)		12 (4.8%)		218 (5.1%)		8 (11.6%)	
High > 41.1	100 (59.9%)		38 (59.4%)		813 (73.3%)		238 (95.2%)		4,020 (94.9%)		61 (88.4%)	
Dew point		**<0.001**		**0.015**		**0.012**		**<0.001**		**<0.001**		**0.006**
Medium (13.56–14.82)	28 (16.8%)		5 (7.8%)		61 (5.5%)		2 (0.8%)		34 (0.8%)		2 (2.9%)	
Low <= 13.56	83 (49.7%)		27 (42.2%)		439 (39.6%)		80 (32.0%)		1,331 (31.4%)		18 (26.1%)	
High > 14.83	56 (33.5%)		32 (50.0%)		609 (54.9%)		168 (67.2%)		2,873 (67.8%)		49 (71.0%)	
Wind speed		**<0.001**		0.080		**0.022**		**<0.001**		**<0.001**		**<0.001**
Windy > 6	81 (82.7%)		27 (87.1%)		434 (57%)		10 (5.5%)		183 (6.4%)		10 (20.8%)	
Calm <= 6	17 (17.3%)		4 (12.9%)		328 (43%)		171 (94.5%)		2,675 (93.6%)		38 (79.3%)	

* Total count of tested MERS samples are the numbers of repeated or ordered samples usually for the same patients. Bold values indicate statistical significance at $p < 0.05$.

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TABLE 2 Comparison of mean meteorological variables on days with and without detection of the 8 main respiratory viruses.

Agent / number of days tested	Meteorological factors	Mean of days virus was		Difference in means	95% CI/ lower	Upper	*p*-value
		Not detected	Detected				
ADV	Temperature	29.079	30.481	−1.4018	−1.7173	−1.0863	**<0.001**
	Dew point	17.7286	18.3039	−0.57527	−0.83790	−0.31263	**<0.001**
	Wind speed	6.819	7.100	−0.2808	−0.3272	−0.2343	**<0.001**
	Pressure	1008.487	1006.394	2.0938	1.7562	2.4313	**<0.001**
	Humidity (relative)	43.248	39.115	4.1327	3.6820	4.5835	**<0.001**
	Solar	248.189	270.610	−22.4217	−24.8764	−19.9670	**<0.001**
hBoV	Temperature	29.788	31.26	−1.4785	−1.9720	−0.9851	**<0.001**
	Dew point	18.34	19.086	−0.70198	−1.11665	−0.28732	**<0.001**
	wind speed	6.764	6.913	−0.1497	−0.2241	−0.0754	**<0.001**
	Pressure	1007.761	1005.896	1.8646	1.3235	2.4058	**<0.001**
	Humidity (relative)	42.98	39.099	3.8827	3.1727	4.5926	**<0.001**
	Solar	251.244	270.853	−19.6086	−23.5594	−15.6578	**<0.001**
hMPV	Temperature	29.982	26.551	3.4311	2.9194	3.9428	**<0.001**
	Dew point	18.5258	15.5676	2.95818	2.52863	3.38773	**<0.001**
	Wind speed	6.758	7.054	−0.2957	−0.3725	−0.2189	**<0.001**
	Pressure	1007.561	1010.752	−3.1905	−3.7526	−2.6283	**<0.001**
	Humidity (relative)	42.721	45.085	−2.3645	−3.1058	−1.6231	**<0.001**
	Solar	252.706	236.362	16.3445	12.2262	20.4627	**<0.001**
Flu-A	Temperature	27.936	30.016	−2.0798	−2.2565	−1.9032	**<0.001**
	Dew point	17.0386	19.2820	−2.24345	−2.39189	−2.09501	**<0.001**
	Wind speed	6.636	6.139	0.4970	0.4679	0.5262	**<0.001**
	Pressure	1010.089	1009.009	1.0797	0.8881	1.2714	**<0.001**
	Humidity (relative)	45.512	46.330	−0.8180	−1.0685	−0.5675	**<0.001**
	Solar	231.501	232.243	−0.7420	−2.2506	0.7665	0.335
Flu-B	Temperature	28.460	25.035	3.4247	3.1809	3.6685	**<0.001**
	Dew point	17.5314	14.9032	2.62821	2.42215	2.83427	**<0.001**
	wind speed	6.567	6.601	−0.0346	−0.0746	0.0055	0.091
	Pressure	1009.690	1013.345	−3.6548	−3.9181	−3.3916	**<0.001**
	Humidity (relative)	45.358	49.341	−3.9826	−4.3273	−3.6380	**<0.001**
	Solar	233.411	206.698	26.7129	24.6414	28.7844	**<0.001**
hPIV-3	Temperature	29.830	30.515	−0.6849	−1.2509	−0.1189	0.018
	Dew point	18.3997	18.8413	−0.44150	−0.91679	0.03378	0.069
	wind speed	6.769	6.784	−0.0146	−0.1004	0.0713	0.740
	Pressure	1007.710	1006.839	0.8708	0.2499	1.4916	**0.006**
	Humidity (relative)	42.848	41.631	1.2170	0.4003	2.0338	**0.003**
	Solar	251.868	258.874	−7.0059	−11.5456	−2.4662	**0.002**
HRV	Temperature	27.372	28.211	−0.8384	−1.2723	−0.4045	**<0.001**
	Dew point	16.7158	17.3702	−0.65447	−1.02629	−0.28265	**<0.001**
	Wind speed	6.677	6.725	−0.0481	−0.1302	0.0340	0.251
	Pressure	1010.592	1009.646	0.9464	0.4991	1.3938	**<0.001**
	Humidity (relative)	46.718	45.798	0.9196	0.3357	1.5034	**0.002**
	Solar	226.216	234.990	−8.7740	−12.3712	−5.1769	**<0.001**

(Continued)

TABLE 2 (Continued)

Agent / number of days tested	Meteorological factors	Mean of days virus was		Difference in means	95% CI/ lower	Upper	*p*-value
		Not detected	Detected				
RSV A/B	Temperature	28.489	27.154	1.3350	1.1318	1.5383	**<0.001**
	Dew point	17.4841	16.9551	0.52907	0.35742	0.70072	**<0.001**
	Wind speed	6.658	5.789	0.8689	0.8363	0.9015	**<0.001**
	Pressure	1009.463	1012.737	−3.2742	−3.4927	−3.0558	**<0.001**
	Humidity (relative)	44.975	49.005	−4.0298	−4.3154	−3.7443	**<0.001**
	Solar	237.206	197.070	40.1360	38.4570	41.8150	**<0.001**

Bold values indicate statistical significance at $p < 0.05$.

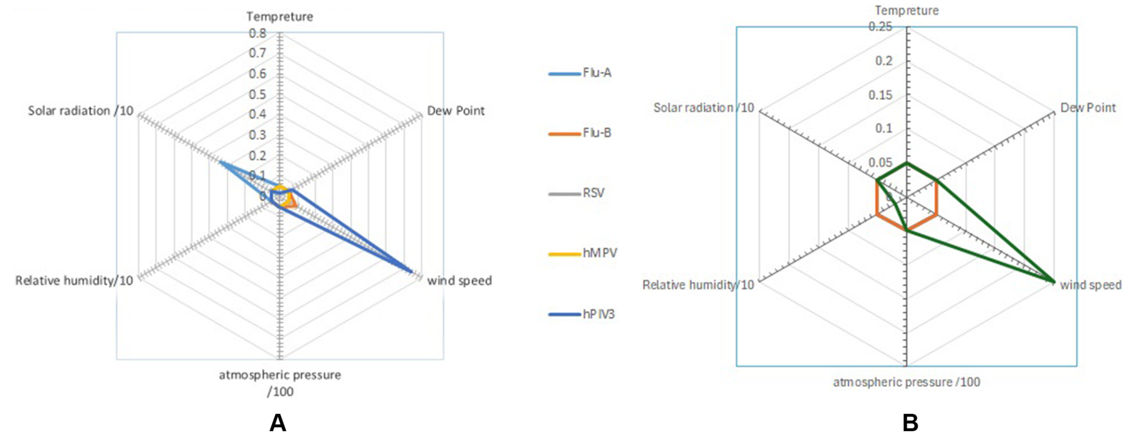

FIGURE 3
Radar chart presents the impact of dew point, relative humidity, wind speed, atmospheric pressure, and solar radiation on the main **(A)** enveloped and **(B)** non-enveloped viruses (student *T*-test).

Discussion

In this study, we investigated the epidemiological patterns of viral RTIs that had ≥500 confirmed infections over the 12-month period of the study in a country with a sub-tropical arid climate. Transmission was compared against demographics and meteorological data; confirmed infections acted as surrogates of viral transmission. The associations of each virus behaved as expected, providing reassurance that the observations with meteorological variables were likely to be real. The lack of seasonality of hPIV-3, in contrast to the spring/summer seasonality seen in temperate climates, deserves further study. Viruses with <500 confirmed cases were excluded.

Demographic discussion

The large waves seen with Flu-A, RSV and HRV suggested introduction of a new variant or variants capable of triggering significant transmission. This was similar for the smaller Flu-B and hMPV waves, which straddled the respective ends of the year. The smaller summer Flu-A wave and perennial high prevalence of HRV suggested minor variant transmissions – multiple in the case of HRV. The long, 7-month, atypical waves of the non-enveloped hBoV and ADV, straddling the summer months, suggested transmission driven by a series of variants or alternative modes of transmission. These align with the findings of Chen et al. (11) who demonstrated that ADV transmission reached its peak during the summer months. In the case of ADV this could be linked to fecal-oral transmission of gastrointestinal ADVs as the qPCR assay used did not discriminate type Khanal et al. (12). The transmission pattern of hPIV3 was unique in lacking any seasonal pattern, transmitting throughout the year. This is different from transmission seen in temperate climates where it shows a spring/summer pattern, suggesting an environmental association that differs in the two climates Li et al. (13) and Xu et al. (14).

The data confirmed infants, pre-school, and school-age children were significantly associated with the transmission of all of the viruses, similarly reported by Tian et al. (15) for RSV in infants up to 6 months of age. RSV was the dominant virus in infants, and with ADV and hBoV the dominant respective virus in pre-school and school-age children. All viruses, except hPIV3, transmitted significantly in the 5–12-year age group but only ADV and Flu-A showed significant association with adolescence, aligning with the findings of Janusz et al. (16). Surprisingly, hMPV showed significant transmission in the 46–60-year age group as it is commonly regarded as sharing a similar pathophysiology to RSV. Influenza viruses showed additional significant transmission in adults and older adult patients, although individuals >60 years of age showed relatively less levels of transmission which may reflect the impact of the annual flu vaccination program. RSV, however, was not significantly seen in patients > 60 years of age, being confirmed in 1.5% of those tested. This group is now recommended to receive the new RSV vaccine because of the risk of severe disease in this age group.

Reflecting the demographic makeup of the country, there was a bias in non-Qatari persons tested, but for ADV, hBoV and RSV, transmission was significantly seen in local Qataris, reflecting the transmission pattern of these viruses in young children and the ease of access to family healthcare networks in Qatar. A similar but stronger link with Flu-A was seen and could have the same explanation and supports the use of influenza vaccine in young children. Only ADV, hMPV and Flu-A showed an association with male gender and interestingly this was not confirmed for RSV, which may contradict the received understanding that male children are more at risk of a serious clinical presentation Hall et al. (17) but reflects that most confirmed infections are not normally clinically serious.

Meteorology discussion

Most transmission events took place in a restricted period covering the last 3 months of the year and we hypothesize that the

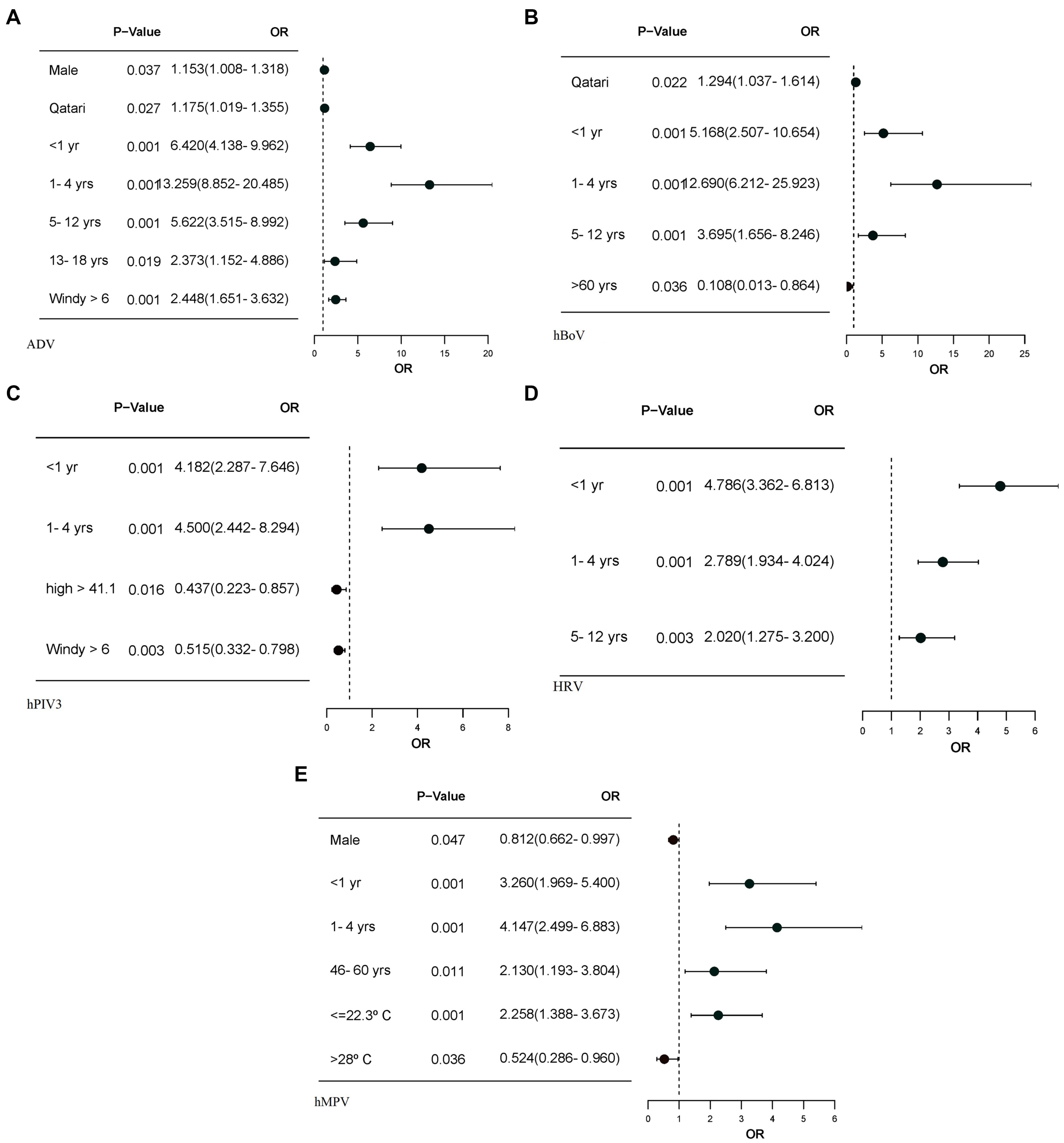

FIGURE 4 (Continued)

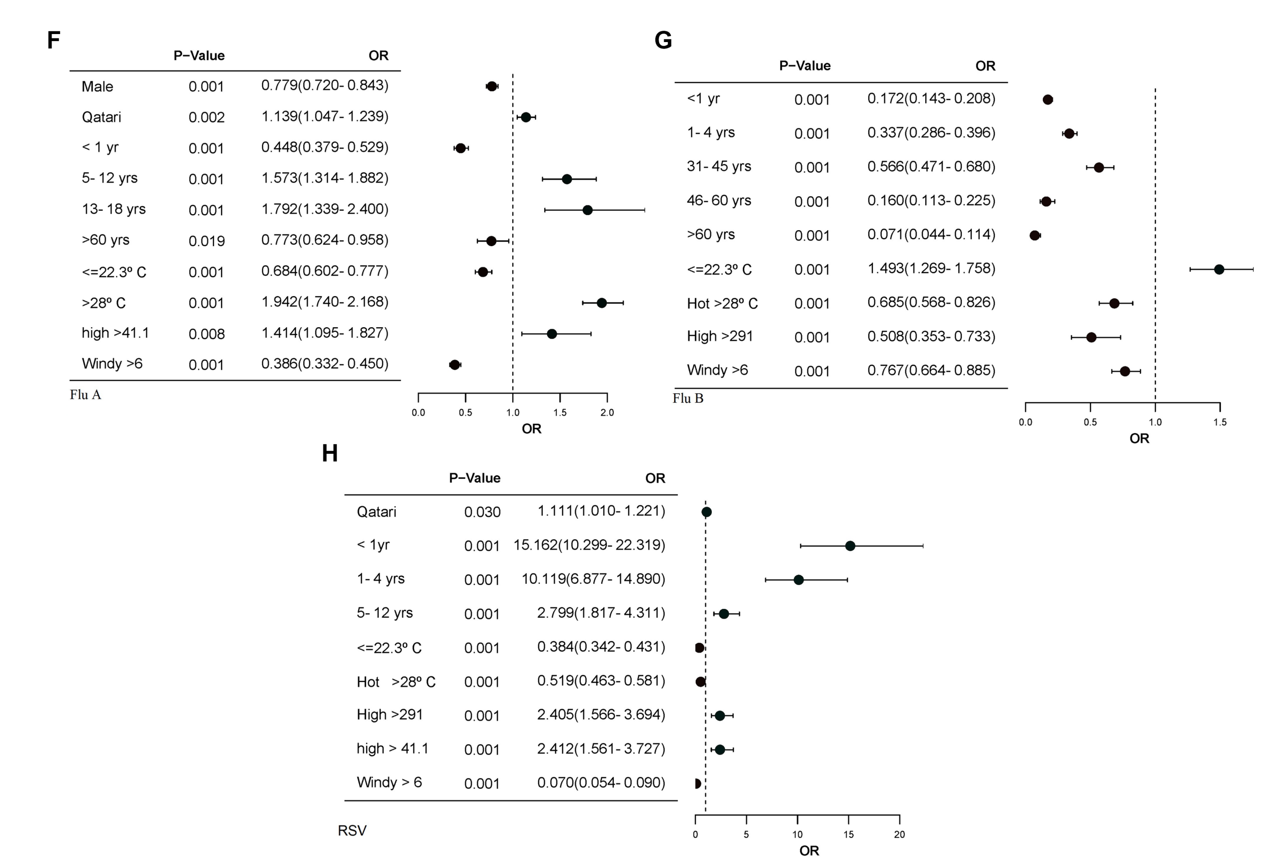

FIGURE 4
The forest plots display only the factors with significant *p*-values, along with their corresponding odds ratios. Logistic regression models were calculated for each of the meteorological, and demographic factors, adjusting for other meteorological factors. **(A)** Forest plot for ADV association with meteorological and demographic factors. **(B)** Forest plot for hBoV association with demographic factors. **(C)** Forest plot for hPIV3 association with meteorological and demographic factors. **(D)** Forest plot for HRV association with demographic factors. **(E)** Forest plot for hMPV association with meteorological and demographic factors. **(F)** Forest plot for Flu A association with meteorological and demographic factors. **(G)** Forest plot for Flu B association with meteorological and demographic factors. **(H)** Forest plot for RSV association with meteorological and demographic factors. OR, odds ratio; CI 95%, confidence interval. Windspeed >=6, RH>=50.38, solar radiation>=291, relative humidity >=41.1 and warm temperature (22.4–27°C) have been used as reference. Young age band (19–30), male gender and Qatari nationality are reference.

meteorology associations during this period increased the risk of viral transmission. Temperature fluctuations for hMPV, RSV, Flu A, and Flu B were observed within the range of ≤23°C to ≥28°C. These enveloped viruses are particularly susceptible to temperature fluctuations, especially during the winter months. Polozov et al. (18) highlighted that lipid ordering in the viral envelope plays a crucial role in maintaining the virus's stability at lower temperatures, which helps extend its survival outside the host. This lipid organization is essential for the virus to remain stable in the air, facilitating airborne transmission. Conversely, higher temperatures can disrupt the lipid membranes, impairing the virus's ability to spread effectively Health (19). Additionally, hPIV3 has been shown to be more prevalent in conditions with lower humidity. Our observations are consistent with the findings of Price et al. (9), who noted that viruses such as ADV, Flu-A, RSV, and hMPV tend to thrive in colder environments. This understanding underscores the importance of environmental conditions, such as temperature and humidity, in influencing the transmission and survival of these viruses.

