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Urban heat, air pollution, greenness and health

Edited by
Yunquan Zhang, Ruoyu Wang, Zhiming Yang
and Ang Li

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Urban heat, air pollution, greenness and health

Topic editors
Yunquan Zhang — Wuhan University of Science and Technology, China
Ruoyu Wang — University of Edinburgh, United Kingdom
Zhiming Yang — University of Science and Technology Beijing, China
Ang Li — Chinese Academy of Medical Sciences and Peking Union Medical College, China

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EDITED BY
Ang Li,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

REVIEWED BY
Junhua Han,
Chinese Nutrition Society, China
Fengqin Li,
China National Center for Food Safety Risk Assessment, China
Ronghua Zhang,
Zhejiang Center for Disease Control and Prevention (Zhejiang CDC), China

*CORRESPONDENCE
Min Yang
ymin36@zju.edu.cn
Yunfeng Zhao
yunfeng.zhao@zju.edu.cn

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Consumers' knowledge, attitude, and behavior towards antimicrobial resistance and antimicrobial use in food production in China

Qianyun Ding[1], Jiuzhi Gao[2], Xianfeng Ding[3], Dan Huang[4,5], Yunfeng Zhao[4,5]* and Min Yang[5,6]*

[1]Department of 'A', The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou, China, [2]National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention, Beijing, China, [3]College of Life Sciences and Medicine, Zhejiang Sci-Tech University, Hangzhou, China, [4]Department of Big Data in Health Science, School of Public Health, Zhejiang University School of Medicine, Hangzhou, China, [5]Center of Clinical Big Data and Analytics of the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, [6]Department of Nutrition and Food Hygiene, School of Public Health, Zhejiang University School of Medicine, Hangzhou, China

Background: Antimicrobial resistance (AMR) can be induced by overuse or misuse of antimicrobials. Few researches were involved in consumers' knowledge and attitude toward antimicrobial use (AMU) in food production. This study was designed to investigate the knowledge and awareness, perception, and attitude of Chinese consumers toward AMU in food production. Their behavior, purchase intention of antimicrobial-free food products, and confidence in information sources were also investigated.

Methods: As a descriptive cross-sectional study, an online electronic survey questionnaire was conducted between February 25 and March 8, 2022, involving 1,065 consumers in China. Factor analysis was conducted to identify underlying patterns of the attitudes and information sources. Spearman correlations were employed to determine the relationship between knowledge, attitudes and the intention to pay extra. The differences in knowledge and attitudes were performed by independent t-test and one-way analysis of variance (ANOVA) test, and the difference in intention was performed by Chi-square test, when compared with demographic factors.

Results: The findings showed that even though 75.0% of them heard of AMR, and 48.2% knew the definition of AMR, the level of consumers' knowledge of AMU in farming production and food regulations in China was not high (48.9% of participants replied correctly). About half viewed AMU and AMR as a potential risk to their health. Of these participants, 61.3% claimed that they were more likely looking for specific information about AMU on food packaging, and 58.3% changed their eating or cooking habits due to the concern. In addition, 79.8% were willing to pay extra for antimicrobial-free food products. Information sources from professionals and authorities were considered more accurate than those from media, the internet, word of mouth, and others.

Conclusions: Chinese consumers had insufficient knowledge and neutral attitudes about AMU in farming production and food regulations in China. A large proportion of the participants were willing to purchase antimicrobial-free food products. Most of them obtained related information from the media. This study highlighted the importance of updated education and effective communication with consumers in China. It helps to develop the reliable foodborne AMR surveillance system along food chain and improve government communication and consumer awareness.

KEYWORDS

antimicrobial resistance (AMR), antimicrobial use (AMU), food production, consumer, knowledge-attitude-behavior, China

Introduction

The emergence and spread of food pathogens resistant to antimicrobial drugs, especially those multi- and pan-drug resistant bacteria also known as "superbugs" has created alarming concerns over public health due to significant economic and health impacts (1). AMR is the resistance of a microorganism to an antimicrobial agents that it was previously sensitive to, resulting in medicines ineffective (2). AMR can be induced by overuse and misuse of antimicrobials in human medicine and agriculture or food animal production (3). AMR in human also develops due to the antibiotic residues in animal-derived foods as well as the transmission of resistant bacteria or genes from animals and the environment (4).