Despite the absence of a winter season in non-temperate climates, Goes et al. (20) discussed the lack of hMPV detections and the absence of typical flu seasonal patterns. However, RSV and influenza infections are primarily observed during the rainy seasons in regions of Asia, Africa, and South America Shek and Lee (21). Both hMPV and Flu-B were associated with increased transmission in cooler months, with respective ODs of 2.258 and 1.493, in keeping with transmission during the cooler months at the respective ends of the 12 months of the study. In contrast, Flu A transmission appeared to increase by warmer temperatures, with a mean temperature of 30.02°C, which could reflect the effect of the small summer wave (Table 2; Figures 3, 4).

Solar radiation was found to be associated with RSV transmission, particularly linked to the start of its transmission wave in late summer. Similarly, lower solar radiation was associated with the transmission of Flu-B ($p < 0.001$), which was explained by Flu-B primarily spreading during the winter months. This association is especially related to the seasonality of the viruses, particularly during early spring, which often happens with the shift from winter to spring season.

Relative humidity was typically higher in the later months of the year, allowing a significant correlation to be observed with the transmission of Flu A and RSV that was transmitted predominantly at this time. Elevated humidity is thought to sustain the airborne duration of aerosolized respiratory droplets, allowing them to travel further and increase the likelihood of virus transmission between individuals as seen with Flu-A (Figure 4F) and RSV (Figure 4H). This observation supported the findings of Kramer et al. (22) which reported transmission rates of both influenza and RSV are reduced by lower temperatures when absolute humidity is accounted for, and conversely are increased by higher absolute humidity when temperature is controlled. However, since most respiratory viral transmission takes place indoors over relatively short distances, increasing the length of airborne viability of viruses in respiratory droplets, coupled with a large atmospheric dilution factor, would make any association potentially incidental.

There was no consistent relationship between wind speed and transmission patterns, as some viruses showed increased transmission while others had reduced or no effect. Jiang et al. (23) proposed that strong wind speeds can carry larger droplets over greater distances, thereby increasing the risk of exposure to individuals downstream. Our findings showed that when wind speeds >6 kt, the odds ratio (OR) for ADV increased to 2.448, indicating a higher likelihood of transmission, which aligns with the results of Oh et al. (24). In contrast, the OR for other viruses is < 1.00, suggesting that higher wind speeds may either reduce or have no impact on their transmission. Xu et al. (14) found that only Coronaviruses in southern China show a relationship with wind speed. Additionally, certain viruses were identified at lower wind speeds, suggesting that outdoor transmission of COVID-19 could occur, with the risk being greater on calm days in the summer, as highlighted by Clouston et al. (25). For Flu-A, Flu-B, and RSV, it seemed that wind speeds > 6 kt reduced transmission, which aligns with findings from Zhu et al. (26). However, for HRV and hPIV3, which transmitted year-round without a seasonal pattern, no association with wind speed was observed, as shown in Figure 1. This transmission pattern of hPIV3 aligns with the findings reported by Cui et al. (27). Comparing Flu A and RSV, which had seasonal patterns, with HRV and hPIV3, which did not have seasonal patterns, revealed a stronger apparent link between the former viruses and meteorological factors, as seen in Table 2. The absence of wind speed's impact on HRV and hPIV3 reflects their constant year-round transmission, while the apparent connection between solar energy and Flu A is probably due to an additional summer wave that occurred that year, as shown in Figure 3.

The research findings in this study can be generalized to other tropical arid climate regions that have similar climate and meteorological conditions.

Conclusion

The results showed that school-aged children were significantly impacted by the transmission of the virus, suggesting that school attendance may have played a key role in facilitating its spread over the 12-month study period. Additionally, the observed correlation between viral transmission and meteorological factors—such as temperature, humidity, and seasonal changes—indicates that environmental conditions may have further increased the risk of transmission among this age group.

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 authors.

Ethics statement

The studies involving humans were approved by the Hamad Medical Corporation (HMC), Institutional Review Board (IRB), Ethics Committee-reference number (01-20-429) with a waiver of consent. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing – original draft, Validation, Writing – review & editing. SY: Formal analysis, Methodology, Writing – review & editing. MS: Data curation, Methodology, Supervision, Validation, Writing – review & editing. MA: Investigation, Resources, Visualization, Writing – review & editing. AK: Resources, Writing – review & editing. MM: Resources, Writing – review & editing. GN: Resources, Writing – review & editing. EK: Resources, Writing – review & editing. AA-k: Supervision, Writing – review & editing. PC: Conceptualization, Data curation, Resources, Supervision, Validation, Writing – review & editing, Writing – original draft. NA-D: Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

MH, SY, AK, EK, AA-k, PC, and NA-D were employed by Hamad Medical Corporation.

The remaining 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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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Glossary

AQI - Air Quality Index

URTI - Upper respiratory tract infection

LRTI - Lower respiratory tract infection

RSV - Respiratory syncytial virus

RSV A - Respiratory syncytial virus A

RSV B - Respiratory syncytial virus B

COVID-19 - Coronavirus disease 2019

SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2

RT-PCR - Real-time polymerase chain reaction

ARI - Acute respiratory infection

Flu-A - Influenza A

Flu-B - Influenza B

ADV - Adenovirus

MPN - Mycoplasma pneumonia

MERS-CoV - Middle East Respiratory Syndrome Coronavirus

hBoV - Human bocavirus type

hCoV - Human coronavirus

HCoV 229E - *Human coronavirus 229E*

HCoV NL63 - Human coronavirus NL63

HCoV-HKU1 - *Human coronavirus HKU1*

HCoV-OC43 - Human coronavirus OC43

hMPV - Human metapneumovirus

HPIV - Human parainfluenza virus

hPIV-1 - Human parainfluenza 1

hPIV-2 - Human parainfluenza 2

hPIV-3 - Human parainfluenza 3

hPIV-4 - Human parainfluenza 4

HRV - Human rhinovirus

ILI - Influenza-like illness

VP - Vapour Pressure

hPa - hectopascals

W/m^2 - Watts per square meter

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Preliminary investigation of the association between air pollution exposure and childhood asthma hospitalizations from 2015 to 2018 in East China

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Objectives: This study investigated whether exposure to air pollution remains a significant factor contributing to childhood asthma in China.

Methods: Short-term exposure to air pollutants was assessed using daily average concentrations of pollutants at current and lag intervals (0–6 days) from 2015 to 2018. Long-term individual exposure in 2016 was estimated using land-use regression (LUR) models. The effects of short- and long-term exposure on childhood asthma hospitalizations were evaluated using generalized additive models and multiple time-dependent Cox regression models, respectively.

Results: Hospitalizations for childhood asthma typically peaked in late spring and fall, with a higher prevalence of wheezing or asthma observed in male individuals than in female individuals. Hospital admissions were most frequent among children aged 0–3 years. However, no significant positive associations were observed between short- or long-term air pollutant exposure and daily childhood asthma hospitalizations, based on the applied statistical models and the levels of air pollution exposure measured during the study period.

Conclusion: In this study, variability in air pollution exposure was not associated with variability in hospitalizations of children with asthma. Instead, asthma onset exhibited unique seasonal and demographic patterns.

KEYWORDS
air pollution, exposure, asthma, childhood, association

1 Introduction

Over the last 30 years, China's rapid economic growth and urbanization have exacerbated air pollution, leading to an increase in respiratory diseases (1). Asthma, in particular, has become a growing public health concern. According to the 2013 national survey conducted by the China Asthma Alliance, the overall prevalence of asthma in China was 1.24%. In cities such as Beijing and Shanghai, the prevalence increased by 147.9% and 190.2%, respectively, compared to a previous survey conducted a decade earlier (2). The rise in childhood asthma has been particularly alarming. The first national survey in 1990 reported a prevalence of 0.91% among children aged 0–14 years, which increased to 1.5% (3) by 2000 and reached 3.02% (4) in the 2010–2011 survey on childhood asthma and allergic diseases. Asthma is a multifactorial disease influenced by both genetic and environmental factors. Epidemiological studies have consistently linked air pollution exposure to increased prevalence and severity of asthma (5–8). For instance, one study evaluated the association between gaseous pollutants and emergency ambulance dispatches for asthma in southwestern China (9). However, some cohort studies in Europe and the United States have reported no significant association between air pollution and the prevalence of asthma (10, 11), highlighting the need for context-specific evaluations. Differences in ambient air pollution levels across regions may partly explain these discrepancies. According to China's Environmental Status Bulletin (2014–2017), $PM_{2.5}$ concentrations in the Yangtze River Delta decreased by 34.3% from 2013 to 2017, indicating an improvement in air quality. However, the beneficial effects of improved air quality on asthma have not been sufficiently investigated. Studies conducted in Taiwan have shown that improved air quality reduces the effect of $PM_{2.5}$ on childhood asthma (12, 13). These findings emphasize the importance of considering regional pollution trends and population characteristics in assessing the relationship between air pollution and asthma. Recent evidence regarding the association between air pollution exposure and childhood asthma in China remains limited. This study aimed to assess whether air pollutants continue to significantly contribute to the increasing prevalence of asthma in children in China. Utilizing public data from 2015 to 2018, we analyzed the relationship between six common air pollutants (SO_2, NO_2, CO, O_3, $PM_{2.5}$, and PM_{10}) and childhood asthma hospitalizations in Nanjing, located in the Yangtze River Delta region of East China.

2 Materials and methods

2.1 Data collection

Hospitalization data from 1 January 2015 to 31 December 2018 were collected from the Department of Respiratory Medicine at the Children's Hospital of Nanjing Medical University (Hospital A) and Jiangsu Women and Children Health Hospital of Nanjing Medical University (Hospital B). This study included hospitalized cases with diagnoses of bronchial asthma (J45) and suspected asthma-acute asthmatic bronchitis (J21.901), based on the International Classification of Diseases, 10th revision. All cases were validated by a study physician.

Air pollution data, including daily concentrations of SO_2, NO_2, CO, O_3-(8 h), $PM_{2.5}$, and PM_{10}, were obtained from the China National Environmental Monitoring Centre. Meteorological data, such as temperature, relative humidity, and wind speed, were obtained from the China Meteorological Administration and adjusted to account for the confounding effects of weather conditions.

2.2 Association between short-term exposure to air pollutants and childhood asthma hospitalizations using a generalized additive model

The relationship between air pollutants and meteorological variables was assessed using Spearman's rank correlation coefficients. Time series analysis using a generalized additive model (GAM) was performed to evaluate the effects of each air pollutant (SO_2, NO_2, CO, O_3, $PM_{2.5}$, and PM_{10}) on childhood asthma hospitalizations. Given that the hospitalization data followed an over-dispersed Poisson distribution, a quasi-Poisson regression was employed within the GAM framework.

To control for unmeasured confounders such as seasonal and long-term trends, the following adjustments were made: (1) natural cubic spline functions of calendar time with 5 degrees of freedom (df) per year, (2) natural smooth functions of the present-day temperature difference (3 df) and relative humidity (3 df) to exclude the confounding effects of weather, and (3) indicator variables for "day of the week" and "holidays." The data were also stratified by sex, age group, and hospital level. A single-pollutant model was used to examine the effects of air pollution on asthma hospitalization, considering both single lag days (lag 0, 1, 2, 3, 4, 5, and 6) and multiple lag days (lag 0–1, 0–2, 0–3, 0–4, 0–5, and 0–6). The pollutant effect was quantified as the percentage change in daily asthma admissions per interquartile range increase, along with the corresponding 95% confidence interval (CI). Sensitivity analyses were conducted within subgroups. All analyses were performed using R software (version 3.5.3) with the mgcv package, and statistical significance was set at a p-value < 0.05.

2.3 Association between long-term exposure to air pollutants and childhood asthma hospitalizations using multiple time-dependent cox regression models

Individual exposures to air pollutants in 2016 were estimated based on residential locations using a spatiotemporal (ST) land-use regression (LUR) model for long-term exposure (details provided in Supplementary material). Data from nine monitoring stations in Nanjing in 2016 were used to measure the six air pollutants, with station details provided in Supplementary Table S1. The model's independent variables included traffic, land use, meteorology, socioeconomic factors, and other relevant data, as detailed in Supplementary Table S2. Following standard LUR methodology, each independent variable was normalized before further analysis (Supplementary Table S3). The ST model was developed using the SpatioTemporal package (version 1.1.9) in R (version 3.5.1), with hyperparameters determined via cross-validation (Supplementary Table S4). The leave-one-out cross-validation method was used to assess the performance of the model. The coefficients of determination (R2cv) for SO_2, NO_2, CO, O_3, $PM_{2.5}$, and PM_{10}, were 0.929, 0.876, 0.903, 0.959, 0.951, and 0.936, respectively. Subsequently, individual address coordinates replaced the monitoring sites, and air pollutant concentrations were predicted based on the address coordinates using buffer and distance parameters. Multiple time-dependent Cox regression models were used with asthma as the dependent variable, adjusting for age and sex. Time-dependent hazard ratios (HRs) and 95% CIs were estimated for air pollutants (SO_2, NO_2, CO, O_3, $PM_{2.5}$, and PM_{10}) across all days in 2016. In addition, exposure was censored at the time of the first hospitalization, and a p-value of <0.05 was considered statistically significant.

3 Results

Nanjing, the provincial capital of Jiangsu Province, is located in the Yangtze River Delta region of China. Children's Hospital of

Nanjing Medical University and Jiangsu Women and Children Health Hospital of Nanjing Medical University are the two main pediatric hospitals in Nanjing. According to the Nanjing Hygiene Almanac (2015–2018), hospitalization data for children are reported only from these two hospitals. Table 1 shows the number of hospitalized cases of childhood asthma by age group and sex over the 4-year period. The cases were subdivided into three age groups (1–3) each year. The number of cases in age level 1 was significantly higher than that in the other two subgroups. On average, level 1 accounted for 77.5% of cases, compared to 16.7% in level 2 and 5.8% in level 3. The sex analysis revealed that, on average, 67.7% of asthma cases were male, indicating a sex difference in childhood asthma. Male children were significantly more likely to be sensitized to allergens (14, 15). This can be explained by differences in airway development and immune system function between male and female individuals (16, 17). Hospitalizations for childhood asthma peaked in late spring (March–May) and fall (September–November), as shown in Figure 1, consistent with the seasonal pattern of bronchial asthma exacerbations (18, 19).

The comparison of the trend patterns between the monthly average concentrations of the six air pollutants and childhood asthma hospitalizations is shown in Figure 2. As shown, the concentrations of SO_2, NO_2, CO, $PM_{2.5}$, and PM_{10} were usually higher from November to February of the following year. Unlike SO_2, NO_2, CO, $PM_{2.5}$, and PM_{10}, O_3 concentrations were typically higher from May to September, with June, July, and August showing the highest ozone (O_3) levels. By visual inspection, except for O_3, the peaks in SO_2, NO_2, CO, $PM_{2.5}$, and PM_{10} concentrations occurred after the peaks in asthma hospitalizations. Only the peaks in O_3 concentrations preceded those in asthma hospitalizations, indicating a potential link to increased asthma-related hospital admissions. However, there was no significant positive association between the six common air pollutants and childhood asthma hospitalizations at the levels of air pollution exposure measured during the study period (Figure 3). Sex-stratified analysis revealed no significant association in both females (Figure 4A) and males (Figure 4B). Age-stratified analysis (0–3, 4–6, >6 years) showed no significant association across all subgroups (Figures 5A–C). However, as stratified by hospital level (Figures 6A, B), PM2.5 exposure at lag 4 day in Hospital B had a positive association with childhood asthmatic hospitalization. Monthly variations in temperature, average relative humidity, and average wind speed also aligned with hospital admissions, as shown in Figure 7, although the associations were not statistically significant.

Although the exposure estimates were derived from the LUR model, which offered improved accuracy, the results of the time-dependent Cox regression models indicated that SO_2, NO_2, CO, O_3, $PM_{2.5}$, and PM_{10} were not significant risk factors for asthma exacerbations requiring hospitalization, as shown in Table 2.

4 Discussion

By the end of 2013, the majority of cities in China had established real-time monitoring for $PM_{2.5}$ levels, and the new air quality standards were fully implemented nationwide in 2016. In the past 5 years, China has been implemented various policies to reduce fossil fuel combustion and vehicle exhaust emissions. As a result, significant reductions in $PM_{2.5}$, PM_{10}, and SO_2 concentrations have been observed in the Yangtze River Delta, as shown in Table 1. While the positive effects of these policies on air quality are well-documented, their impact on childhood asthma remains insufficiently understood. In our study, we found that childhood asthma hospitalizations followed a seasonal pattern that did not entirely align with trends in air pollution. Pollen counts in Nanjing usually peak during April–May and September–October (20). The onset of spring leads to pollen allergies caused by grasses, weeds, and trees, while the transition to colder weather in the fall also exacerbates asthma attacks. The seasonal peaks in asthma hospitalizations observed in our study were consistent with these trends. However, we did not find a clear or significant positive association between the six air pollutants and childhood asthma hospitalizations from 2015 to 2018 in Nanjing (Supplementary Figure S1). However, the impact of O_3 on asthma

TABLE 1 Summary of information about hospitalized childhood asthma cases (*N* = 2,529) and air pollutant indices in the Yangtze River Delta region during the study period (1 January 2015–31 December 2018).

Variables	2015 (*N* = 703)	2016 (*N* = 574)	2017 (*N* = 676)	2018 (*N* = 576)
Age level, *n* (%)				
Level 1 (0–3 years)	537 (76.4)	448 (78.0)	533 (78.8)	441 (76.6)
Level 2 (4–6 years)	119 (16.9)	98 (17.1)	105 (15.5)	100 (17.4)
Level 3 (>6 years)	47 (6.7)	28 (4.9)	38 (5.6)	35 (6.1)
Gender, *n* (%)				
Female	213 (30.3)	189 (32.9)	221 (32.7)	192 (33.3)
Male	490 (69.7)	385 (67.1)	455 (67.3)	384 (66.7)
Air pollutant indice				
$PM_{2.5}$ (μg/m^3)	53	46	44	44
PM_{10} (μg/m^3)	83	75	71	70
SO_2 (μg/m^3)	21	17	14	11
NO_2 (μg/m^3)	37	36	37	35
CO (mg/m^3) (95%)	1.5	1.5	1.3	1.3
O_3 (8h) (μg/m^3) (90%)	163	159	170	167

The data of air pollutant indices are from Report on the State of the Environment in China (http://www.mee.gov.cn/).

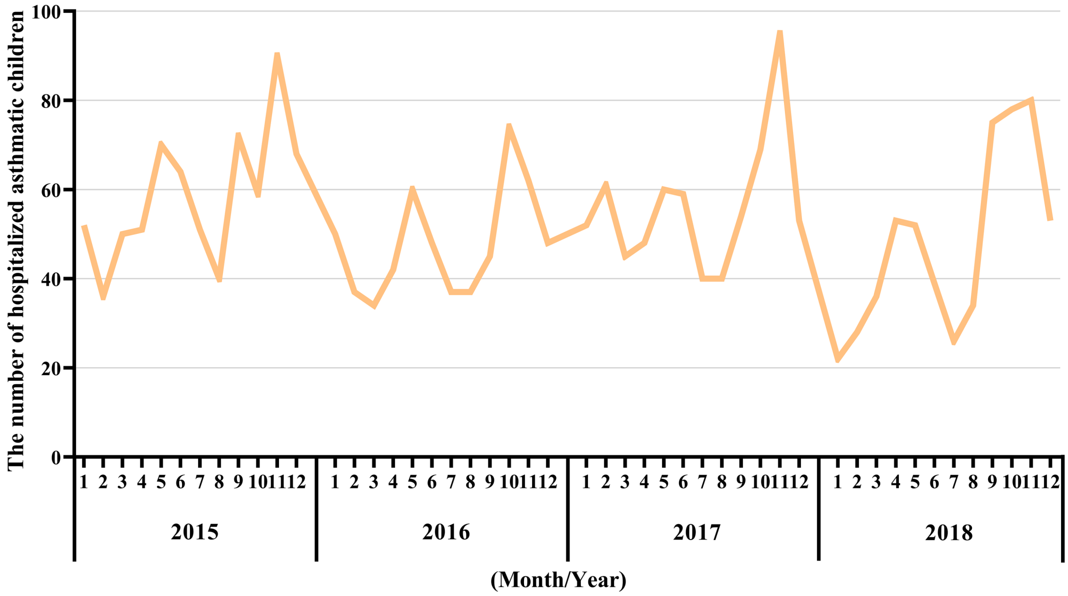

FIGURE 1
Monthly asthma-related hospital admissions during the study period (2015–2018). The X-axis represents the month and year, while the Y-axis represents the number of hospitalized asthmatic children in the corresponding month.

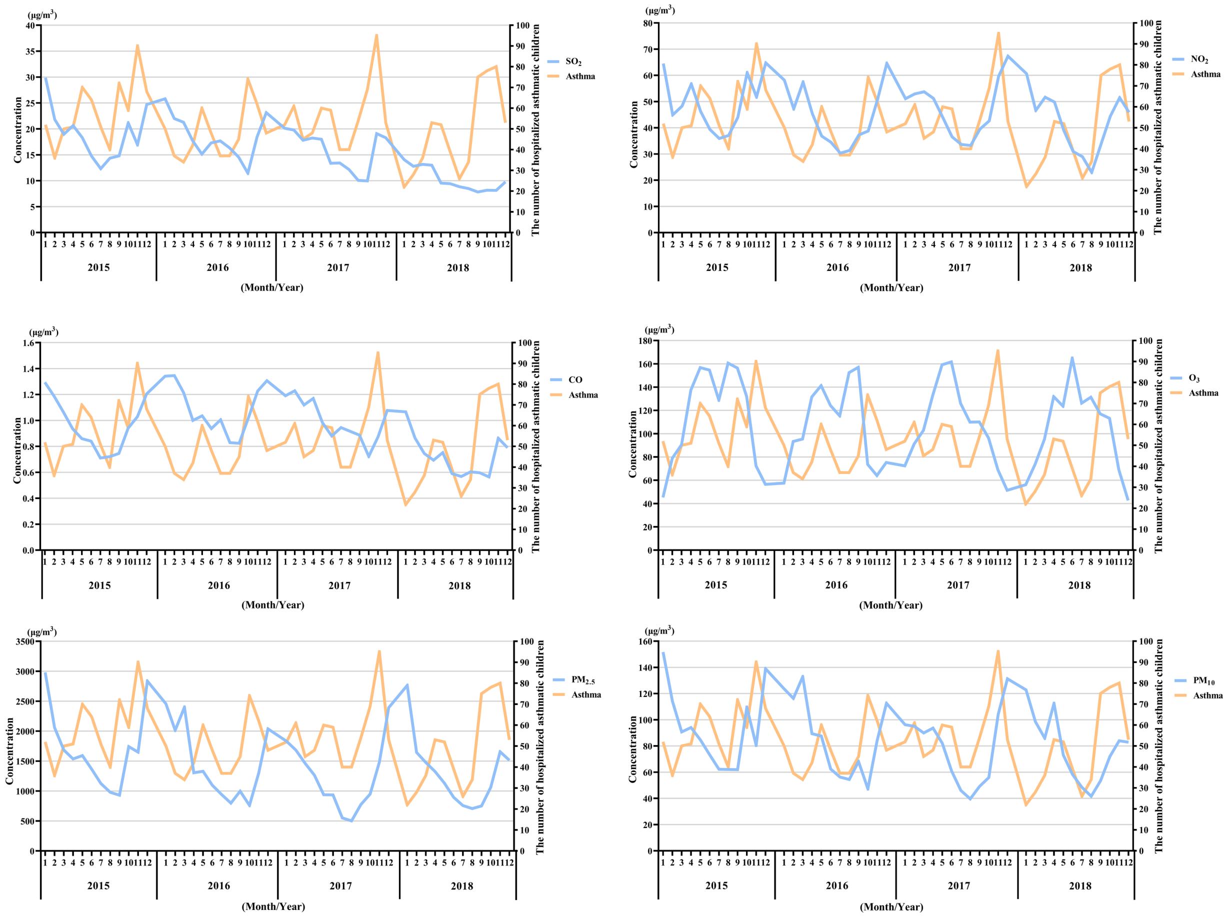

FIGURE 2
Pattern matching between the concentration trends of the six air pollutants and asthma-related hospital admissions during the study period (2015–2018). The X-axis represents the month and year, while the Y-axis on the left represents the monthly mean concentration of the pollutants, and the Y-axis on the right represents the number of hospitalized asthmatic children in the corresponding month.

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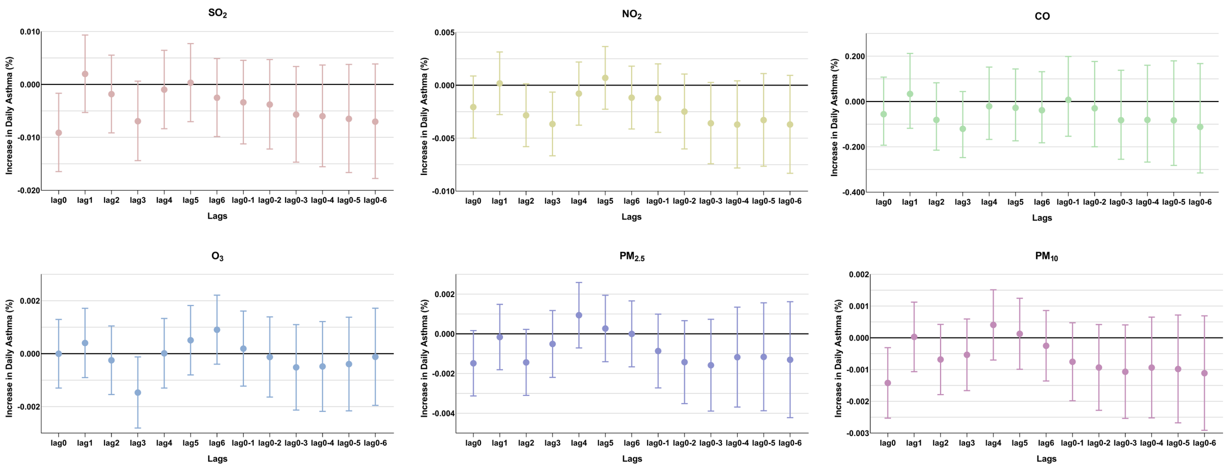

FIGURE 3
Percentage changes in daily asthma-related hospitalizations, with 95% confidence intervals, expressed as percentage deviations (%). In the single-pollutant model, an interquartile range (IQR) increase in the concentrations of SO_2, NO_2, CO, O_3, $PM_{2.5}$, and PM_{10} was associated with changes in asthma-related hospitalizations at different lag days.

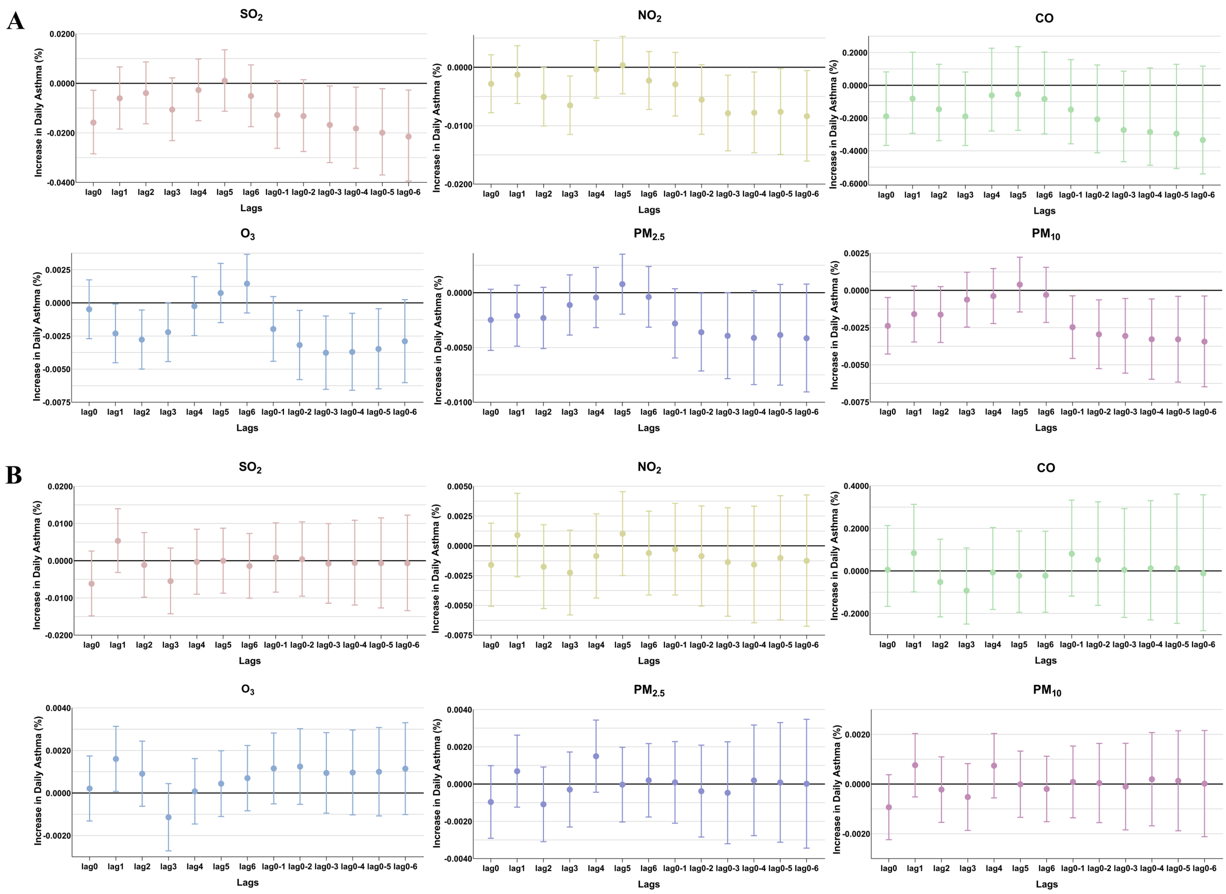

FIGURE 4
The patients were stratified by sex to analyze the association. Percent changes (95% CI) in daily asthma hospitalization deviations (%) stratified by sex: **(A)** female; **(B)** male.

prevalence varies compared to the effects of other pollutants such as SO_2, NO_2, CO, $PM_{2.5}$, and PM_{10}. Ozone acts as an oxidizing agent, which may induce respiratory tract inflammation (21, 22). It is also recognized as a secondary pollutant. Its formation is influenced by the presence of nitrogen oxides and photochemical transformation processes. Consequently, the exposure patterns of ozone can deviate substantially

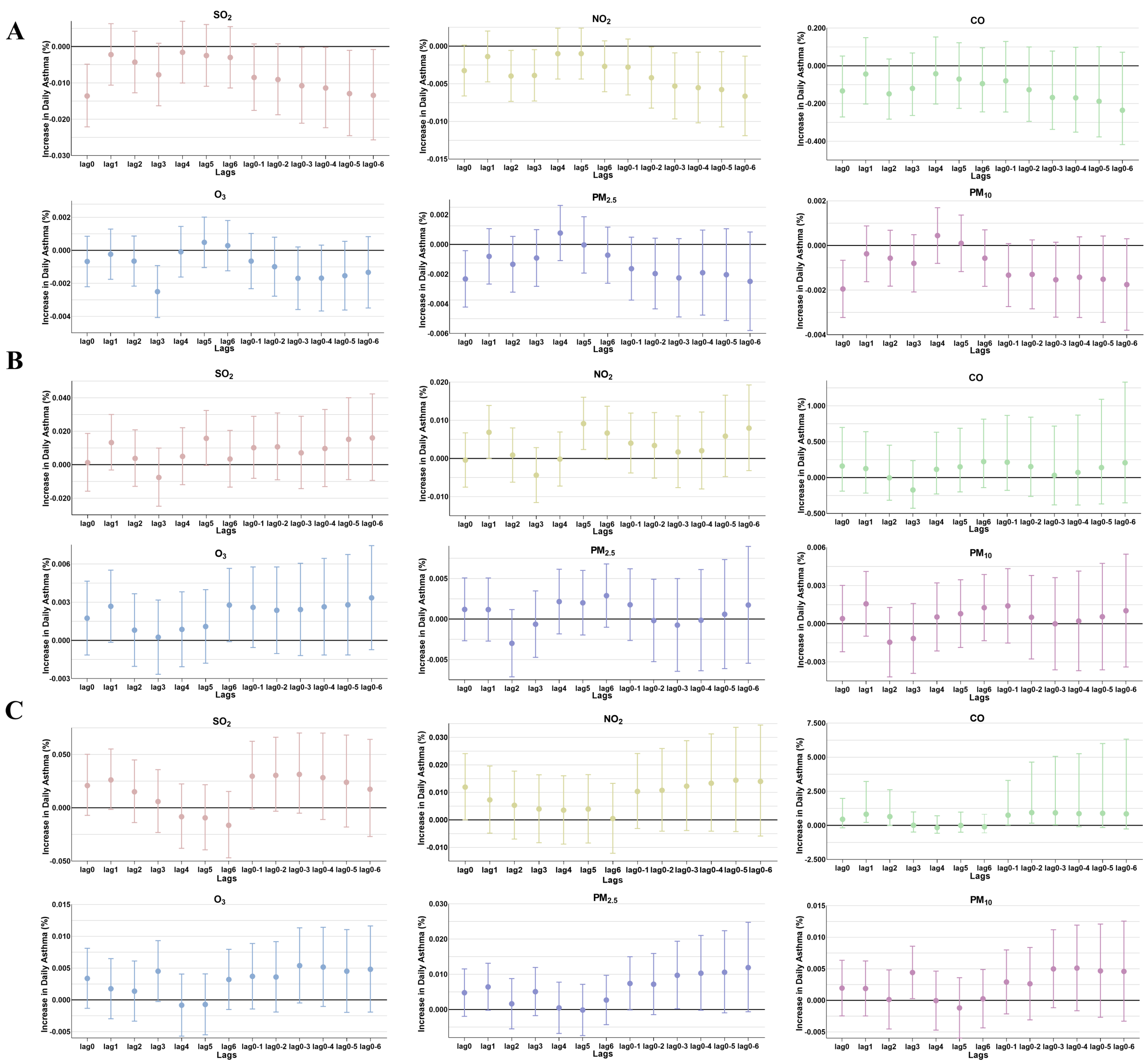

FIGURE 5
The patients were stratified by age to analyze the association. Percent changes (95% CI) in daily asthma hospitalization deviations (%) stratified by age: **(A)** 0–3 years; **(B)** 4–6 years; **(C)** >6 years.

from those of other pollutants, such as nitrogen dioxide and fine particulate matter (23). In our study, during the observational years, ozone levels remained relatively high in the Yangtze River Delta region, partly due to the decrease in PM and increased solar radiation. This pattern is similar to the ozone pollution observed in the Pearl River Delta region (24), which may help explain the relationship between ozone concentrations and asthma outcomes. Although the associations between air pollutants and respiratory diseases have been widely studied, the results are complex and often inconclusive. Not all studies support a causal link between long-term exposure to air pollution and the prevalence of asthma (25). Indeed, etiological analyses from the International Study of Asthma and Allergies in Childhood (ISAAC) have revealed that the prevalence of asthma in less-polluted developed countries is generally much higher compared to those with higher levels of air pollution (26). In addition, two birth cohort studies found no association between traffic-related air pollution and atopic eczema, allergic sensitization, or bronchial hyperresponsiveness (27, 28), raising questions about the underlying mechanisms—whether irritation is caused by air pollution or allergic reactions due to allergens. Some studies have demonstrated that children residing in urban areas exhibit a higher susceptibility to asthma compared to those dwelling in rural or suburban regions. This elevated risk is, in part, attributed to their greater exposure to air pollution due to rapid urbanization and industrialization (29, 30). Nevertheless, cross-sectional studies carried out in Lanzhou, China, in 2017 and in Belgium have both revealed that the urban environment does not have a significant influence on children's wheezing or asthma-related symptoms (31, 32). It is well known that children are susceptible to adverse effects of air pollution due to their developing lungs, immature immune systems, and metabolic pathways. In addition, even prenatal exposures might increase the postnatal risk of developing asthma later in life (33, 34). Reported associations in children have shown highly variable results. For example, a systematic review of cohort studies found that only prenatal exposure to NO_2 (OR = 1.04, 95%CI: 1.01–1.07) and PM_{10} (1.08, 1.05–1.12) was

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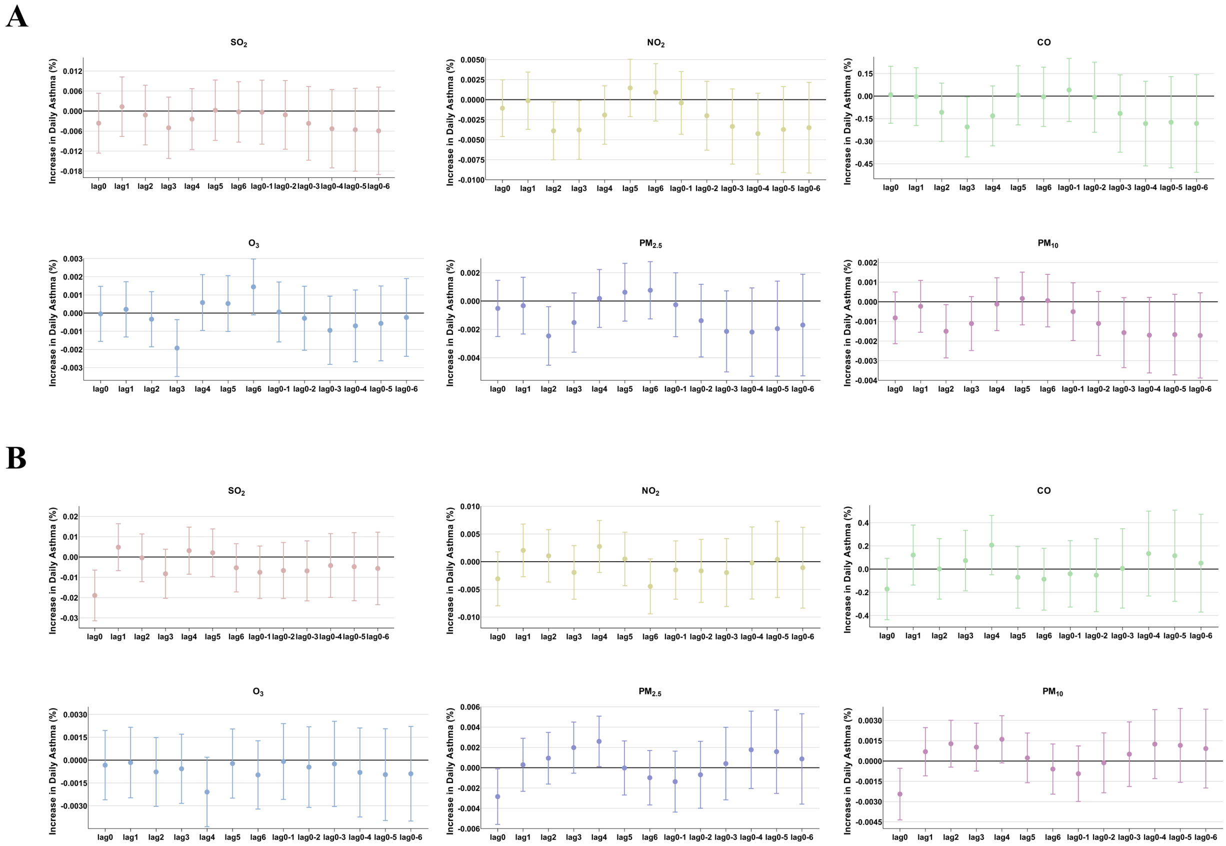

FIGURE 6
The patients were stratified by hospital level to analyze the association. Percent changes (95% CI) in daily asthma hospitalization deviations (%) stratified by hospital level: **(A)** Hospital A; **(B)** Hospital B.

associated with an increased risk of wheezing and asthma development in childhood. The effect was most pronounced in children aged 0–5 years, becoming weaker in older age groups. The researchers suggested that individual pollutant exposure assessments—such as LUR, inverse distance weighting (IDW), and personal monitors—used in these cohort studies might strengthen the observed positive associations between air pollution and wheezing and asthma (5). However, another systematic review published in the same year indicated that PM_{10} was not associated with asthma exacerbation in children. The researchers suggested that differences in methodologies for estimating air pollution concentrations across studies could lead to exposure misclassification (7). Alternatively, weaker associations have been observed in regions with lower levels of air pollution (35). Furthermore, the association between changes in ambient air pollution and incident asthma should be investigated in areas with predominantly low air pollution levels to avoid saturation effects.