Since the 1940s, veterinarians and animal scientists have demonstrated that adding small amounts of antimicrobials (<200 g/ton feed) to feed or water could promote animal growth and higher feed conversion rates, reduce production diseases and improve food animal welfare, which had created a livestock production standard that has resulted in lower production costs and lower meat prices (5). In 2013, the global consumption of antimicrobials used in food-producing animals was around 13,000 tons per year for therapy, prophylaxis, and growth promotion (6), and are expected to be 104,079 tons by 2030 (7). It was equivalent to an estimated use of 100 milligrams of antimicrobials in the livestock for food production of every kilogram of meat for human consumption (8). Previous studies suggested that antimicrobials given in feed for livestock has a significant impact on human health (9, 10).

Association between interventions to reduce AMU in farm animals and decrease in the level of antimicrobial-resistant bacteria in livestock was identified (11). Owing to its importance in the food industry and the potential health risks to the public, AMU in food production has attracted a great deal of societal attention which led to government policy adjustments in recent years (12, 13). To curtail food risk in the spread of AMR via human consumption, it is critical to restrict the presence of AMR bacteria in livestock and animal-derived foods processing by regulations (14). Since 2006, countries such as European Union (EU) members, the United States, Australia, South Korea, and China have limited AMU as animal growth promoters. However, there is still a lack of legislative restrictions in many developing and even some developed countries (15, 16). As one of the largest consumer markets of veterinary antimicrobials, China released revised legislation to further ban AMU as growth promoters in 2019 (17). Starting from January 2020, the antimicrobials which have growth-promoting, prophylaxis, and therapy effects are not allowed in the application for growth-promotion but they can still be used for prophylaxis and therapy in China (18).

Consumers, as one of the important stakeholders, play a significant role in the food supply chain (19). It is imperative to take into consideration the views, concerns, and attitude of the public and consumers so that effective regulations can be elicited and developed to improve the monitoring and surveillance of the food production industry (20). Besides, consumer demand drives market needs for food products without AMU. Therefore, understanding concerns, preferences, and intentions of consumers is crucial for the food industry in the production of acceptable and healthy animal food products (21). In addition, investigation of consumers' willingness to pay extra for the quality as well as consumer concerns helps the development of effective foodborne AMR education systems and communication strategies. This will be ultimately beneficial to societal trust and confidence in the food industry (22).

A scientific report across the EU conducted by European Food Safety Authority (EFSA) showed that European consumers were aware of antimicrobials and AMR, however, the level of understanding of AMU in farming production was not high (23). Similarly, only a few Chilean consumers recognized that the antimicrobials had been widely used in animal farming, and how antimicrobial-resistant bacteria and AMR were transferred via food consumption (24). In some European countries and Canada, consumers also knew little about the farming production diseases (25) and how antimicrobials were being used in livestock production for therapy and prophylaxis use (26). Although the majority of consumers were concerned about AMU and AMR, they believed that AMU in livestock was indispensable as long as it was authorized by veterinarians for productivity, animal welfare, and food quality (27). They preferred that it was exclusively used for therapy, but not for prophylaxis, and assumed that treating healthy animals with antimicrobials might be one of the most important factors contributing to AMR (23). In addition, Chilean consumers recognized that the risk of other chemical residues in food might have a negative effect on their health, such as fertilizers and pesticides (24). This concern urged food companies to provide more information to the consumers about the drug residues in the food provided to the human table.

There were some differences in concerns and intentions regarding AMU in food animals from country to country. Most Chilean consumers considered AMU as a potential risk to their health, so they believed that it was a necessary practice to avoid AMU and were more likely to purchase antimicrobial-free products certified by trusted authorities (24). Nevertheless, Dutch consumers did not regard it as an important issue (27). Another survey conducted in the United States indicated that most consumers thought that animal-derived foods with antimicrobial treatment were safe to eat as long as they were authorized by the Food and Drug Administration (FDA). However, about one-third of consumers still would not purchase foods (28) for consumption if antimicrobials were used. The differences among countries may be related to the different levels of restriction and monitoring by governmental regulations as well as the degrees of policy education, consumer's awareness and knowledge.

As few studies focused on the investigation of consumers' knowledge, attitude, and behavior toward AMU in food production, and there were conflicts and gaps of information among previous studies, further research is needed to identify more convincing evidence and potential reasons contributed to this issue, especially after different levels of limitation were enforced due to changes in regulations. In China, as one of the largest consumer markets globally, research was not done on the Chinese consumers' knowledge, attitude, and behavior since China released the updated restriction on AMU in food production in 2019. This study aimed to investigate the knowledge and awareness, perception and attitude of Chinese consumers toward AMU in food production, and to evaluate their behavioral changes, purchase intention, and confidence in information sources of antimicrobial-free food products.

Methods

Survey design and data collection

The online survey questionnaire, consisted of seven sections and 28 questions (Supplementary Appendix), was improved and developed from the previous surveys (23, 29). It could be completed in about 10 minutes. The ethical approval for the survey was obtained from Ethics Committee of Zhejiang University School of Public Health, Reference number ZGL202201-4 Supplementary Image. The consent was obtained from each participant after being explained the aims of the study at the beginning of the survey questionnaire.

The survey was piloted in a sample of 15 participants to ensure that it was easy to understand in the Mandarin version and that there were no technical problems in consent instructions, order and category of questions, and response duration. Then the questionnaire was revised and finalized according to the suggestions before the formal data collection.

The online survey was conducted between February 25 and March 8, 2022. The questionnaire was distributed by Tencent Questionnaire and Wechat app as a web link to invite public consumers to participate in the survey. The minimum recommended sample size was 385 participants based on the standard formula for sample size calculation of simple random sampling, with a 5% margin of error, a confidence interval of 95%, and the current population in China. Given potential missing data, sample size was added by 20% extra to reach 481 samples. The survey was completed by 1065 respondents, which met the required number of samples.

Data analysis

Descriptive statistics included frequencies or percentages of categorical variables, and means ± standard deviations (SD) and 95% confidence interval (CI) of continuous variables. In terms of Shapiro-Wilk test, histogram, Q-Q plot, and the numbers of samples, all the continuous variables were considered as near normal distribution. Levene test was used to determine the homogeneity of variances. If variances showed heterogeneity, t-test was replaced by t'-test, and one-way analysis of variance (ANOVA) test was replaced by Welch test.

The differences in knowledge and awareness were performed by independent t-test when compared with "gender," and by ANOVA test and Bonferroni *post-hoc* test for other demographic groups. Factor analysis with Direct Oblimin rotation was conducted to identify underlying patterns of the attitudes. Initial eigenvalues were used to screen the number of factors. Kaiser-Meyer-Olkin (KMO) measure and Bartlett's test of Sphericity were used to verify the adequacy of factor analysis. The internal reliability of each scale was then tested to evaluate the contribution of each item to the factor with Cronbach's α coefficient. Spearman correlations between the identified scales were employed, to determine the relationship between the mean scores of attitudes. The differences in attitudes among demographic characteristics were also evaluated. Spearman correlations were employed to determine the relationship between the percentage of the intention to pay extra. The difference in intention was performed by Chi-square test for all demographic groups. Similarly, factor analysis with Direct Oblimin rotation was conducted to identify information sources. The confidence scales of information sources were constructed by computing the mean value of the loading items for each factor. Measure of sampling adequacy and internal reliability test were also performed. The dependence value of Cronbach's α coefficient was defined as acceptable when it was ≥0.70. $P < 0.05$ was considered statistically significant. Data analysis was conducted in IBM SPSS Statistics for Mac version 26 (IBM Corporation, Armonk, NY, USA). GraphPad Prism for Mac version 8.0 (GraphPad Software Inc., San Diego, CA, USA) was used to create charts.

Results

Demographic information

Demographic characteristics were presented (Supplementary Table 1), including gender, age, highest education level, work status, occupation, household income, the number of household adults and children, and place of residence. It showed that the majority of the participants were female (62.5%, 666/1,065), at the age of 18 to 40 years (60.7%, 646/1,065), with education degree of bachelor and higher (61.7%, 657/1,065), and employed full-time (57.9%, 617/1,065).

Knowledge and awareness of AMR and AMU in food production, and the current situation in China

General awareness of AMR or antibiotic resistance was high. Of respondents, 75.0% (799/1,065) claimed that they had heard of antibiotic resistance or AMR, 48.2% (513/1,065) knew what AMR was, 18.4% (196/1,065) felt that they did not know it, while 33.4% (356/1,065) were not sure about the definition of AMR.