In the present study, we raise the question of whether the role of air pollution in the prevalence of asthma has attenuated. It is also possible that the impacts of air pollution on asthma are overshadowed by other seasonal triggers that have a more substantial influence, such as bacterial, fungal, and viral infections. For example, recent studies have reported that air pollutants could significantly impact the city microbiome, which could further impact the prevalence of allergic diseases in a season-specific manner (36–38).

In summary, we believe that it is too arbitrary to draw a precise conclusion. In addition, even if air quality has improved significantly in recent years, the accumulated effects of environmental pollution still exist, preventing a decline in the prevalence of asthma. There are limitations in our study, such as the lack of a multicenter database evaluation and the use of single-year data for a long-term period, highlighting the need for further original studies to explore the relationship between air pollution exposure and childhood asthma. Nevertheless, a significant proportion of childhood asthma incidence/development may be attributable to air pollution (39–41). In the future, additional data should provide insights into the number of asthma cases that could potentially be prevented by reducing exposure to air pollution.

5 Conclusion

In our study, six nationally supervised air pollutant indices showed no clear or significant association with asthma hospitalizations in the studied population from 2015 to 2018 in East China, based on the levels of air pollution exposure measured during the study period. Our findings provide fundamental data and public health insights. The three national surveys on asthma prevalence among children aged 0–14 years in China were conducted in 1990, 2000, and 2010. These surveys indicated that the prevalence of asthma has continued to increase. A new round of national-level surveys on asthma prevalence is expected soon. As global emissions continue to rise, future research efforts should focus on identifying the pollutants most relevant to asthma, determining the most vulnerable children, and reducing exposure to improve child health.

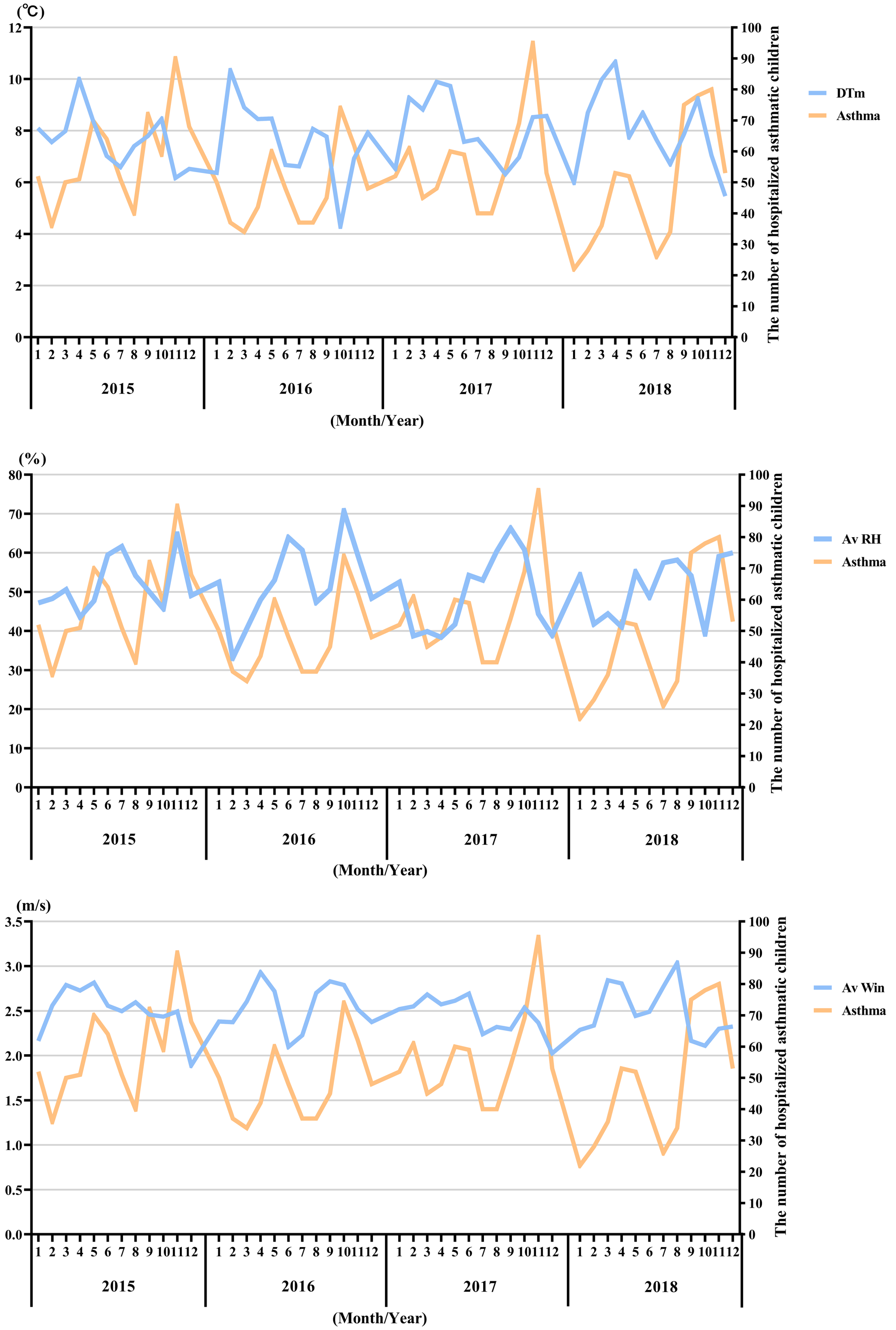

FIGURE 7
Pattern matching between temperature (°C), average relative humidity (%), average wind speed (m/s), and asthma-related hospital admissions during the study period (2015–2018). The X-axis represents the month and year, while the Y-axis on the left represents temperature (DTm, °C), average relative humidity (Av HR, %), and average wind speed (Av Win, m/s), respectively, and the Y-axis on the right represents the number of hospitalized asthmatic children in the corresponding month.

TABLE 2 Descriptive statistics from the time-dependent Cox regression models.

Air pollutant	Hazard ratios (HRs)	95% CI	*p* value
SO_2	0.98	0.95, 1.02	0.389
NO_2	1.01	0.98,1.05	0.566
CO	0.64	0.29, 1.42	0.270
O_3	0.99	0.97, 1.01	0.308
$PM_{2.5}$	1.01	0.97, 1.05	0.599
PM_{10}	1.01	0.99, 1.03	0.271

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 authors.

Ethics statement

The studies involving humans were approved by the Nanjing Medical University Clinical Research Ethics Committee, Nanjing, China. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

YB: Resources, Writing – original draft. JW: Formal analysis, Writing – review & editing. HH: Investigation, Writing – review & editing, Formal analysis. ZS: Formal analysis, Investigation, Writing – review & editing. MX: Investigation, Writing – review & editing. ZB: Investigation, Writing – review & editing. RJ: Conceptualization, Resources, Writing – original draft. QW: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

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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.2025.1527214/full#supplementary-material

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Critical insights on fungal contamination in schools: a comprehensive review of assessment methods

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This review addresses the increasing problem of fungal contamination in schools, which has a profound impact on indoor air quality and student health. Fungal contamination creates health problems such as respiratory problems, allergies, which can be particularly harmful in schools (e.g., *Aspergillus fumigatus* and *Fusarium* sp. are especially important as they are a well-known indoor allergens and can induce serious respiratory diseases). The aim of this study is to determine the effect of geographic location as well as season of filamentous fungi in school context. Through a comprehensive screening of 6,659 articles, 47 studies were selected for data extraction, detailing sampling techniques, analysis methods, climatic conditions, and relevant fungal species. The study highlights the importance of regularly measuring IAQ and utilizing both active and passive sampling methodologies in addition to molecular genetic analysis to complement identification and improve comparability across studies. A targeted monitoring is also proposed for species such as *Aspergillus fumigatus* (*Aspergillus* section *Fumigati*), *Fusarium* sp., and Mucorales order, which are therapeutically relevant, as well as *Stachybotrys atra* and *Aspergillus* section *Flavi*, in terms of their toxicological potential. Additionally, the article discusses the importance of consistent data formatting for effective meta-analysis and the need for further research to inform regulatory frameworks protecting student health. Recommendations for minimizing fungal threats include evaluating building structure, ventilation, cleaning practices, and gathering information from parents about school activities. Overall, the study underscores the global health risks posed by fungi in schools and calls for extensive investigations combining various sampling and analytical techniques. Additionally, the article discusses the importance of consistent data formatting for effective meta-analysis and the need for further research to inform regulatory frameworks protecting student health. Recommendations for minimizing fungal threats include evaluating building structure, ventilation, cleaning practices, and gathering information from parents about school activities. Overall, the study underscores the global health risks posed by fungi in schools and calls for extensive investigations combining various sampling and analytical techniques.

KEYWORDS

Fungi, exposure assessment, schools, IAQ, target fungal pathogens

1 Introduction

In 2022, the Health Emergency Preparedness and Response Authority (HERA) presented a priority list of top-3 health threats that require coordination of measures at the EU level, since they have the potential of spreading across Member States. All three health threats highlight the importance of microbes and stress the need to assess exposure to: pathogens with high pandemic potential; chemical, biological, radiological and nuclear threats; and threats resulting from antimicrobial resistance.[1] Also in 2022 focusing on fungi, the World Health Organization (WHO) release a list of fungal priority pathogens focusing on their clinical relevance to guide research, development, and public health action (1). The list is divided into three groups: critical, high, and medium priority groups and the ones listed are mostly important due to their clinical relevance (1). However, the concern regarding the toxigenic potential of specific fungal species and strains was not considered, hindering a more accurate intervention when assessing IAQ.

A warmer, wetter climate driven by human induced climate change is driving range shifts, increased dispersal, and the emergence of new fungal pathogens (2). In addition, many of the antifungals (e.g., azoles) used in clinical settings are also used in crop protection fostering azole resistance among fungal species (3, 4) also found in various indoor environments (5, 6).

A variety of regulations exist for microbial and chemical pollutants in indoor spaces, with the goal of enhancing indoor air quality and health. An open database was created by a scientific committee (7) to gather and distribute information on indoor environmental quality (IEQ), containing guidelines and standards from numerous countries and organizations (8). Overall, the guidelines and standards assembled in the IEQ guidelines (9) database present a great diversity, complexity, and inconsistency not only among countries but also within countries. Table 1 summarizes the database regarding fungal colony-forming units (CFU).

Specifically for fungi in indoor air, the database includes guidelines from 12 countries. Eight countries have numerical limit values but there is little consensus, with values ranging from as little as 50 CFU/m^3 to 10,000 CFU/m^3. The large range of values reflects the current lack of an established dose–response relationship between concentrations of airborne fungi and health outcomes. Due to the lack of a scientific basis for defining numerical health-based values for indoor fungal concentrations, many guidelines are based on the assessment of dampness and mold, as these have been most consistently associated with adverse health outcomes, including respiratory conditions such as asthma, rhinitis, and other respiratory tract infections, particularly in vulnerable populations like children, individuals with pre-existing respiratory conditions, and those with immune deficiencies (10). Indeed, WHO (11) has concluded sufficient epidemiological evidence from studies conducted in different countries and under different climatic conditions to show that the occupants of damp or moldy buildings, both residential and public buildings, are at increased risk of respiratory symptoms, respiratory infections, and exacerbation of asthma. The definition of dampness and mold based on the WHO guidelines is "any visible, measurable or perceived outcome of excess moisture that causes problems in buildings, such as mold, leaks or material degradation, mold odor or directly measured excess moisture (in terms of relative humidity or moisture content) or microbial growth." The WHO has also proposed data collection regarding dampness in buildings via inspections in schools in the WHO region (12). Reflecting this, many countries set guidelines based on visible inspection only (e.g., Ministry of Social Affairs and Health, Finland, 2015), (Danish Enterprise and Construction Authority, Copenhagen 12. Of December 2010).

While establishing upper limits based on clear links between exposure and health outcomes is critical, it is unlikely that it is optimal to eliminate exposure to fungi in indoor air entirely. As postulated in the "Hygiene" hypothesis, as humans co-evolved in the presence of various microorganisms, they may play a significant role in the regulation and childhood development of the immune system (13). This would suggest that increasing rates of inflammatory disease (such as asthma) with urbanization may be partly explained by reduced exposure to microorganism diversity and parasites in childhood as humans moved away from rural lifestyles in the mid-19th century. In the context of airborne molds/fungi, this could be used to support the argument that thresholds for airborne fungi in schools should not be zero and that some sort of "Goldilocks Zone" of exposure should be established. However, it is known that exposure to some viral and bacterial respiratory infections does not provide protection against asthma, indeed the opposite has been observed (14, 15).

Currently, established dose–response relationships between concentrations of airborne fungi and health outcomes are limited and complex. Research has shown clear associations, particularly in allergic and respiratory conditions such as asthma and allergic rhinitis, where exposure to high levels of fungi like *Aspergillus*, *Cladosporium*, and *Penicillium* exacerbates symptoms (16) however, specific dose–response data are often unclear due to variations in individual sensitivities and environmental factors. Immunocompromised individuals are known to be at greater risk for fungal infections at higher exposure levels, yet precise thresholds remain undefined (17). Fungal contamination in schools has potential negative outcomes on both the health and learning ability of students (18). The presence of fungi such as *Aspergillus*, *Penicillium*, and *Cladosporium* in school environments can lead to a range of health issues, including respiratory problems, allergies, and asthma exacerbation. Moreover, fungal contamination may compromise the structural integrity of buildings and contribute to indoor air quality degradation (11). Beyond health implications, the presence of fungi in schools can significantly impact students' concentration, cognitive function, and academic performance (19,

1 https://ec.europa.eu/commission/presscorner/detail/en/ip_22_4474

TABLE 1 Summary table regarding international fungal exposure guideline values (7), focused on indoor air quality (IAQ) parameters (8).

Country (nation with regulations)	Parameter (mold or moisture issue)	Threshold (acceptable contamination level)	Criteria (evaluation method or risk classification)
South Korea	Mold	500 CFU.m^{-3}	Mixture of species
United Arab Emirates	Mold	500 CFU.m^{-3}	Mixture of species
Singapore	Mold	<500 CFU.m^{-3}	>500 CFU/m^{3} if predominant species is *Cladosporium* spp.
Malaysia	Mold	1,000 CFU.m^{-3}	Mixture of species
Brazil	Mold	750 CFU.m^{-3}	Mixture of species
	Mold	Indoor/Outdoor ratio < 1.5	Mixture of species
Spain	Mold	200 CFU.m^{-3}	Mixture of species
Belgium	Mold	<50 CFU.m^{-3}—very low risk <200 CFU.m^{-3}—low risk <1,000 CFU.m^{-3}—medium risk <10,000 CFU.m^{-3}—high risk >10,000 CFU.m^{-3}—very high risk	Mixture of species
Portugal	Mold	Indoor/Outdoor ratio < 1	Mixture of species
Norway	Dampness	Visible mold damage or odor of mold	
United Kingdom	Dampness	Visible mold on external walls in a properly heated dwelling	
Finland	Dampness	Unrepaired moisture/rot damage on the inner surface, internal structure, or thermal insulation of a building	
Denmark	Dampness	0 cm^{2}—habitation/occupable room 400 cm^{2}—wet rooms 2,500 cm^{2}—roof spaces and basements	

20). Furthermore, prolonged exposure to fungal toxins may result in chronic health conditions, exacerbating absenteeism rates among students and educators (21, 22). Fungal contamination in schools poses significant health risks, including respiratory issues, allergic reactions, and potential infections. Since fungi can enter the body through airways, food, and water, it is crucial to emphasize the importance of regular monitoring and mitigation strategies (23). Currently, addressing fungal contamination lacks comprehensive strategies, including regular inspections, effective moisture control, and prompt remediation, all essential to safeguard health and optimize educational outcomes. It also needs to be noted that decreased exposure to beneficial microorganisms is not the only driver of inflammatory diseases, for example, increased exposure to particulate air pollution is a key contributor. The focus needs to be specifically on the now absent beneficial microorganisms. The specific fungal microbiome that is helpful for the human immune system cannot be replaced with new microorganisms that we did not co-evolve with. It is therefore critical to define the principal airborne fungi, we should (and in particular children with developing immune systems) be exposed to along with the numerical concentrations.

Despite this, there is still a lack of *consensus* on how to assess exposure to fungal contamination indoors, hampering the possibility of comparing results and identifying suitable fungal "sentinels" specific to each indoor environment. As such, it is of utmost importance to identify the best protocol regarding sampling collection and analyses regarding fungal exposure assessment, as well as to identify the most suitable fungal targets for the school environment (24). Although the literature reports a wide range of sampling methods and assays currently applied to assess fungal contamination indoors, there is no harmonized evaluation or even common approach regarding IAQ assessment among researchers, even when complying with the legal requirements. Thus, the aim of this scope review was to identify the methods used for fungal sampling and analyses and to list the fungal species that can be suggested as targets to assess IAQ regarding fungal contamination. The results retrieved from studies may contribute to setting future protocols (from the field to the lab) to assess fungal contamination in schools and to identify indicators of harmful fungal contamination for this specific environment. Furthermore, we are stressing the importance of a *consensus* regarding exposure assessment and considering the potential health effects due to exposure. This work will be also important to ensure both an accurate risk characterization and, consequently, the suggestion of effective control measures.

2 Materials and methods

Give a comprehensive overview of the literature available on the topic described above, a systematic literature review of studies was performed to identify the sampling strategy, methods used for fungal sampling and analyses applied and to list the fungal species that can be suggested as targets to assess IAQ regarding fungal contamination.

To aid in the identification of search terms and inclusion/exclusion criteria required to address this systematic review, a PEO (Population, Exposure and Outcome) (104, 106), statement was developed by the authors´ team (Supplementary Table S1).

2.1 Registration

In this study, the PRISMA methodology was adopted and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist (107) was completed, which encompass three phases: Identification, Screening, and Included (25).

2.2 Search strategy, inclusion and exclusion criteria

This study reports the search of available data published between January 1st, 2010, and February 29th, 2024. The search aimed at selecting studies on fungal assessment in different indoor school environments and included the terms presented in Supplementary Table S2, with English as the chosen language. The databases chosen were PubMed, Scopus, and Web of Science (WoS). Articles that did not meet the inclusion criteria and duplicates were excluded from further analysis (Table 2).

2.3 Studies selection and data extraction

The selection of the articles was performed through Rayyan, which is a free web tool that greatly speeds up the process of screening and selecting papers for academics working on systematic reviews. The screening was performed in three rounds by two investigators (RC and PP,). The first round consisted of a screening of all titles to exclude papers that were duplicated or unrelated to the subject and subsequent adding of included papers to Rayyan for further analysis. The second round consisted of a screening of all abstracts and in the third round, the full texts of all potentially relevant studies were reviewed considering the inclusion and exclusion criteria. Potential divergences in the selection of the study were discussed and ultimately resolved by the remaining investigators who contributed to this study. Data extraction was performed by five investigators (RC, PP, DH, EN and SG) and reviewed by the other two (CV and MS). The following information was manually extracted: (1) Database, (2) Title, (3) Country, (4) Occupational Environment, (5) Climate region, (6) Sampling sites, (7) Environmental samples description, (8) Sampling methods, (9) Analytical methods, (10) Fungi targeted, (11) Observed concentrations (CFU/m3 or other units depending of the applied methods), (12) Components/metabolites, and (13) reference (Supplementary Table S3). The prevalence analysis was based on the number of studies that identified each fungal genus or species. A higher proportion of studies reporting a particular genus or species indicates its more frequent detection in the selected literature.

TABLE 2 Inclusion and exclusion criteria in the articles selected.

Inclusion criteria	Exclusion criteria
Articles published in the English language	Articles published in other languages
Articles published from 1st January, 2010	Articles published after February 2024
Articles published in any country	
Articles related to IAQ in elementary schools.	Articles related to IAQ in elementary schools, without mention the fungal contamination.
Articles applying all types of sampling methods	Articles related to other school years (not elementary)
Original scientific articles on the topic	Abstracts of congress, reports, reviews/ state of the art articles

3 Results and discussion

In the systematic search for papers, multiple combinations of search terms were used in every round of the search. Each time the terms "school," "children," and/or "indoor air" were used and, at least three different terms were combined at once. Literature reviews were excluded from the search. The diagram describes the different phases of the selection of papers and the papers that were obtained in the final phase (Figure 1). The initial database search yielded 6,659 studies, from which 1,473 titles and abstracts were examined, and 101 full texts were evaluated for eligibility. A total of 3,902 studies were rejected after examining the inclusion and exclusion criteria, primarily because they were related to chemical evaluation, not performed in schools, or others (viruses, bacteria, reviews, surveys, etc.). After evaluation, a total of 70 papers on fungi in school environments were selected, from which 47 papers were eligible for data retrieval. The excluded papers did not meet the inclusion criteria, as they lacked essential details such as species identification, methodology, or other critical information required for the analysis.

In this comprehensive review, we encompassed rigorous evaluations of sampling methods, analytical techniques, and climatic conditions across different seasons. The outcomes disclosed in this document are organized in a graphic configuration, focusing on essential aspects such as the country of study, specific sampling sites, employed sampling and analytical methodologies, the identified agents, and the prevailing climate or seasonal conditions. The reported health effects, other associated problems, and study limitations have been meticulously documented, providing a holistic overview of the intricate relationships between environmental variables and human health outcomes. Understanding indoor microbial communities requires a broader perspective that includes interactions between fungi, bacteria, and viruses. Studies employing vacuum dust collection and sequencing methods have provided valuable insights into the total microbial composition in school environments, linking these multi-kingdom microbiomes to respiratory health outcomes. While such studies offer a more integrated approach to microbial exposure assessment, they fall outside the scope of this review due to differences in selection criteria, which focus specifically on fungal contaminants. However, acknowledging the complex interplay between different microbial groups is essential, as their combined presence may have synergistic or antagonistic effects on indoor air quality and health. Future research integrating diverse microbial communities could provide a more comprehensive understanding of exposure risks in school settings.

3.1 Spatial distribution of sampling sites

The distribution of research efforts across various geographical regions is crucial for understanding school indoor air quality (IAQ).

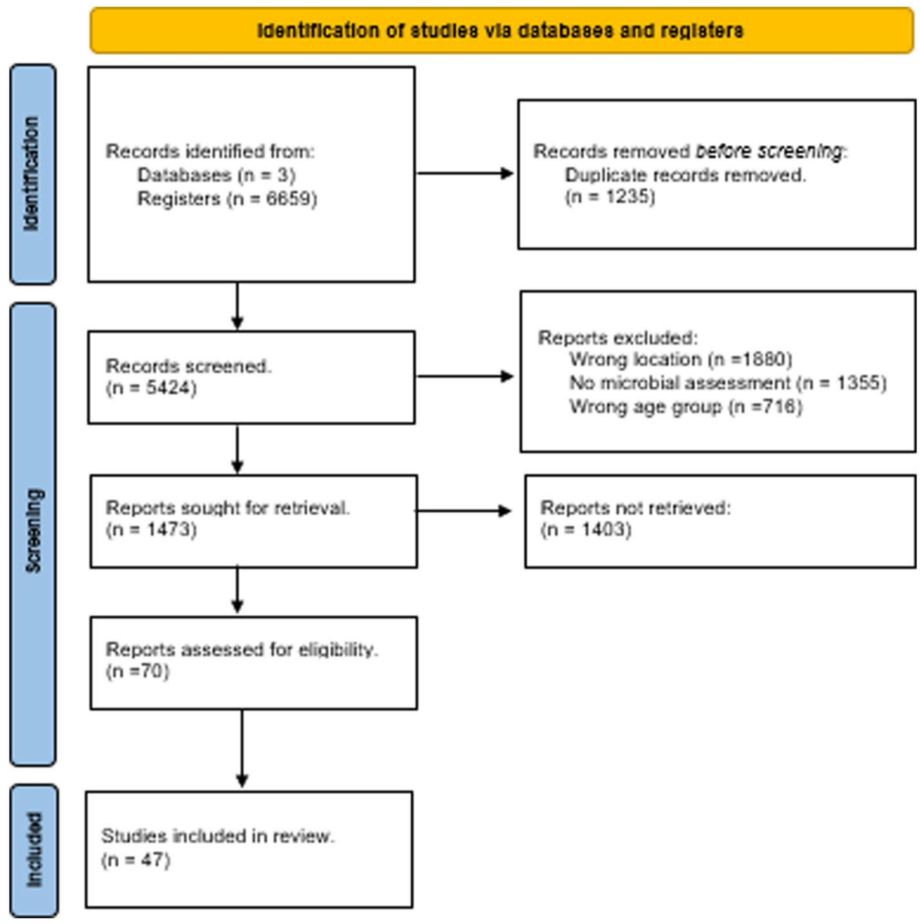

FIGURE 1
PRISMA based selection of articles (73).

Among the 47 studies assessed, data from 25 countries were included. Some of the studies were performed in more than one country (Figure 2). Notably, a substantial proportion of studies, accounting for 54% of the overall dataset, have been conducted on the European continent, followed by America (21%) and Asia (19%) (Figure 2). This proportion may be attributed to factors such as ecological significance, accessibility, or the presence of unique environmental features relevant to the research domain (26), or also due to the resources available and the focus on air quality and health. But it also represents a significant blind spot in our understanding, for example only 2 of the studies were conducted in Africa, and 3 in the Global South.

3.2 Seasonal effects

The examination of the climatic aspect within the analyzed studies indicates a significant focus on considering climate conditions during the sampling process. Out of the total 47 studies, 33 refer to seasonal variations, with 17 of them implementing a bi-seasonal approach, covering two distinct periods of the year and 16 mentioning the selection of a specific time frame (either warm or cold season). The selection of one season shows a predominance of data collection during the cold seasons, indicating a purposeful decision influenced by the particular environmental characteristics of these periods (13 out of 47). The preference for these specific periods may have implications for the interpretation of study results, as environmental factors can significantly influence outcomes. To enhance the temporal understanding of the subject matter, five longitudinal studies were included reporting durations of 1 and 2 years which provide a comprehensive perspective on how variables evolve, offering valuable insights into trends and patterns, and the dynamic interplay between geographic and climatic factors over extended periods, that may not be evident in shorter-term studies (27).

Airborne fungal concentrations vary based on factors like season, location, outdoor levels and ventilation. Studies show that indoor fungal concentrations can range from low to high levels, with values typically above 500–1,000 CFU/m3 being a cause for concern, indicating possible building contamination (28). Specific genera like *Cladosporium*, *Penicillium*, *Aspergillus*, and *Alternaria* have been linked to health effects like asthma exacerbations, with concentrations fluctuating based on temperature, relative humidity, and particulate matter levels (29, 30). Additionally, research highlights the importance of assessing fungal exposure in different environments like homes and schools, with concentrations being notably higher in winter compared to summer in certain regions (31, 32). Significant variations between cold and warm seasons in indoor environments have been observed in multiple studies. Additionally, fungal spore richness differs between seasons, with Basidiomycota richness higher in hot seasons and

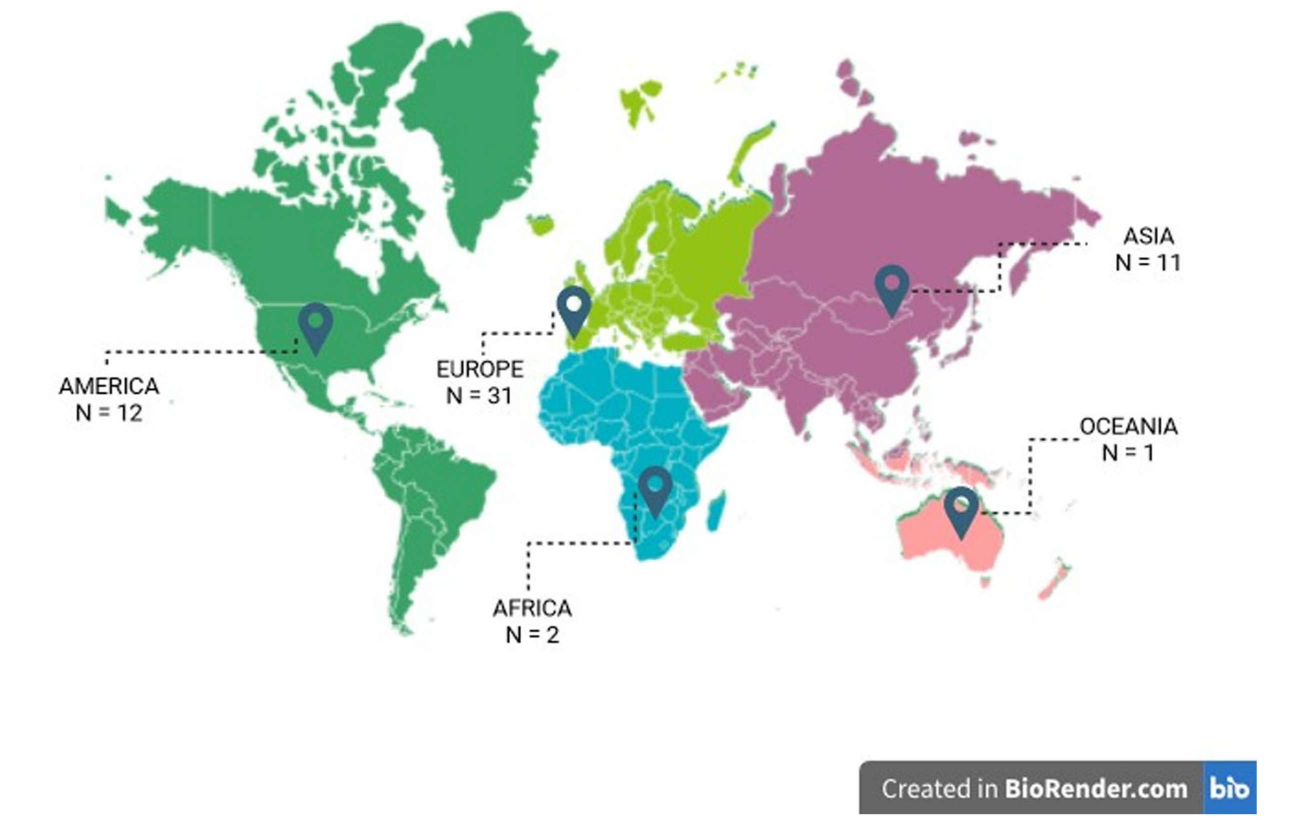

FIGURE 2
World map showing the geographic distribution of the studies.

Ascomycota richness higher in cool seasons (33). During the warm season, insights contribute to designing strategies for managing environmental quality in schools (34). In contrast, the winter season shows higher indoor fungal growth due to closed windows and poor ventilation, leading to increased bioaerosol concentrations with rising indoor temperatures (35). Additionally, indoor *Cladosporium* levels are affected by outdoor conditions, with higher concentrations in winter due to low humidity and high wind speeds (32).

3.3 Sampling location

In the vast majority of the studies, the process of sampling was conducted within the confines of the classrooms (38 out of 47). However, it is worth noting that numerous studies also conducted sample collection in various areas of the school building, such as the canteens, corridors, and even on surfaces, such as walls, working tables, and floors and some outdoor samples were also collected in some of the studies.

The findings presented show the profound variation in used sampling approaches and the need for the inclusion of contextual information in research studies. Given that fungi exposure is influenced by multiple factors, it is crucial to describe all relevant information in the publications and consider the context of the study design in the interpretation of the results to achieve accurate exposure assessment. The collection of information regarding building structure, ventilation, cleaning practices, and the activities description allows the identification of hazards (36, 37). The application of a walkthrough survey to collect such information allows a comprehensive understanding of the contamination context and supports the implementation of control measures (38). Moreover, the mention of contextual information, including surveys on school operational and structural conditions as well as reports from parents regarding children's health-related issues, highlights a step toward holistic understanding within research (39, 40). Such data provide valuable insights into the broader circumstances surrounding the research subject, offering a more nuanced interpretation of the findings (39, 40). However, the relatively low percentage (7%) of the reviewed articles including contextual information suggests a need for greater emphasis on contextual factors in research methodologies. In the articles reviewed, the association between mildew presence and increased mold concentrations is emphasized (32, 41, 42), alongside the repercussions observed in moisture-damaged schools, including elevated microbial markers, heightened respiratory symptoms, and higher fungal DNA concentrations (43). Carpeting was associated with the presence of bioaerosols, indicating the importance of regular cleaning and monitoring for signs of dampness or moisture damage (44–46).

3.4 Sampling methods

In terms of sampling, the majority (32 out of 47) employ active sampling methods, which involve drawing air through a collection device using a pump, utilizing air samplers, impactors, impingers, and other aerosol devices. In contrast, 15 out of 47 exclusively use passive methods, which rely on natural air deposition onto a surface or medium without mechanical assistance, employing techniques such as settled dust, electrostatic dust cloths, and the open-dish method (24) (Table 3).

With only 7 out of the 47 studies utilizing both active and passive methods for sampling, there's a clear opportunity for improvement in achieving a more comprehensive understanding of climate change and seasonal sampling impact. Active sampling requires a pump, collecting a specific volume of air for a defined period by the researcher/exposure assessor. Air can be collected onto culture media, liquid media, or any kind of membrane or filter (polyvinylchloride, polycarbonate, cellulose acetate, or gelatine filters). These methods allow the application of culture-based methods (allowing the identification of viable particles) (47–49). On the other hand, passive sampling methods do not require a pump or any other mechanical equipment. They are based on settled dust collection onto a Swiffer, agar plate, filter, or swabs. They allow sampling for longer periods, as they enable the accumulation of dust over extended durations, such as days, weeks, or even months, providing a more integrated representation of airborne fungal exposure. However, the sample needs to be extracted through a liquid solution for subsequent use of a culture-based method (allowing the identification of viable particles) and molecular tools, as in the case of Electrostatic Dust Cloths (EDC) (3, 49). By using both sampling approaches, researchers can capture a wider range of perspectives and nuances, potentially enhancing the validity and reliability of their findings (50). The articles present their results using disparate methodologies, with many offering only statistical data that are difficult to compare with those from other studies, thereby limiting the scope for broader analyses.

3.5 Analytical methods

Among the studies that were examined, a substantial proportion (32 out of 47) chose to use culture-based methods with macroscopic and microscopic observations as part of their analytical approach. This conventional methodology enables researchers to directly visualize the morphological characteristics of both colonies and fungi, thus facilitating thorough examinations (51). However, it is well documented that only a small percentage of fungi recovered from air samples are culturable. Thus, using culture-based methods may lead to an underestimation of the real fungal contamination (52, 53).

However, a significant subset of the studies (11 out of 47) exclusively employed molecular genetic assays for analyzing their samples. Molecular genetic techniques, such as qPCR and DNA sequencing, offer robust mechanisms for detecting and characterizing genetic material with high sensitivity and specificity (54). Nevertheless, these methods have limitations, including detection bias, inability to assess organism viability or morphology, reliance on amplifiable DNA, and high costs (52, 54). Notably, one study (55) combined culture-based methods with molecular techniques (qPCR and antifungal resistance testing), leveraging the strengths of both approaches to identify viable organisms and characterize genetic profiles. Meanwhile, 11 studies integrated culture-based methods with biochemical/enzyme assays, providing insights into functional properties like toxicity or allergenicity. The majority of studies (30/47) relied on single-method approaches—either culture or molecular—highlighting a gap in multi-method frameworks that could address the limitations of standalone techniques. These findings underscore the need for future research to adopt hybrid methodologies that balance viability assessment, morphological identification, and genetic specificity for comprehensive risk evaluations. The array of analytical methods observed underscores the significance of having methodological adaptability in scientific investigations. To provide a more nuanced discussion on the strengths and weaknesses of these methods, a larger number of studies utilizing both approaches would be required. Currently, the limited number of studies makes it difficult to definitively address whether there are specific scenarios in schools where one method is clearly preferable or more informative than the other. This progress fosters innovation in research despite some constraints. By combining culture-based observations with molecular genetic assays, researchers can gain a more comprehensive understanding of specimens, uncovering insights that might be missed using only one method. However, comparing culture-based techniques and molecular genetic assays poses challenges. The main issue is aligning macroscopic colony morphology and microscopic identification with genetic data. To overcome this, researchers may need to develop standardized criteria or conduct simultaneous use of culture-based and molecular identification methods on the same sample together to take advantage of their strengths and minimize their individual limitations. Furthermore, since culture-based methods allow the comparison with quantitative cut-offs referred to in many international guidelines (Table 1), integrating molecular techniques for the identification and confirmation of pathogenic species can enhance the accuracy, sensitivity, comprehensiveness, and comparability of assessments, thereby supporting improved risk management and more effective public health interventions (56–59). Furthermore, the screening of azole resistance is dependent on obtaining an isolate from the species under study and thus relying on culture-based methods, at least as first step of the screening (60). Additionally, numerous articles considered in this review included supplementary analyses, including endotoxin and cytotoxicity assessment, as well as antifungal (azole) resistance testing as indicated in Supplementary Table S3.

3.6 Most prevalent fungal taxa

Figure 3 presents the most prevalent fungal genera identified across the selected studies. The prevalence reflects the number of studies that reported each genus, with higher representation indicating more frequent detection in the literature., among 47 studies analyzed, 42 mention the presence of *Aspergillus* species, of which merely 16 were identified up to the section (Figure 4), and only 5 identified as *Aspergillus fumigatus*. Since *Aspergillus fumigatus* is on the list of priority pathogenic fungi as a critical priority, which is based on criteria such as antifungal resistance, mortality, evidence-based treatment, access to diagnostics, annual incidence and complications and sequelae, it is of the utmost importance to be identified (1). Furthermore, two other high priority species were identified in 20 of the 47 studies, where 11 mentioned the presence of *Fusarium* sp., and 9 identified the presence of Mucorales.

The most prevalent genera was *Aspergillus* (Figure 3). It is noteworthy that among the top 46 identified genera examined in various studies, 11 were predominantly found in indoor settings

TABLE 3 Summary of active and passive sampling methods and respective samplers used in various studies.