However, the knowledge and awareness of AMR and AMU in food production was not high. Respondents gave 8.8±3.7 (95%CI 8.6–9.0) correct answers for 18 statements from Q9 to Q11, which meant that participants were able to reply correctly with 48.9% (8.8/18) on average to these statements (Figures 1A,C). For the general knowledge in Q9, the respondents gave 3.9 ± 2.0 (95%CI 3.8–4.0) correct answers for nine statements, i.e., 43.5% (3.9/9) on average of these statements. Most respondents correctly answered that antimicrobial agents could kill or inhibit the growth of bacteria (52.6%, 560/1,065) but not viruses (50.9%, 542/1,065). It was used to cure infections or preventing diseases in animals (62.1%, 661/1,065). A large majority of participants were aware that unnecessary use of the antimicrobials in animals made antimicrobials ineffective in the needed treatment of animal diseases (68.3%, 727/1,065), and humans will not be able to be cured if having AMR foodborne pathogens infected (63.0%, 671/1,065). Whereas, only a few respondents were aware that the antimicrobial could stimulate the growth of animals (34.9%, 372/1,065 assessed correctly); the antimicrobials were more often used to treat animals than humans (34.4%, 366/1,065 assessed correctly); the antimicrobials used on farm animals were usually the same with those used on humans (13.7%, 146/1,065 assessed correctly); if food-producing animals were treated with antimicrobials, antimicrobials were not always present in the meat, depending on the dosage (12.0%, 128/1,065 assessed correctly). Besides, participants were not highly aware of how resistant bacteria could be transferred from animals to humans in Q10. They gave 2.7±1.6 (95%CI 2.6–2.8) correct answers for 6 statements, i.e., 45.4% (2.7/6) on average of these statements. Most respondents correctly answered that antimicrobial-resistant bacteria could be transferred when eating rare or lightly cooked meat (69.5%, 740/1,065), as well as when drinking water tainted by animal excrement (68.5%, 730/1,065). Nearly half (41.7%, 444/1,065) of respondents were aware that antimicrobial-resistant bacteria could be transferred through consumption of food from soil that was fertilized with animal excrement. Nevertheless, they underestimated the risk of transfer from handling raw meat (21.5%, 229/1,065 replied correctly) and from contacting live farm animals (22.7%, 242/1,065 replied correctly). They were overly worried about the risk of eating well-cooked meat (48.5%, 517/1,065 replied correctly). In addition, as for the contribution of AMR in Q11, respondents gave 2.2 ± 1.3 (95%CI 2.1–2.2) correct answers for four statements, i.e., 54.0% (2.2/4) on average was correct for these statements. The majority of respondents knew that AMR could be induced by giving antimicrobials to healthy animals for disease prevention (62.4%, 665/1,065) and growth stimulation (63.9%, 681/1,065), and by treating unhealthy or weak animals without veterinary prescribed antimicrobials (57.2%, 609/1,065). While only 32.5% (346/1,065) correctly answered that treating sick animals with veterinary prescribed antimicrobials would not contribute to AMR under normal situations.

It was discovered that there was a significant difference in the knowledge between the education levels ($F = 16.3$, $P < 0.001$) (Supplementary Table 2). Those who had completed higher education, i.e., bachelor, postgraduate and higher degrees, were significantly more knowledgeable about AMR and AMU in food production, compared to other groups of respondents with junior high school or lower education (both $P < 0.001$), senior high school (both $P < 0.001$), and college (both $P < 0.001$). Participants in the "postgraduate and higher degrees"

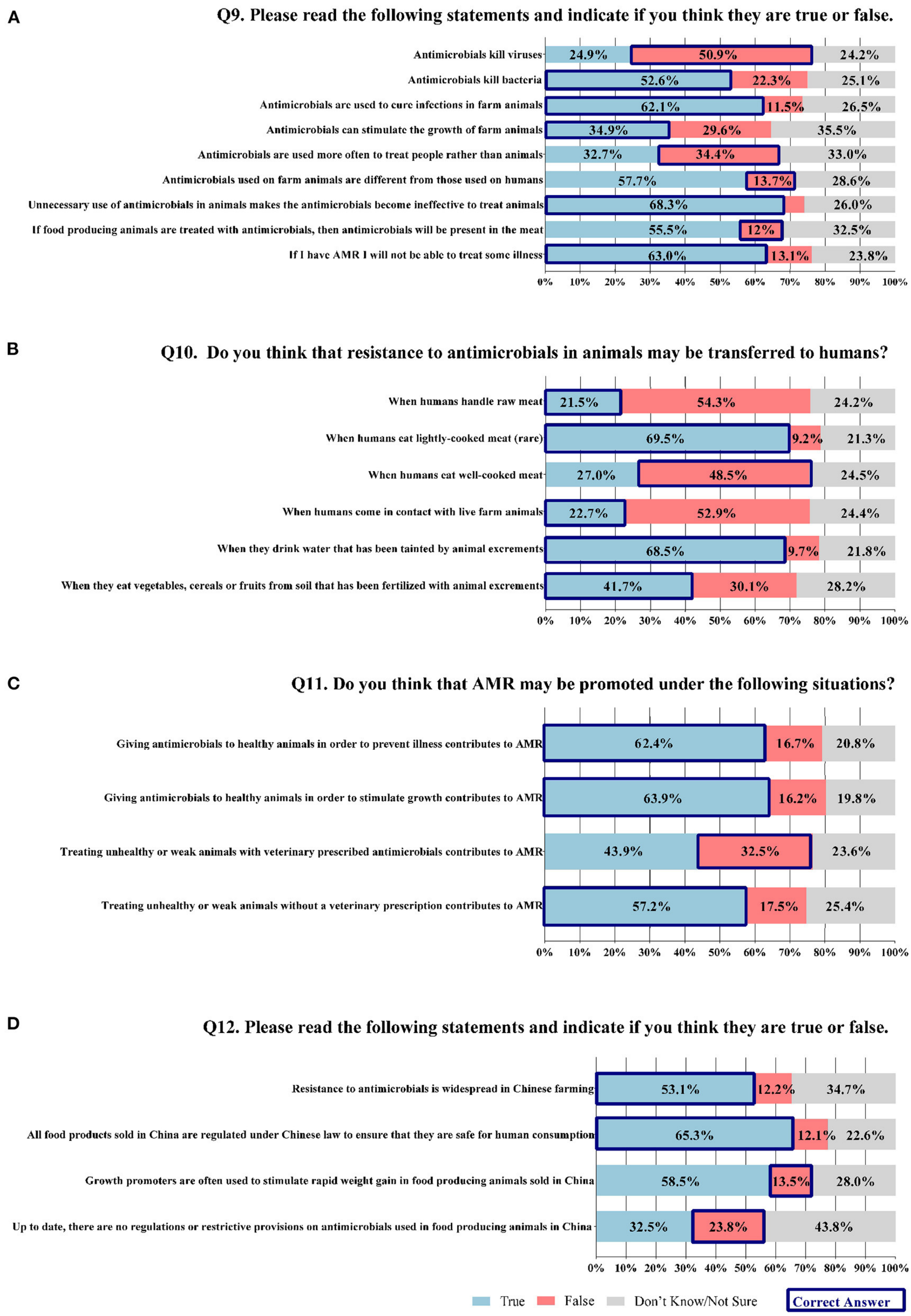


FIGURE 1
Consumers' knowledge and awareness of AMR and AMU in food production. (N=1065). **(A)** Q9: 9 questions investigating general knowledge of AMR and AMU in food production. **(B)** Q10: 6 questions assessing knowledge of how resistant bacteria transferred from animals to humans. **(C)** Q11: 4 questions measuring knowledge of how AMR may be promoted. **(D)** Q12: 4 questions evaluating knowledge and awareness of current situation in China.

group were also significantly more knowledgeable than those who were bachelors (P = 0.044). When compared with work status, those who were "employed full-time (≥30 h per week)" had significantly higher awareness than those who were "unemployed" (P= 0.008). In addition, there was a significant difference among multiple income groups. Those "prefer not to say" had lower knowledge level than respondents whose total income was "¥ 500,000–¥ 1,000,000 per annum" (P = 0.014). Those with total household income "¥ 200,000–¥ 500,000 per annum" had higher awareness of AMR and AMU in food production, compared to respondents with household income "under ¥ 50,000 per annum" (P < 0.001), and "¥ 50,000–¥ 100,000 per annum" group (P = 0.007). There was no statistically significant difference in comparisons among "gender," "age," "household adults" and "household children" (all P > 0.05).