Active/passive	Method category	Sampling method/samplers	References
Active	Impaction	Burkard indoor recording air sampler	(30–32, 74, 75)
		Single-stage microbiologic air impactor (Merck MAS-100)	(76, 77)
		Single-stage AirIdeal 3P impactor	(34, 35)
		Andersen N6 single-stage impactor	(28, 78–80)
		Six-stage Andersen 10–800 impactor	(42, 81, 82)
		Mattson–Garvin slit-to-agar impactor	(44)
		Andersen two-stage cascade impactor	(83, 84)
	Filter	IOM inhalable dust sampler (SKC Inc.)	(85, 86)
		Air-O-cell cassette (SKC/Zefon)	(16, 45)
		Nucleopore filters (0.4 µm)	(87, 88)
		Millipore cassettes (0.45 µm)	(89)
		Fine particle sampler (PM2.5 filters)	(44)
		MCE filter cassettes (0.8 µm)	(28, 90)
	Vacuum	Micro-vacuum sampler (IAQ-1294)	(28, 86)
		Siemens Super XS vacuum cleaner	(88, 91)
		Li'l Hummer backpack vacuum	(92)
		HVS-3 vacuum sampler	(86)
		Generic vacuum cleaners	(93, 94)
	Tracer gas	Tracer-gas decay method (acetone)	(87)
	Other	Sampling pumps (unspecified)	(95)
		Spot sampler (aerosol devices)	(90)
Passive	Electrostatic dust collectors (EDC)	Electrostatic dust collectors (EDCs)	(41, 55, 85, 96, 97)
	Settled dust	Settled dust boxes (SDBs)	(43, 85, 86, 96, 105)
		Passive sedimentation (open-dish/gravity plates)	(23, 98–101)
	Swab/surface sampling	Surface swabs	(23, 101–103),

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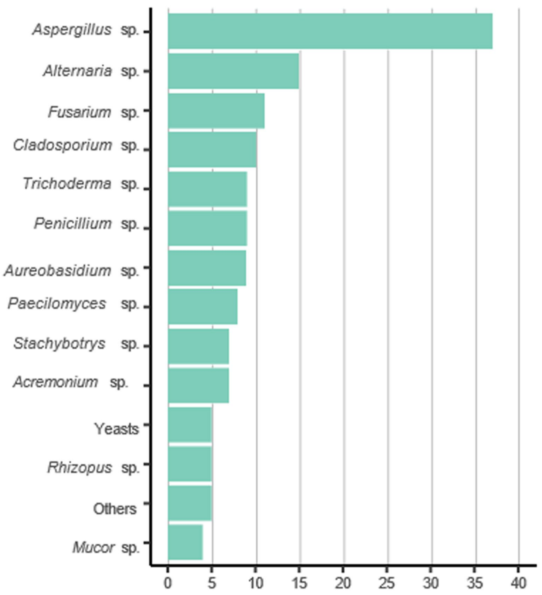

FIGURE 3
Topmost prevalent genera found in the selected articles.

within elementary schools, (Figure 3). These particular genera encompassed *Aspergillus*, *Alternaria*, *Cladosporium*, *Aureobasidium*, *Penicillium*, *Trichoderma*, *Fusarium*, *Paecilomyces*, *Acremonium*, *Stachybotrys*, *Rhizopus, Mucor* and yeasts. Considering that some genera are easily identified macroscopically, there may be a bias in statistics toward those that have been analyzed. If most studies focus primarily on these genera, this could explain the absence of others in the findings.

Figure 4 summarizes the distribution of Aspergillus species identified in the selected studies. The prevalence is based on the number of studies reporting each species, highlighting the most commonly detected ones either based on optical analysis and/or molecular genetic tools. The most frequently encountered were *Aspergillus niger*, *Aspergillus fumigatus*, and *Aspergillus versicolor* (Figure 4). *Aspergillus* species identification is crucial due to the emerging resistance profile and consequently clinical implications (61). Nowadays, the taxonomic classification of fungi is undergoing a transformation. *Aspergillus* species are classified into taxonomic groups based on their morphological characteristics (62). *Aspergillus* sections may encompass multiple species, and accurate identification often requires a combination of morphological, biochemical, and molecular genetic methods (63). However, more recently, genetic approaches, especially focusing on rRNA genes, have found that many fungi do not fit neatly into the categories used based morphological and biochemical characteristics (64). For example, among the *Aspergillus* genus, the designations represent sections of closely related species (also referred to as cryptic species) that cannot be clearly distinguished morphologically (65). These sections include *Aspergilli, Fumigati, Circumdati, Terrei, Nidulantes, Ornati, Warcupi, Candidi, Restricti, Usti*, and *Flavi*, among others. *Aspergillus* identification to, at least, section level provides a comprehensive understanding of the diversity, ecology, and significance of this genus (66). In fact, accurate identification of *Aspergillus* species within clinically relevant sections informs diagnostic strategies, treatment decisions, infection control measures, and public health interventions (67, 68).

Regarding yeasts, many papers suggest the possibility of yeasts in schools being mainly derived from different parts of the human body, potentially explaining their high concentrations indoors (Supplementary Table S3).

The growth of mycotoxin-producing fungi (e.g. *Stachybotrus atra*) was reported in one study (10). In one study, *Aspergillus* concentrations indoors correlated significantly with the concentration of particulate matter (16), and in one study dust was reported as a major contribution to fungal and bacterial flora in schools (18). Also the age of buildings, area of classrooms, temperature, humidity, and particulate matter (PM10) were reported as predictors of the concentration of culturable fungi (19). Finally, it was suggested that increased ventilation rates may mitigate overheating, alleviate sick building syndrome symptoms, and improve satisfaction with IAQ (28). All the studies underscored the importance of routine testing for fungal contamination in schools and emphasized the need to address poor ventilation to mitigate health risks such as allergies and respiratory illnesses.

The comprehensive summary of the found species in school environments shows that it is crucial to highlight the prioritization of research and evaluation efforts regarding indoor air quality in school health programs, with an emphasis on investigating, quantifying, and recognizing fungal pathogens with significant clinical implications on human health, as the ones listed in the WHO priority list and in Table 4. Since the toxicological potential of the fungal species was not considered in the WHO list, we also recommend the inclusion of mycotoxin-producing fungi, such as *Stachybotrus atra* and *Aspergillus* section *Flavi*. The latter is the main producer of the carcinogenic mycotoxin Aflatoxin B1 (AFB1), which is predicted to increase due to climate changes in Europe (69–71), as rising temperatures, humidity, and extreme weather events create favorable conditions for fungal proliferation—trends that are also observed globally in regions experiencing similar climatic shifts (72).

4 Conclusion

In summary, understanding and monitoring fungal concentrations is crucial for assessing indoor air quality and potential health risks, as geographic distribution, climatic conditions, and outdoor air significantly influence fungal diversity and activity. Given that much of the research has focused on specific regions and climate periods—resulting in a biased understanding of the implications for human health—and that most studies rely on active sampling and culture-based methods, which form the cornerstone of fungal contamination assessment, their complementary integration with passive sampling and molecular genetic tools can significantly enhance the overall approach. Additionally, the comparability of fungal contamination data depends on detailed contextual information, including anthropogenic activity, structural information, ventilation, and cleaning practices. Overall, we recommend:

- Standardized Protocols: Develop standardized protocols for sampling and analysis to ensure consistency in fungal assessments across studies.

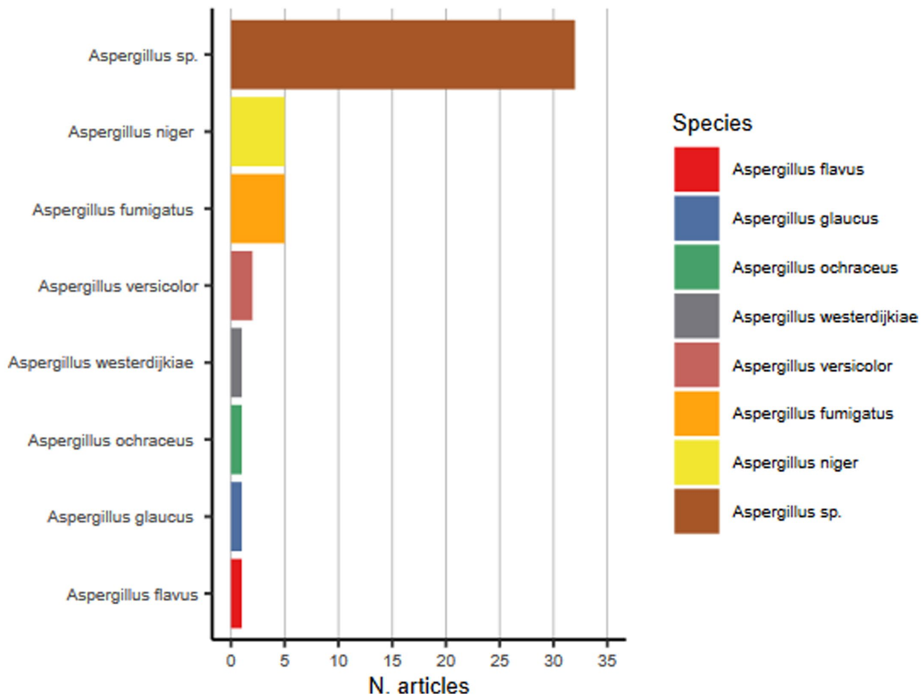

FIGURE 4
Aspergillus species identified in the selected articles.

TABLE 4 Comparative analysis of WHO fungal priority pathogens list and other pathogens with health impact.

WHO fungal priority pathogens list (WHO FPPL)		Pathogens identified in the reviewed papers (*n*)	Paper references
Critical Priority group	*Aspergillus fumigatus*	5	(28, 35, 76, 81, 83)
High priority group	*Fusarium* spp.	11	(23, 28, 30, 32, 35, 75, 83, 97–99, 101)
	Mucorales	9	(23, 28, 34, 76, 83, 91, 97, 99, 102)

Papers reviewed are listed in the last column, providing a reference for further studies and analysis.

- Integration of Molecular Methods: Use molecular methods alongside traditional culture-based techniques for a comprehensive understanding of fungal diversity and its implications.
- Species-Specific Monitoring: Focus on targeting *Aspergillus fumigatus*, *Fusarium* sp., Mucorales order, *Stachybotrys atra*, and *Aspergillus* section *Flavi* due to their clinical and toxicological relevance.
- Seasonal and Geographical Variations: Explore the prevalence of these fungi across different educational environments to allow for targeted interventions and clearer guidelines.
- Regulatory Frameworks: Implement guidelines that consider both fungal species and environmental factors (e.g., humidity, ventilation, building materials). Integrate fungal monitoring into broader public health strategies.

A major limitation in this type of review is the disparate methodologies used in presenting results across various articles. Many studies offer only statistical summaries that lack comparability with others, posing significant challenges when attempting to synthesize findings or draw broader conclusions. Therefore, it is crucial to standardize the way data is presented:

- Measurement Protocols: Develop standardized measurement protocols and use unified units of measurement, such as spores per cubic meter of air, to ensure consistency.
- Meta-Analyses Frameworks: Create frameworks for meta-analyses to aggregate and standardize diverse data.
- Centralized Data Repositories: Establish centralized data repositories for sharing raw data, along with comprehensive reporting guidelines detailing study methods to facilitate comparisons.
- Interdisciplinary Collaboration: Promote interdisciplinary collaboration and secure regulatory and policy support for standardized methodologies.
- Education and Training: Provide education and training on best practices for data collection and reporting to improve the quality and comparability of research on airborne fungi and health outcomes.

Such standardization would enhance the comparability of results across studies, facilitate new research, and promote information sharing among researchers, ultimately advancing the field. Linking environmental exposure to health outcomes underscores the importance of establishing regulatory limits based on health outcomes. While there are recognized health impacts linked to airborne fungal exposure, the exact exposure-response relationships are inadequately characterized, highlighting the need for further research to address these complexities. This interconnectedness of the environment, exposure, and health outcomes emphasizes the need for comprehensive regulatory frameworks that consider these interdependencies. Ongoing research efforts aimed at elucidating the relationship between environmental fungal exposure and health outcomes will be instrumental in informing evidence-based regulatory policies to safeguard public health.

Author contributions

RC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. PP: Data curation, Formal analysis, Methodology, Writing – original draft. BR: Data curation, Writing – original draft. MR: Data curation, Writing – original draft. DH: Data curation, Writing – original draft. SG: Data curation, Writing – original draft. EN: Data curation, Writing – original draft. CP: Writing – review & editing. HS: Writing – review & editing. MA: Validation, Writing – review & editing. RF: Formal analysis, Supervision, Writing – review & editing. UH-S: Writing – review & editing. CV: Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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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.2025.1557506/full#supplementary-material

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Association between insecticide exposomics and cognitive function in older adults: an observational study based on NHANES 2011–2014

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Objective: This study aims to investigate the association between exposure to insecticide exposomics and cognitive function, among adults aged 60 and above.

Methods: We employed a multi-stage probability sampling method to analyze data derived from the National Health and Nutrition Examination Survey (NHANES) conducted between 2011 and 2014. The study investigated the impact of insecticides exposure on cognitive performance, as measured by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word Learning Test (CERAD-WL), CERAD Delayed Recall Test (CERAD-DR), Animal Fluency Test (ATF), and Digit Symbol Substitution Test (DSST). Logistic regression models were used to evaluate the impact, with adjustments for sociodemographic and lifestyle variables, and subgroup analyses were conducted to further elucidate the findings.

Results: A total of 1,544 participants were included after applying strict exclusion criteria. Logistic regression analysis disclosed a significant association between insecticides exposure and the risk of cognitive impairment. Specifically, for CERAD-WL, the unadjusted model showed an Odds Ratio (OR) of 0.68 (95% CI: 0.49–0.93), $p = 0.0174$, and the adjusted model showed an OR of 0.71 (95% CI: 0.51–0.99), $p = 0.0466$. CERAD-DR demonstrated an unadjusted OR of 0.64 (95% CI: 0.46–0.88), $p = 0.0060$, and an adjusted OR of 0.67 (95% CI: 0.47–0.94), $p = 0.021$. The DSST indicated a correlation with pesticide exposure in the unadjusted model with $p = 0.0214$. Herbicides were notably associated with ATF in the unadjusted model with an OR of 1.70 (95% CI: 1.14–2.53), $p = 0.0093$. However, after adjusting for sociodemographic and lifestyle variables, some associations were no longer statistically significant. For instance, the association between insecticides exposure and CERAD-WL performance became non-significant (OR: 0.80, 95% CI: 0.56–1.15, $p = 0.2284$), and similarly for CERAD-DR (OR: 0.72, 95% CI: 0.50–1.03, $p = 0.0734$).

Conclusion: Our study indicates an association between insecticides exposure and cognitive impairment, particularly affecting memory and delayed recall. Yet, the cross-sectional design prevents conclusive causality claims. Future research should adopt longitudinal approaches, utilize biological markers for precise exposure measurement, and apply advanced statistical techniques to better understand the exposure-outcome relationship. Including a broader age range and detailed confounder data will also strengthen causal inferences.

While our findings offer preliminary evidence, more robust studies are necessary to confirm causality and guide preventive measures.

KEYWORDS

insecticide exposomics, cognitive function, older adult population, NHANES data, pesticide exposure, cognitive decline, public health research

1 Introduction

Cognitive decline, predominantly affecting individuals aged 60 and above, is characterized by a diminished capacity for daily activities and a significant reduction in social functioning. It is considered an intermediate stage between normal aging and dementia (1–3). As one age, cognitive decline often progresses to dementia, primarily in the form of Alzheimer's disease (AD), with an estimated annual rate ranging from 5 to 17% (4). AD affects an estimated 50 million people worldwide, a number expected to triple by 2050, driven largely by the aging global population (5). Currently, the annual global cost of dementia exceeds \$1.3 trillion and is projected to rise to \$2.8 trillion by 2030 (6). However, effective treatments for dementia remain elusive, and early-stage diagnosis lacks definitive indicators. Focusing on cognitive function is a novel target, as some causes of cognitive decline might be reversible or potentially treatable. Therefore, leveraging cognitive test performance in the older adult to predict cognitive function levels and identify risk factors for cognitive decline offers a potential avenue for early intervention (1, 7).

Pesticides, defined as substances or mixtures of substances used for the prevention, destruction, removal, mitigation of any pest, include insecticides, herbicides, fungicides and many other types. These pesticides contain a variety of chemical structures and are commonly used in household and outdoor products (8, 9). However, their use can lead to food and water contamination, increasing the risk of exposure to these substances and potentially causing harm to human health (10, 11). Pesticide exposure has been linked to multiple diseases, including Hodgkin's disease (HD), non-Hodgkin's lymphoma (NHL), and Parkinson's disease, as well as disorders affecting the endocrine, respiratory, and reproductive systems (12, 13).

Mechanistically, insecticides inhibit acetylcholinesterase (AChE), causing synaptic acetylcholine accumulation and neuronal overexcitation (14). In chronic exposure scenarios, this triggers secondary cascades involving oxidative stress, neuroinflammation, and mitochondrial dysfunction, ultimately leading to synaptic loss and neuronal apoptosis (15, 16). Animal models corroborate these pathways: Malathion exposure induces hippocampal oxidative stress and spatial memory deficits in rats (17), while rotenone disrupts blood–brain barrier integrity, activates microglial, and triggering neuronal apoptosis in mice (18). Crucially, even subacute paraquat administration promotes complement-mediated synaptic pruning, highlighting the diversity of pesticide-induced neurotoxic mechanisms (19).

Human studies further support this association. Event-related potential (ERP) analyses reveal persistent neurophysiological deficits in acute insecicides poisoning survivors, including delayed attentional processing lasting up to 6 months post-exposure (20). Chronic low-dose effects are suggested by NHANES-based analyses, where elevated urinary 3-phenoxybenzoic acid (3-PBA), a pyrethroid metabolite, correlates with poorer cognitive scores in older adults (21). However, population-level evidence specifically linking insecticides to cognitive decline remains scarce, particularly regarding daily low-dose exposure in aging populations.

To further understand the effects of pesticides on cognitive function, this study utilizes data from the National Health and Nutrition Examination Survey (NHANES) in the United States to assess the relationship between the use of insecticides and cognitive function levels in older adults, aiming to provide key epidemiological insights. The NHANES is a series of investigations designed to assess the health and nutritional status of the U.S. population. Utilizing a layered, probabilistic sampling method, it pinpoints a sample that mirrors the national demographic of the civilian, noninstitutionalized population in the U.S.

2 Methods

2.1 Study design and ethical considerations

Our research primarily uses data from the NHANES database. NHANES provides a comprehensive overview of the socioeconomic, health, behavioral, and nutritional aspects of both adults and children within the U.S. populace. Participants undergo a comprehensive examination at a mobile examination center (MEC) after a household interview, which includes a physical examination, specialized measurements, and laboratory tests. Acknowledged for its reliability and multifaceted nature, this approach enables the creation of nationwide estimates. Further information regarding the NHANES database and the methodology of data collection can be accessed at the official NHANES website.[1]

2.2 Pesticide use

To obtain an accurate assessment of insecticides usage, we collected data from NHANES on all pesticides used by individuals in domestic, horticultural, and garden contexts over the past 7 days. One of the questions posed during the interview was: "Has any chemical product been used in your home to control fleas, cockroaches, ants, termites, or other insects within the past 7 days?" Additionally, participants were asked: "In the past 7 days, were any chemical products used in your lawn or garden to kill weeds?" While self-reported data provide a useful proxy for exposure, they are subject to misclassification bias.

Participants' responses in 2011–2012 can be categorized as follows: A total of 716 respondents indicated that they had used a chemical product in their home to control insects, while 6,439 respondents stated that they had not. Additionally, 666 respondents indicated that they did not know or provided an invalid response.

1 http://www.cdc.gov/nchs/nhanes/

Similarly, in 2013–2014, 789 respondents reported using a chemical product to control fleas, roaches, ants, termites, or other insects within the past 7 days. However, 6,991 respondents stated that they had not used such a product, while 511 respondents indicated that they did not know or provided an invalid response.

The other question was "In the past 7 days, were any chemical products used in your lawn or garden to kill weeds?" A total of 260 respondents indicated that they had used a chemical product in their lawn or garden to kill weeds, while 6,818 respondents stated that they had not used such a product in 2011–2012. Additionally, in 2013–2014, 424 respondents indicated that they had used such products, while 7,258 respondents indicated that they had not used a chemical product in their lawn or garden to kill weeds.

2.3 Cognitive assessment

Assessing cognitive function involves either home interviews or comprehensive evaluations at mobile examination centers. Tools like the CERAD Word Learning Test (CERAD-WL), CERAD Delayed Recall Test (CERAD-DR), Animal Fluency Test (ATF), and Digit Symbol Substitution Test (DSST) are employed to provide a comprehensive evaluation of cognitive abilities.

The CERAD assesses memory capability by testing the retention of new verbal information over time, consisting of three consecutive immediate learning trials with delayed recall tests. During the CERAD learning phases, participants are required to verbalize ten distinct words (22, 23). After the Animal Fluency test (AFT) and DSST assessments, participants proceed to the delayed word recall segment. Each trial is awarded a score on a scale of 10, and the composite CERAD score is the total of all trial scores.

Concurrently, the AFT assesses executive function by evaluating categorical verbal fluency. Participants are tasked with enumerating as many animals as possible within 1 min, with scores typically ranging from 3 to 39 (24). The DSST, part of the Wechsler Adult Intelligence Scale, is designed to assess processing speed, attention, and working memory. The assessment employs a paper-based format comprising a key with nine digits, each associated with a distinct symbol. Participants are permitted a two-minute timeframe in which to accurately transfer the corresponding symbols into the 133 allocated boxes adjacent to the numbers. The test is scored based on the number of correct pairings, with a maximum achievable score of 105 (25).