Knowledge and awareness of current situations of AMU in food production in China were also low. Respondents gave 1.6±1.0 (95%CI 1.5–1.6) correct answers for 4 statements, which meant that participants were able to answer correctly to 38.9% (1.6/4) on average of these statements (Figure 1D). Over half of the respondents were aware that AMR was widespread in Chinese farming (53.1%, 565/1,065), and all food products sold in China were regulated under Chinese law to ensure that they were safe for human consumption (65.3%, 695/1,065). Most of them had little knowledge of the current provisions on the restriction of antimicrobials used in farming and growth promotion (23.8%, 253/1,065, and 13.5%, 144/1,065 replied correctly). In addition, it was found that the awareness of AMU in China was significantly influenced by work status (F = 3.2, P = 0.007). The respondents who were employed full-time gave 1.6 ± 1.0 (95%CI 1.6-1.7) correct answers which was significantly higher than those who were retired, 1.2 ± 0.9 (95%CI 1.0-1.4), (P = 0.011). There was no significant difference among different groups of "gender," "age," "highest level of education," "household income", "household adults," and "household children" (all P > 0.05).

Perception and attitude toward AMR and AMU in food production, and the current situation in China

The percentage scores of participants for each statement were reported (Figure 2). Results revealed that 49.5% (527/1,065) of them were concerned that animal-derived food products they bought might contain antimicrobial residues, while 60.7% (646/1,065) thought that it might have an adverse impact on their health after consumption of food products containing antimicrobial residues. In addition, 43.7% (465/1,065) were worried that it might have an impact on human health after contact with live farm animals which already had AMR. As to the supervision and guidance measures in Chinese farming industry, 33.7% (359/1,065) of respondents considered that policies and actions taken to control or prevent the overuse of antimicrobials in food-producing animals were not sufficient.

The exploratory factor analysis of perception and attitude was yielded with a two-factor solution which explained 82.3% of the variance. Factor one consisted of three concern statements related to AMR and AMU in food production, which was renamed the scale of antimicrobial-use attitude. Factor two included one perception related to current situations of that in China, which was renamed the scale of China-situation attitude (Table 1). The internal consistency for factor one was estimated using Cronbach's α coefficient, which was α = 0.84. Scale scores and factor correlations (Mean ± SD, 95% CI) were presented (Table 2). There was a significant negative correlation between the two factors (r = −0.220, P < 0.01), meaning that the participants who were more concerned about the issue were less likely to perceive that insufficient measures were being taken to limit the overuse of antimicrobials.

In addition, it was found that the scales of antimicrobial-use attitude and China-situation attitude were affected by age (F = 9.2, P < 0.001) (Supplementary Table 3). The middle-aged respondents aged 31–40, 41–50, and 51–60 were more worried about AMU in food production than the younger respondents who were 18–30 years old (P < 0.001, P < 0.001, P = 0.038). Similarly, the younger respondents who were 18–30 years old perceived to a less extent that insufficient measures were being taken to control the overuse of antimicrobials, compared to those aged 41-50 (P < 0.001), and 51–60 (P < 0.001). Differences could also be observed among the household income groups both in the scales of antimicrobial-use attitude and China-situation attitude. For the scale of antimicrobial-use attitude, the respondents whose household income was "¥ 200,000–¥ 500,000 per annum" replied with higher concern than those with "under ¥ 50,000 per annum" (P = 0.026) and "¥ 100,000–¥ 200,000 per annum" (P = 0.033). For the scale of China-situation attitude, the respondents whose household income was "¥ 50,000–¥ 100,000 per annum" perceived to a less extent that insufficient measures were being taken to control the overuse of antimicrobials than the groups with household income at "¥ 200,000–¥ 500,000 per annum" (P = 0.003) and "¥ 500,000–¥ 1,000,000 per annum" (P = 0.015). Similarly, the respondents whose household income was "not stable/not sure" perceived to a less degree that insufficient measures were being taken to control the overuse of antimicrobials than the groups "¥ 200,000–¥ 500,000 per annum" (P = 0.027) and "¥ 500,000–¥ 1,000,000 per annum" (P = 0.019). When compared with the work status, the participants who were students were less worried about AMU in food production than those who were employed full-time (P = 0.005). Likewise, students perceived less that insufficient measures were taken to control the overuse of

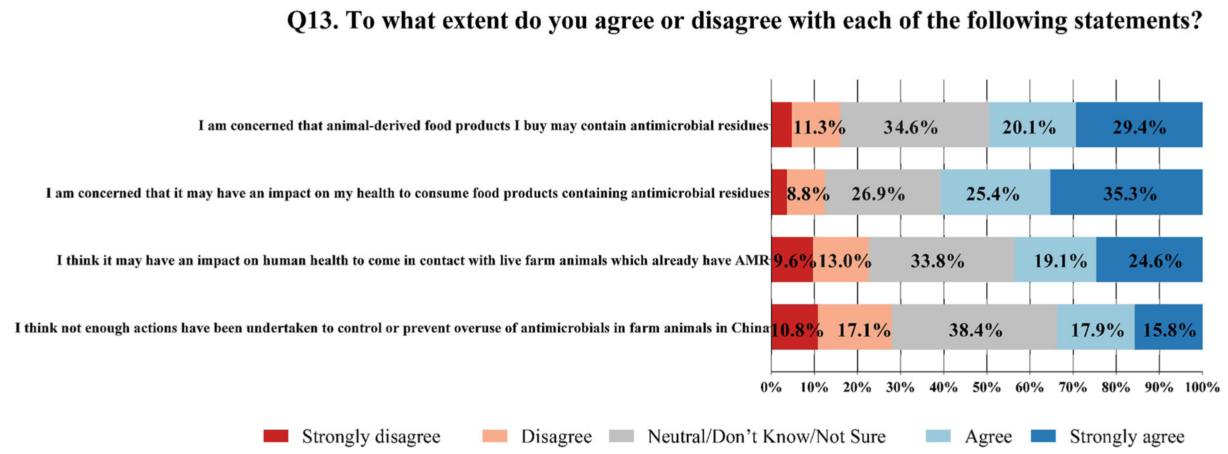


FIGURE 2
Consumers' perceptions and attitudes towards AMR and AMU in food production, and the current situation of that in China (N = 1065).

TABLE 1 The pattern matrix of exploratory factor analysis of perceptions and attitudes.

Statements of perceptions and attitudes	Factor 1	Factor 2
I am concerned that animal-derived food products I buy may contain antimicrobial residues	0.921	
I am concerned that it may have an impact on my health to consume food products containing antimicrobial residues	0.912	
I think it may have an impact on human health to come in contact with live farm animals which already have AMR	0.743	
I think not enough actions have been undertaken to control or prevent the overuse of antimicrobials in farm animals in China		0.982

Principal component analysis was used as the extraction method and Oblimin with Kaiser Normalization as the rotation method. Factor loadings <0.30 were suppressed and not presented in the table. KMO measure of sampling adequacy = 0.679, Bartlett's test of Sphericity *P*-value <0.001.

TABLE 2 Spearman correlation between knowledge, attitudes, and intentions.

Scale	Mean ± SD (95%CI) Or N (%)	Spearman correlation r_S				
		a	b	c	d	e
Antimicrobial-use knowledge[a]	8.8 ± 3.7(8.6–9.0)	1				
China-situation knowledge[b]	1.6 ± 1.0(1.5–1.6)	0.364**	1			
Antimicrobial-use attitude[c]	3.6 ± 1.0(3.5–3.6)	0.153**	0.061*	1		
China-situation attitude[d]	2.9 ± 1.2(2.8–3.0)	0.033	−0.103**	−0.220**	1	
Willingness to pay[e]	Yes: 850 (79.8%)	−0.166**	−0.125*	0.142**	0.049	1

[a]Sum score of the answers from Q9 to Q11 (0 = don't know/not sure, 0 = false answer, 1 = correct answer).
[b]Sum score of the answers in Q12 (0 = don't know/not sure, 0 = false answer, 1 = correct answer).
[c]Mean score of the first three statements in Q13 (1 = strongly disagree, 2=disagree, 3 = neutral/don't know/not sure, 4=agree, 5=strongly agree).
[d]Mean score of the fourth statement in Q13 (1 = strongly disagree, 2 = disagree, 3 = neutral/don't know/not sure, 4=agree, 5=strongly agree).
[e]Rank answer of Q15 respondence (1 = yes, 2 = no).
*$P < 0.05$, **$P < 0.01$.

antimicrobials than those who were retired ($P = 0.028$). When compared with the highest education level, the respondents who had completed postgraduate and higher degrees perceived to a higher extent that insufficient measures were taken to control the overuse of antimicrobials, compared to others who completed the education of senior high school ($P = 0.002$), college ($P < 0.001$), and bachelor ($P = 0.001$). However, there was no significant difference in comparison among "gender," "household adults," and "household children" for both the scales (all $P > 0.05$).

Behavioral changes due to the concern of AMR and AMU in farm animals

Of the participants, 61.3% (653/1,065) claimed that they were more likely to look for specific information about AMU on food packaging when they purchased food products, and 58.3% (621/1,065) changed their eating or cooking habits due to the concern of AMR and AMU in farming (Figure 3A). In addition, 41.0% (437/1,065) discussed AMR with their families or friends more often, 27.3% (291/1,065) changed their behavior such as using enhanced protective measures when contacting live food-producing animals, and 17.7% (189/1,065) talked to authorities or government about AMR, while 14.6% (155/1,065) answered that no actions were taken.