Scoring criteria for cognitive impairment are typically set at 25% below the total possible score. Consistent with this standard, potential cognitive impairment is indicated by scores below 17 for CERAD-WL, below 5 for CERAD-DR, below 14 for ATF, and below 34 for DSST (26, 27). This threshold aligns with prior NHANES-based research, which has utilized similar cutoffs to identify cognitive impairment in older adult populations (28). Adopting these established thresholds enables a standardized approach to classifying cognitive impairment, facilitating comparisons across studies, and enhancing the generalizability of our findings.

2.4 Covariates

This study evaluated various potential confounders, including sociodemographics (age, gender, race/ethnicity, education, marital status, income, and Poverty Income Ratio [PIR]), lifestyle factors (smoking, alcohol, BMI, and sleep), and medical conditions (hypertension, diabetes, heart failure, stroke, and depression).

Participants were categorized by age groups (60–69, 70–79, and 80+), gender (male/female), and race and ethnicity (Mexican American, other Hispanic, non-Hispanic Caucasian, non-Hispanic African American, and others). Education levels were divided into those without a high school diploma and those with higher education. Marital status was categorized as never married, married/cohabiting, widowed, divorced, or separated. Household income was split into four brackets: under \$20,000, \$20,000–\$45,000, \$45,000–\$75,000, and over \$75,000. PIR was categorized as low (below 5) or high (5 or above).

Lifestyle factors were assessed as follows: smokers were defined as those with at least 100-lifetime cigarettes; alcohol use was based on at least 12 annual drinks; BMI was classified as normal (under 25 kg/m^2), overweight (25–30 kg/m^2), or obese (30 kg/m^2 or more); and sleep duration was self-reported and categorized as 10 h or less, or over 10 h.

Medical conditions were identified through self-reported diagnoses by healthcare providers for hypertension, diabetes, heart failure, and stroke, and depressive symptoms were assessed using the PHQ-9, with scores of 10 or higher indicating depression.

To assess the robustness of our findings, we conducted sensitivity analyses to exclude participants with missing data. In the analysed tables it was shown that the ORs of insecticides with the CERAD-DR and DSST tests remained statistically significant (p-values of 0.014 and <0.001, respectively).

Missing data rates were low across variables: alcohol (0.39%), BMI (1.42%), education (0.06%), marital status (0.06%), income (4.53%), PIR (7.57%), diabetes (0.06%), heart disease (0.26%), stroke (0.19%), hypertension (0.26%), sleep duration (0.25%), and smoking status (0.06%). Multiple imputation was performed using the "MICE" package in R, following the methodology of Van Buuren and Groothuis-Oudshoorn.

2.5 Statistical analysis

Our statistical approach encompassed sample weights, clustering, and stratification, which are crucial for estimating national trends and enhancing the generalizability of our findings. To assess the normality of the data, we employed the Kolmogorov–Smirnov test. Categorical variables were reported as counts and percentages, while normally distributed continuous variables were presented as mean ± standard error (SE), and non-normally distributed continuous variables were described using the median and interquartile range (IQR). For comparative tests, we used the Student's t-test for the mean values of normally distributed continuous variables between groups, the Mann–Whitney U test for non-normally distributed continuous variables, and chi-square tests for categorical variable comparisons.

Furthermore, we conducted a logistic regression analysis to explore the relationship between pesticide exposure and cognitive function, which included an unadjusted model (Model 1), a model adjusted for basic demographic variables (Model 2), and a model that encompassed a broader range of factors (Model 3). ORs and their corresponding 95% CIs were determined. To further investigate potential interactions, we performed subgroup analyses using eXtreme Statistical Software 4.1, assessing the interactive effects of covariates such as age, gender, income, alcohol consumption, BMI, and hypertension on cognitive function. We also used the Research Analytics website for sensitivity analyses, and GraphPad Prism 10.1.2 to make clearer dot plots of *p*-values in the research demographic characteristics.

3 Results

3.1 Study population

A comprehensive sample of 19,931 individuals was initially included from the 2011–2012 and 2013–2014 cycles of the NHANES. Subsequently, participants with incomplete data regarding pesticide exposure were systematically excluded: totaling 12,121 individuals (12,120 defends insects and 1 kills weeds). Following this, those lacking results from four key dementia assessment tests were excluded: 142 individuals (54 CERAD-WL test; 0 CERAD-DR test; 18 AFT test and 70 DSST test). Additionally, individuals under the age of 60 were excluded, totaling 6,124 individuals. This strict exclusion process resulted in a high-quality dataset comprising 1,544 participants (Figure 1). Since this article focuses on mainly insecticides and the sample size regarding herbicide use after screening, the sample was too small to be convincing, so the discussion focuses on the relationship between insecticides and cognitive function.

3.2 Demographic characteristics of the study population

Table 1 presents the demographics and characteristics data of the 1,544 participants, categorized based on CERAD-WL scores and insecticides exposure. Among these participants, 217 were reported to have used insecticides pesticide in the past week. With a CERAD-WL score of 17 as the cognitive decline threshold, the age distribution was as follows: 53.4% were aged 60–70 years, 29.8% were aged 70–80 years, and 16.8% were over 80 years old. The cohort was 52% female and 48% male, with the majority of participants (51.2%) being non-Hispanic white, non-Hispanic black (20.4%), Mexican American (12.4%), and

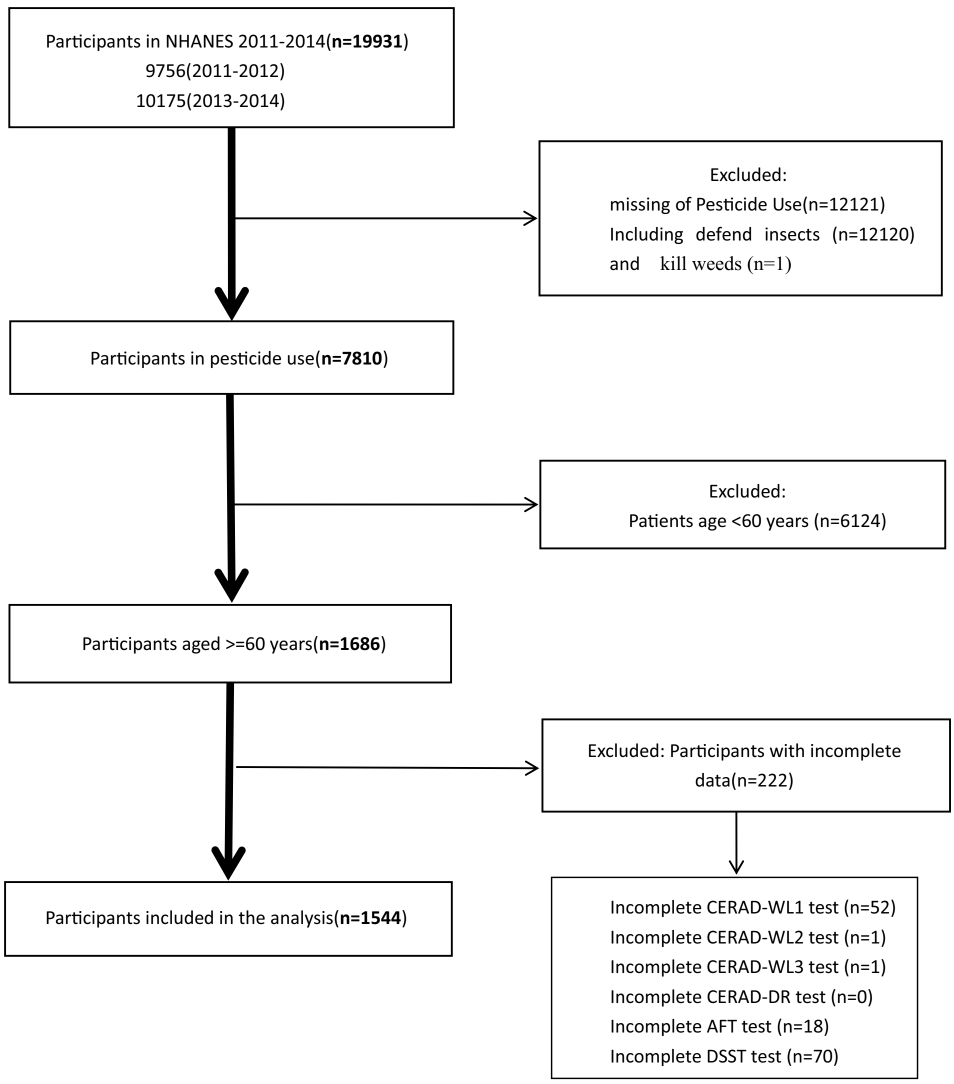

FIGURE 1
Flowchart of the sample selection from the National Health and Nutrition Examination Survey (NHANES).

TABLE 1 Demographic characteristics of participants in the National Health and Nutrition Examination Survey conducted in the US of the 2011–2012 and 2013–2014 cycles.

Characteristics (CERAD-WL)	Has used Pesticide (*N* = 217)		*p*- Value	Lacks used pesticide (*N* = 1,327)		*p*- value
	> = 17	<17		> = 17	<17	
Age (years) Age categories			**0.095**			**<0.001**
60–70	93 (60.39%)	28 (44.44%)		595 (57.27%)	109 (37.85%)	
70–80	40 (25.97%)	24 (38.10%)		304 (29.26%)	93 (32.29%)	
>80	21 (13.64%)	11 (17.46%)		140 (13.47%)	86 (29.86%)	
Gender *n* (%)			**0.006**			**<0.001**
Male	64 (41.56%)	39 (61.90%)		470 (45.24%)	169 (58.68%)	
Female	90 (58.44%)	24 (38.10%)		569 (54.76%)	119 (41.32%)	
Race			**0.232**			**0.054**
Mexican American	26 (16.88%)	7 (11.11%)		119 (41.32%)	39 (13.54%)	
Other Hispanic	23 (14.94%)	9 (14.29%)		74 (7.12%)	29 (10.07%)	
Non-Hispanic White	64 (41.56%)	21 (33.33%)		564 (54.28%)	141 (48.96%)	
Non-Hispanic Black	36 (23.38%)	21 (33.33%)		204 (19.63%)	54 (18.75%)	
Other Race	5 (3.25%)	5 (7.94%)		105 (10.11%)	25 (8.68%)	
Education level			**0.021**			**<0.001**
Less than high school	18 (11.69%)	17 (26.98%)		60 (5.77%)	50 (17.36%)	
High school	69 (44.81%)	23 (36.51%)		369 (35.51%)	126 (43.75%)	
More than high school	67 (43.51%)	23 (36.51%)		609 (58.61%)	112 (38.89%)	
Married			**0.129**			**0.538**
Never married	12 (7.79%)	3 (4.76%)		52 (5.00%)	16 (5.56%)	
Married or living with a partner	84 (54.55%)	27 (42.86%)		634 (61.02%)	163 (56.60%)	
Widowed or divorced or separated	58 (37.66%)	33 (52.38%)		352 (33.88%)	109 (37.85%)	
Annual family income ($)			**0.066**			**<0.001**
<$20,000	41 (26.62%)	23 (36.51%)		200 (19.25%)	84 (29.17%)	
$20,000 to <$45,000	51 (33.12%)	17 (26.98%)		338 (32.53%)	100 (34.72%)	
$45,000 to <$75,000	28 (18.18%)	8 (12.70%)		200 (19.25%)	43 (14.93%)	
≥$75,000	29 (18.83%)	8 (12.70%)		258 (24.83%)	46 (15.97%)	
Missing	5 (3.25%)	7 (11.11%)		43 (4.14%)	15 (5.21%)	
Poverty income ratio (%)			**0.163**			**0.001**
<5	131 (85.06%)	58 (92.06%)		826 (79.50%)	253 (87.85%)	
> = 5	23 (14.94%)	5 (7.94%)		213 (20.50%)	35 (12.15%)	
Smoking status			**0.977**			**0.731**
Yes	81 (52.60%)	33 (52.38%)		525 (50.53%)	140 (48.61%)	
No	73 (47.40%)	30 (47.62%)		513 (49.37%)	148 (51.39%)	
Alcohol consumption			**0.312**			**0.102**
Yes	100 (64.94%)	42 (66.67%)		722 (69.49%)	187 (64.93%)	
No	53 (34.42%)	19 (30.16%)		314 (30.22%)	98 (34.03%)	
Missing	1 (0.65%)	2 (3.17%)		3 (0.29%)	3 (1.04%)	
Body mass weight (kg/m^2)			**0.883**			**0.018**
Normal weight (<25)	38 (24.68%)	17 (26.98%)		272 (26.18%)	78 (27.08%)	

(Continued)

TABLE 1 (Continued)

Characteristics (CERAD-WL)	Has used Pesticide (*N* = 217)		*p*- Value	Lacks used pesticide (*N* = 1,327)		*p*- value
	> = 17	<17		> = 17	<17	
Overweight (25 to <30)	62 (40.26%)	26 (41.27%)		365 (35.13%)	123 (42.71%)	
Obese (> = 30)	54 (35.06%)	20 (31.75%)		402 (38.69%)	87 (30.21%)	
Sleep Duration (hours)			**0.265**			**0.598**
<=10 (hours)	151 (98.05%)	63 (100.00%)		1,038 (99.90%)	288 (100.00%)	
>10 (hours)	3 (1.95%)	0 (0.00%)		1 (0.10%)	0 (0.00%)	
Hypertention			**0.806**			**0.318**
Yes	111 (72.08%)	45 (71.43%)		641 (61.69%)	188 (65.28%)	
No	42 (27.27%)	17 (26.98%)		397 (38.21%)	99 (34.38%)	
Diabetes history			**0.679**			**0.070**
Yes	40 (25.97%)	19 (30.16%)		286 (27.53%)	95 (32.99%)	
No	113 (73.38%)	44 (69.84%)		753 (72.47%)	193 (67.01%)	
Missing	1 (0.65%)	0 (0.00%)				
Heart failure			**0.506**			**0.012**
Yes	14 (9.09%)	4 (6.35%)		60 (5.77%)	31 (10.76%)	
No	140 (90.91%)	59 (93.65%)		976 (93.94%)	256 (88.89%)	
Stroke			**0.030**			**0.081**
Yes	10 (6.49%)	10 (15.87%)		60 (5.77%)	27 (9.38%)	
No	144 (93.51%)	53 (84.13%)		977 (94.03%)	260 (90.28%)	
Depression score			**0.314**			**0.010**
No depression	21 (13.64%)	12 (19.05%)		94 (9.05%)	41 (14.24%)	
Had depression	133 (86.36%)	51 (80.95%)		945 (90.95%)	247 (85.76%)	

Sum of weights = 1,544. The bold black font indicates the *p*-value.

other races (16%). Ninety point 5 % (90.5%) had at least a high school diploma. Regarding marital status, 5.4% were unmarried, 58.8% were married or cohabiting, and 35.8% were widowed, divorced, or separated.

Economically, 72.9% of the participants had incomes between $20,000 and $75,000, 22.5% earned under $20,000, and 82.1% lived below the poverty line. Lifestyle factors showed 50.4% as smokers and 68% as alcohol consumers. In terms of BMI categories, 26.2% were normal, 37.4% were overweight, and 36.4% were obese, with 99.7% reporting sleeping 10 h or less per day. Medically, 63.8% had hypertension, 28.5% had diabetes, 7% had heart disease, and 6.9% had a stroke. PHQ-9 scores indicated 89.1% with depressive symptoms (score ≥10).

Figure 2 is a dot plot to show the statistical significance (*p*-value) between different characteristics (Characteristics) and whether pesticides are used or not (Has used pesticide/Lacks used pesticide), which makes it easy to see the correlation between the data more clearly.

3.3 The association between insecticides exposure and increased cognitive function risk

Logistic regression analysis revealed significant associations between insecticides exposure and cognitive impairment in the unadjusted models. Pesticide use is divided into insecticides and herbicides. Model 1 was unadjusted, Model 2 adjusted for basic demographics, and Model 3 included a broader range of factors such as education, income, health behaviors, and medical history. However, after adjusting for sociodemographic and lifestyle variables, some of these associations were no longer statistically significant. The association was significant for CERAD-WL (unadjusted: 0.68, $p = 0.0174$; adjusted: 0.71, $p = 0.0466$) and CERAD-DR (unadjusted: 0.64, $p = 0.0060$; adjusted: 0.67, $p = 0.021$). DSST also showed a correlation with pesticide exposure (unadjusted: $p = 0.0214$). Herbicides had a notable association with ATF (unadjusted: 1.70, $p = 0.0093$; adjusted: 1.32, $p = 0.2181$). These findings suggest that there may be some association between insecticides exposure and increased risk of cognitive functioning (Table 2), but it is worth noting that the study only differentiated between pesticide use and has not yet considered in depth the differences in their chemical structure. So we analysed three of the more common urinary metabolites based on the data available inside the Nhanes database. As for pyrethroid insecticides and organophosphorus insecticides, which are the two most common types of insecticides, I chose the more representative ones, para-nitrophenol (PNP) and Trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (Trans-DCCA). For the sake of comprehensiveness of the article's findings, I also examined a herbicide, 2,4-dichlorophenoxyacetic acid (2,4-D) (Supplementary Tables 2–4). In addition, we did sensitivity analyses showing that even without some missing data, these results remain statistically significant and are unlikely to lose significance altogether due to missing data (Supplementary Table 1). Due to space limitations and the focus of this paper, the analysis of herbicide exposure

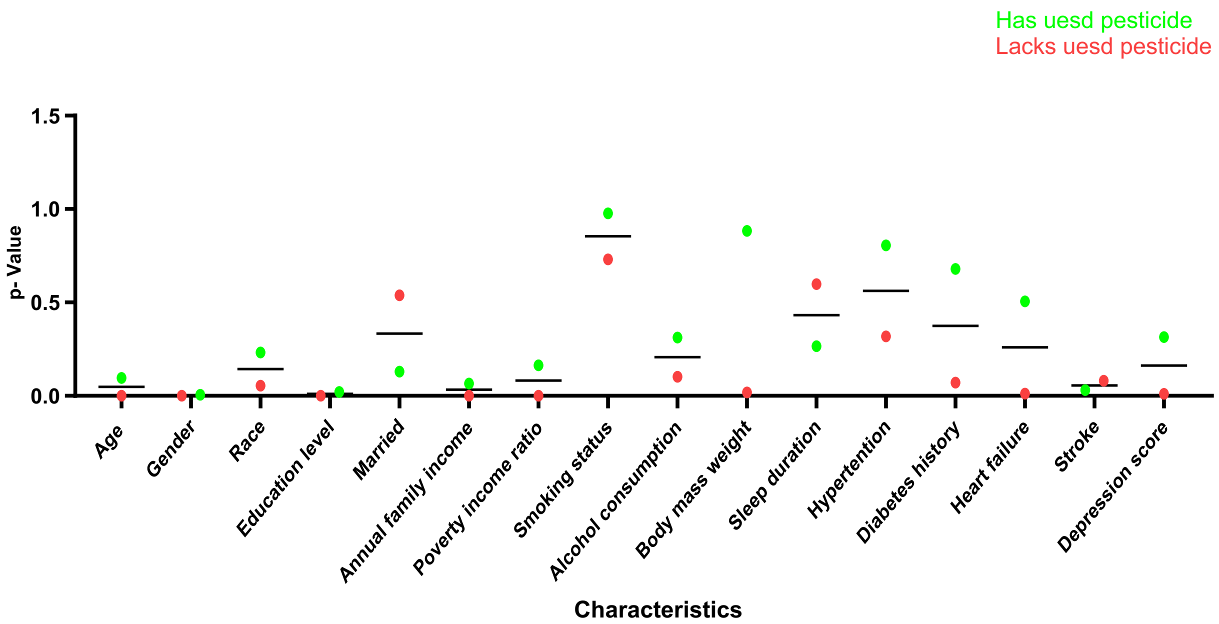

FIGURE 2
p-value dot plots of demographic characteristics of participants in the National Health and Nutrition Examination Survey conducted in the US of the 2011–2012 and 2013–2014. Sum of weights = 1,544.

is only presented in Table 2. The other tables in this study focus solely on the analysis of insecticide exposure. This selective presentation does not imply lesser importance of herbicides but rather a focused approach given the constraints of the study's scope and available data.

3.4 Associations between insecticides exposure and increased cognitive function risk and vulnerable subgroups

Subgroup analyses using eXtreme Statistical Software (XSS) investigated the interactions between cognitive function and various covariates, including age, gender, income, alcohol, BMI, and hypertension. The covariates were categorized according to the criteria outlined in Table 1. P-interaction values were used to assess the significance of these interactions on cognitive outcomes. For DSST, p-interactions were: age (0.785), gender (0.338), income (0.688), alcohol (0.925), BMI (0.125), and hypertension (0.453). For CERAD-WL, the corresponding values were: age (0.369), gender (0.398), income (0.298), alcohol (0.584), BMI (0.992), and hypertension (0.600). For AFT, p-interaction values were: age (0.518), gender (0.649), income (0.513), alcohol (0.872), BMI (0.253), and hypertension (0.986). The results indicate that the majority of covariates exhibit minimal interactive effects on cognitive outcomes, suggesting that they may not significantly influence cognitive performance in this study (Table 3).

4 Discussion

4.1 Summary of results

Our analysis of NHANES data from 2011 to 2014, involving 1,544 older adult participants, suggests an association between insecticides exposure and an increased risk of cognitive impairment, particularly in memory and delayed recall as measured by the CERAD-WL and CERAD-DR tests. However, after adjusting for sociodemographic and lifestyle variables, associations were no longer statistically significant. These findings indicate that the relationship between insecticides exposure and cognitive function may be influenced by various confounding factors and warrants further investigation.

4.2 Potential biological mechanisms between insecticides exposure and increased cognitive function risk

Exposure to insecticides is suspected to elevate the risk of cognitive dysfunction, yet the mechanisms remain not fully elucidated. Existing research suggests that short-term exposure to insecticides, regardless of the type of insecticide, can have long-term neurobehavioural effects in vertebrates (29) and insects (30) and cause a range of health problems (31). A mouse model of acute organophosphorus poisoning was constructed and showed lipid peroxidation, downregulation of antioxidant enzymes and astrocytosis in the hippocampus and prefrontal cortex, as well as altered dopamine levels, molecular and neurochemical changes that have been associated with long-term memory deficits (32). These compounds are known to inhibit acetylcholinesterase activity, resulting in abnormal accumulation of the neurotransmitter acetylcholine within the nervous system (33). Such accumulation may perturb normal neural transmission, consequently impairing cognitive function (34). In the context of aging, acetylcholine levels in the cerebral cortex diminish, a decline that serves as a critical biomarker for assessing brain health, particularly in conditions of dementia and end-stage (35). Additionally, insecticides are implicated in augmenting free radical production, which can induce oxidative stress damaging cell

TABLE 2 Multivariate logistic regression between include insecticides exposure and increased cognitive function risk in the National Health and Nutrition Examination Survey conducted in the US between 2011 and 2014.

	Model 1 OR (95%), *p*	Model 2 OR (95%), *p*	Model 3 OR (95%), *p*
CERAD-WL(<17)			
Defend insect			
Yes	1	1	1
No	0.68 (0.49, 0.93) **0.017**	0.71 (0.51, 0.99) **0.046**	0.80 (0.56, 1.15) **0.228**
Kill weeds			
Yes	1	1	1
No	1.01 (0.69, 1.50) **0.940**	1.14 (0.76, 1.72) **0.534**	0.91 (0.59, 1.40) **0.676**
CERAD-DR(<5)			
Defend insect			
Yes	1	1	1
No	0.64 (0.46, 0.88) **0.006**	0.67 (0.47, 0.94) **0.021**	0.72 (0.50, 1.03) **0.073**
Kill weeds			
Yes	1	1	1
No	1.15 (0.76, 1.74) **0.502**	1.35 (0.87, 2.09) **0.183**	1.10 (0.69, 1.74) **0.686**
ATF(<14)			
Defend insect			
Yes	1	1	1
No	0.80 (0.59, 1.09) **0.160**	0.89 (0.64, 1.23) **0.475**	1.10 (0.77, 1.56) **0.605**
Kill weeds			
Yes	1	1	1
No	1.70 (1.14, 2.53) **0.009**	1.62 (1.06, 2.46) **0.024**	1.32 (0.85, 2.06) **0.212**
DSST(<34)			
Defend insect			
Yes	1	1	1
No	0.69 (0.50, 0.94) **0.018**	0.87 (0.61, 1.22) **0.408**	1.26 (0.83, 1.91) **0.270**
Kill weeds			
Yes	1	1	1
No	1.33 (0.89, 2.00) **0.164**	1.32 (0.85, 2.05) **0.218**	0.82 (0.50, 1.33) **0.411**

Correlation coefficients of β (95%CI) *p*-value / OR (95%CI) *p*-value are used in the table Non-adjusted model adjust for: None; Adjust I model adjust for: AGE; GENDER; RACE; Adjust II model adjust for: ALCOHOL; BMI; GENDER; RACE; AGE; EDUCATION; MARRIED; ANNUAL.FAMILY.INCOME; POVERTY.INCOME.RATIO; PHQ; DMHISTORY; GENERAL.HEALTH. CONDITION; HEART.FAILURE; STROKE; HYPERTENSION; VIGOROUS.WORK.ACTIVITY; MODERATE. WORK.ACTIVITY; SLEEP.HOUR; SMOKING. The bold black font indicates the *p*-value.

membranes and DNA, thereby compromising neuronal health (36). Studies have found that chronic, low-dose exposure to certain insecticides can inhibit mitochondrial complex I and cytochrome oxidase in the brain. This inhibition increases the production of reactive oxygen species, which can disrupt the cell's antioxidant defense system. As a consequence, the release of cytochrome c from the mitochondria into the cytoplasm leads to apoptosis (37). There is also evidence that insecticides may activate microglia, initiating neuroinflammation, a process associated with the development of neurodegenerative diseases (38). Animal experiments have demonstrated that even low doses of certain insecticides can induce a pro-inflammatory state in the brain during subchronic exposure stages, and can enhance the neuroinflammatory response to lipopolysaccharide in a region-specific manner (39). These findings provide important biological insights into the mechanisms by which insecticides impact cognitive function and suggest potential directions for future research.

4.3 Analysis of subgroup results

Subgroup analysis revealed a striking phenomenon: exposure to insecticides significantly impacted the cognitive function of men aged 70 to 80 and individuals with an annual income between $20,000 and $45,000. This finding may be related to the natural increase in the risk of cognitive disorders in the 70 to 80 age group, especially in regions and populations more likely to be involved in the mixing and application of pesticides, thereby increasing exposure risk. But studies have confirmed that environmental toxins, including pesticides, have been identified as important contributors to cardiovascular and brain aging diseases. These toxic substances cause damage to the large blood vessels and microvessels, and many of them also cross the blood–brain barrier, inducing neurotoxic effects, neuroinflammation and neuronal dysfunction. In conclusion, environmental factors play a crucial role in regulating cardiovascular and cerebral aging (40). There was also a study comparing farmers exposed to pesticides with a control group

TABLE 3 Subgroup analyses of the association between insecticides exposure and increased cognitive function risk in the National Health and Nutrition Examination Survey conducted in the US between 2011 and 2014.

	DSST test (<34)		CERAD-WL (<17)		CERAD-DR (<5)		AFT (<14)	
	OR (95% CI)	*p*-interaction	OR (95% CI)	*p*-interaction	OR (95% CI)	*p*-interaction	OR (95% CI)	*p*-interaction
Age (years) Age categories		**0.785**		**0.369**		**0.292**		**0.518**
60–70	Reference		Reference		Reference		Reference	
70–80	16.13 (0.35, 745.84)		3.13 (0.09, 112.75)		3.48 (0.09, 139.53)		3.27 (0.11, 93.85)	
>80	170.10 (1.70, 17032.00)		14.36 (0.24, 863.12)		5.10 (0.09, 289.37)		179.77 (3.22, 10044.44)	
Gender *n* (%)		**0.338**		**0.298**		**0.702**		**0.649**
Male	Reference		Reference		Reference		Reference	
Female	0.59 (0.03, 13.24)		0.19 (0.01, 3.70)		0.31 (0.02, 5.88)		0.68 (0.05, 9.58)	
Annual family income ($)		**0.688**		**0.001**		**0.943**		**0.513**
<$20,000	Reference		Reference		Reference		Reference	
$20,000to < $45,000	1.18 (0.03, 48.51)		0.06 (0.00, 2.46)		0.31 (0.01, 13.62)		0.26 (0.01, 7.99)	
$45,000to < $75,000	–		0.05 (0.00, 9.31)		0.13 (0.00, 24.26)		0.27 (0.00, 27.37)	
≥$75,000	–		0.10 (0.00, 25.48)		1.79 (0.01, 383.12)		0.11 (0.00, 28.99)	
Alcohol		**0.925**		**0.584**		**0.459**		**0.872**
Yes	Reference		Reference		Reference		Reference	
No	0.10 (0.00, 2.58)		0.32 (0.02, 6.64)		3.60 (0.18, 72.39)		0.63 (0.04, 11.14)	
Body mass weight (kg/m^2)		**0.125**		**0.992**		**0.964**		**0.253**
Normalweigh (<25)	Reference		Reference		Reference		Reference	
Overweight (25 to <30)	0.06 (0.00, 3.43)		2.39 (0.07, 79.94)		3.21 (0.07, 148.29)		2.17 (0.07, 70.30)	
Obese (> = 30)	0.32 (0.00, 20.40)		1.70 (0.03, 83.30)		12.64 (0.21, 761.40)		5.14 (0.13, 208.44)	
Hypertension		**0.453**		**0.600**		**0.691**		**0.986**
Have hypertension	Reference		Reference		Reference		Reference	
Haven't hypertension	2.39 (0.08, 69.84)		0.57 (0.02, 14.14)		1.45 (0.06, 32.84)		0.58 (0.03, 10.06)	

The bold black font indicates the *p*-value.

not exposed to pesticides, and significant changes were found in the farmers' group: increased oxidative DNA damage, decreased acetylcholinesterase activity, and elevated levels of IL-10 and CRP (41). And it has been previously demonstrated that short-term exposure to organophosphorus pesticides results in cognitive damage (42) and central system disorders (43) in mice. Furthermore, individuals with an annual income between $20,000 and $45,000 may face more severe external environmental conditions, which could imply a higher likelihood of exposure to pesticides. Evidence shows that the risk of cognitive dysfunction is exacerbated in environments with high levels of insecticides exposure (44). Insecticides may damage cognitive function through mechanisms such as inducing oxidative stress, inflammatory responses, cholinergic neurotoxicity, and mitochondrial dysfunction (45). As age increases, these factors contribute to a higher incidence of cognitive disorders, particularly among men over 60, making it a significant health issue.

4.4 Analysis of specific urinary metabolites

To further explore the relationship between insecticide exposure and cognitive function, we analysed three specific urinary metabolites: trans-DCCA, PNP and 2,4-D. These metabolites correspond toorganophosphorus insecticides, pyrethroid insecticides and a herbicide, respectively. Our findings revealed differential associations between metabolite concentrations and cognitive function indices. Notably, the results of trans-DCCA demonstrated a statistically significant association with CERAD-WL scores (adjusted OR: 0.94, 95% CI: 0.90–0.99, $p = 0.018$), which further confirms the existence of a potential effect of insecticide exposure on cognitive function. The findings align with previous research, It has been shown that prenatal exposure to higher concentrations of trans-DCCA, a metabolite of pyrethroid insecticides, was significantly associated with a 2.24-point decrease in Mental Development Index (MDI) scores and a 1.90-point decrease in Psychomotor Development Index (PDI) scores in boys for every unit increase in first-trimester urine, suggesting that Trans-DCCA has a negative impact on children's cognitive and neurological development (46). Furthermore, prenatal exposure to pyrethroid insecticides may contribute to neurodevelopmental issues in children, particularly when maternal urine concentrations of trans-DCCA exceed detectable thresholds. Consequently, children are at an increased risk of developing symptoms consistent with ADHD, underscoring the potentially detrimental neurodevelopmental effects of trans-DCCA (47). These findings underscore the harmful implications of Trans-DCCA on neurological function. However, other indicators and metabolites in this study did not show statistically significant associations, which highlights the complexity of the relationship between specific insecticide metabolites and cognitive function, and requires more in-depth investigation in future studies.

4.5 Potential association between insecticides exposure and cognitive impairment: limitations in establishing dose–response relationships

Our study suggests a potential association between exposure to insecticides and cognitive impairment, aligning with existing evidence on pesticide neurotoxicity. The absence of exposure gradient data precludes a definitive dose–response assessment, posing a critical limitation for causal inference. Nevertheless, existing literature and biological plausibility provide a basis for suggesting that the dose–response relationship is a promising area for further investigation. For instance, a recent study suggests a significant association between pesticide exposure and cognitive impairment. Chronic exposure to chemical mixtures, including pesticides, is strongly associated with oxidative stress, inflammation and neurodegenerative diseases. Regardless of the dose, pesticide exposure may adversely affect cognitive function through mechanisms such as neuroinflammation and immune activation (48). In Akwesasne Mohawk older adults, high concentrations of PCBs, HCB and DDE were significantly associated with greater cognitive decline. In contrast, among older adults in NHANES, cognitive decline was primarily associated with exposure to highly chlorinated PCBs and DDE. Significant differences in the effects of various chemicals mixtures on cognitive function were observed, with higher the exposure doses correlating with a greater the risk of cognitive decline (49). It has also been shown that there is a significant U-shaped relationship between the exposure dose of 2,4-dichlorophenoxyacetic acid (2,4-D) and cognitive function in the older adult. Generalized linear models showed that high-dose exposure may negatively affect cognitive function. Furthermore, restricted cubic spline regression and generalized additive modelling further revealed a U-shaped relationship between 2,4-D exposure and cognitive function, suggesting that low and high-dose exposures may have different effects on cognitive function. This study highlights that appropriate control of the range of 2,4-D exposure is particularly important for cognitive function, especially among men (50). Because this paper examines chronic low-dose exposures in the home environment, there are a study in Spain showed a significant association between persistent organic pollutants (POPs) and cognitive decline in Hispanic/Latino adults. The study found that each doubling of plasma levels of polychlorinated biphenyls (PCBs) 146, 178, 194, 199/206, and 209 were associated with steeper global cognitive decline (51). There are also some studies suggesting that chronic low-dose exposure to these insecticides may result in neurobehavioural changes and alterations at the molecular level, suggesting potential neurotoxic risks to aquatic organisms (52) and humans (53). Although there is room for improvement in the detailed portrayal of the exposure gradient data in this study, the results of previous studies provide a solid foundation to support the potential link between exposure to insecticides and cognitive impairment observed in our study.

4.6 Strengths and limitations

This study has several important strengths: firstly, we employed three models: weighted multivariate logistic regression, study population description, and subgroup analysis, to comprehensively explore the complexity of how insecticides exposure affects cognitive function. Secondly, the use of the NHANES database, with its large sample size, rich scientific variables, and coverage of multi-stage complex studies, provided valuable data resources for this research (54). Additionally, this study included a variety of confounding variables based on existing research, significantly reducing potential biases from these factors.

However, this study also has some admitted limitations. Despite NHANES being an authoritative data source, it does not include all relevant variables that may affect the relationship between pesticide use and cognitive function. Therefore, while we adjusted for a range of sociodemographic and lifestyle variables, the possibility of residual confounding remains. Unmeasured confounders, such as occupational exposure, rurality, genetic predisposition, and detailed environmental factors, were not accounted for in our analysis. These factors could independently influence cognitive function and, if not adequately controlled, may lead to biased estimates of the association between insecticides exposure and cognitive impairment.

Furthermore, exposure assessment in our study relied on self-reported data regarding pesticide use in domestic, horticultural, and garden contexts. Self-reported data are prone to recall bias and may not accurately reflect actual exposure levels. For instance, participants may overestimate or underestimate their exposure, leading to non-differential misclassification. This type of misclassification tends to bias effect estimates toward the null, potentially masking true associations. Also, insecticides exposures are assessed primarily on the basis of a 7-day recall period, which may not adequately reflect cumulative or chronic exposures. This shorter recall period may be subject to recall bias, as participants may not accurately remember their exposure over a longer period of time.

In addition to this, our study conducted multiple statistical tests to evaluate the association between insecticides exposure and various cognitive outcomes. This approach increases the risk of alpha inflation, where the probability of obtaining a statistically significant result by chance alone (Type I error) is higher than the nominal alpha level (typically 0.05). Given the number of tests performed, some of our significant findings may be due to chance rather than true associations. Future studies should aim to assess cumulative insecticides exposure over an extended period to better capture the chronic nature of exposure.

5 Conclusion

Our findings suggest an association between insecticides exposure and an increased risk of cognitive impairment, particularly in memory and delayed recall as measured by the CERAD-WL and CERAD-DR tests. However, the confidence intervals for some associations were close to the null value, indicating weak evidence for a causal relationship. And it is the cross-sectional study design, we cannot infer causality from these findings. In addition, we need to consider the possibility of reverse causation, particularly due to the cross-sectional nature of the study. Reverse causation means that cognitive impairment may affect reporting or recall of pesticide exposure, rather than exposure causing cognitive impairment. For example, individuals with cognitive impairment may have a reduced ability to accurately recall or identify their pesticide exposure. This may lead to underreporting or overreporting of exposure, introducing bias into the analysis.

So future studies should employ longitudinal designs to assess the long-term effects of insecticides exposure on cognitive function. The use of biological markers, such as urinary metabolites of insecticides, can provide a more accurate exposure assessment. Additionally, advanced statistical methods, such as mediation analysis and structural equation modelling, should be applied to disentangle the complex relationships between exposure, confounders, and outcomes. Collecting detailed data on potential confounders, such as genetic predisposition, socioeconomic status, and lifestyle factors, will enhance the robustness of causal inferences.

In addition, we acknowledge that a limitation of our study is the exclusion of individuals below the age of 60. Early-onset dementia can develop in individuals over the age of 40, and including a younger age group could potentially reveal associations between pesticide exposure and the onset of dementia. Future research would benefit from including a broader range of ages to comprehensively evaluate the impact of pesticides on cognitive function across different age groups. Emphasizing early detection is crucial for effective disease management. Additionally, exploring the relationship between pesticide exposure and early-onset dementia could provide valuable insights for developing better prevention and intervention strategies.

In conclusion, while our study provides preliminary evidence of an association between insecticides exposure and cognitive impairment, further research is needed to establish causality and inform preventive strategies.

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 at: https://www.cdc.gov/nchs/nhanes/.

Ethics statement

The studies involving humans were approved by the Institutional Review Board review as it used de-identified, publicly available data. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MZ: Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Formal analysis. XG: Writing – review & editing, Conceptualization, Methodology, Data curation. YC: Writing – review & editing, Conceptualization, Methodology. XLU: Writing – review & editing, Supervision. XLN: Writing – review & editing, Methodology, Funding acquisition.

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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.

Generative AI statement

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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.2025.1556263/full#supplementary-material

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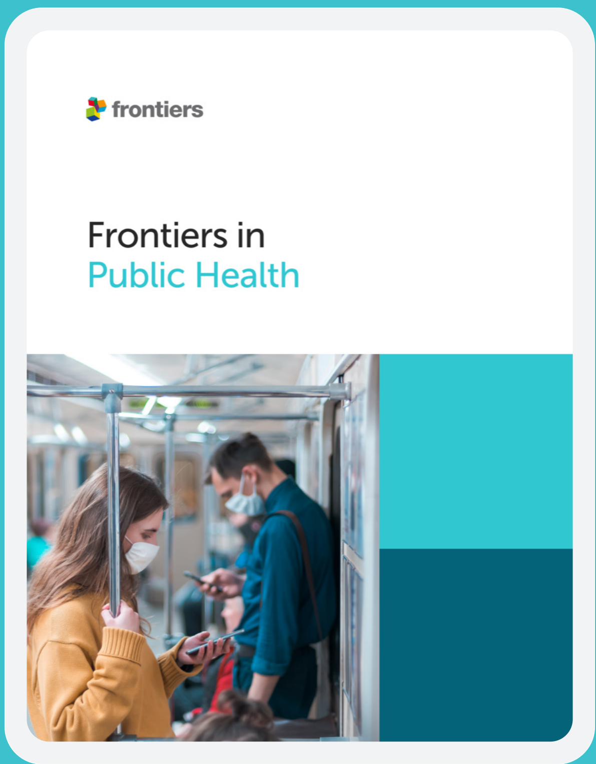

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