Willingness and intention to pay extra for antimicrobial-free food products

A large proportion (79.8%, 850/1,065) of the respondents were willing to pay a higher price for antimicrobial-free food products, whereas 20.2% (215/1,065) were not willing to pay extra. Most respondents viewed AMR and AMU as potential risks to their health, as the Spearman correlation showed a statistical significance in difference between the attitude and the willingness to pay ($r = 0.142$, $P < 0.01$) (Table 2). Among these 215 respondents, 62.3% (134/215) stated that the higher price was one of the barriers to purchasing antimicrobial-free products, and 41.9% (90/215) claimed that they were still concerned about the antimicrobial residues in the products (Figure 3B). Of 215 participants, 28.4% (61/215) thought that AMR might still be transferred to the public, and 16.7% (36/215) considered that the certified authorities could not be trusted. Nevertheless, only 16.7% (36/215) did not regard AMR as a potential risk to health.

It was discovered that there were significant differences in the willingness to pay compared among age ($\chi^2 = 32.9$, $P < 0.001$), work status ($\chi^2 = 21.8$, $P < 0.001$), and household income ($\chi^2 = 40.9$, $P < 0.001$) (Supplementary Table 4). For age groups, 86.1% (155/180) of 31–40 years old ($P = 0.001$), 89.0% (97/109) of 41–50 years old ($P = 0.001$), and 92.5% (74/80) of 51–60 years old ($P < 0.001$), were willing to pay higher prices for antimicrobial-free food products, all significantly >74.6% (482/646) of participants who were 18–30 years old willing to pay a higher price. When compared with the work status, 83.1% (513/617) of the full-time employed respondents showed the willingness to pay more for antimicrobial-free food products, while 71.1% (189/266) of the students showed willingness ($P < 0.001$). When compared with household income, 91.0% (152/167) of the subjects in the "¥ 200,000–¥ 500,000 per annum" group showed the willingness to pay more for antimicrobial-free food products, significantly >67.9% of the participants in the "under ¥ 50,000 per annum" group ($P < 0.001$), 79.4% (224/282) in the "under ¥ 50,000 per annum" group ($P = 0.001$), 73.3% (33/45) in the "Not stable/Not sure" group ($P = 0.002$), and 67.0% (63/94) in the "Prefer not to say" group ($P < 0.001$). Of the subjects, 84.0% (226/269) in the "¥ 100,000–¥ 200,000 per annum" group answered they were willing to pay, significantly more than 67.9% (93/137) in the "under ¥ 50,000 per annum" group and 67.0% (63/94) in the "Prefer not to say" group (both $P < 0.001$). However, there was no significant difference compared among "gender," "highest level of education," "household adults," and "household children" (all $P > 0.05$).

Communication and confidence in sources

The percentage score of participants for each information source were reported (Figure 4A). Most respondents obtained the information on AMR in farm animals from the media (49.6%, 528/1,065), followed by the Internet (47.0%, 501/1,065) and family and friends (42.0%, 447/1,065).

The exploratory factor analysis of information sources yielded a two-factor solution which explained 58.2% of the variance. Factor one consisted of seven sources, i.e., social media, Internet, media (newspaper, TV, radio), farmers, social training, food companies/supermarkets, family and friends, which was renamed as the scale of media, Internet, word of mouth, others. And factor two included five sources, i.e., scientists, health professionals/doctors, veterinarians, education from universities and academic institutions, and the national food safety agencies/governments, which was renamed as the scale of professionals and authorities. The internal consistency for each factor was assessed with Cronbach's α coefficient, whose α were 0.86 and 0.84, respectively for factor 1 and factor 2 (Table 3).

Not all sources were considered accurate information about AMR and AMU in food production. Mean±SD (95%CI) scale scores and factor correlations were presented (Table 4). Five out of twelve sources were deemed to be more accurate, while the other seven sources were perceived as being less accurate (Figure 4B) (Supplementary Table 5). In other words, sources from professionals and authorities were considered more accurate than that from media, the Internet, word of mouth, and others. However, there was a significant positive correlation between the two scales ($r = 0.494$, $P < 0.01$), indicating that those who were confident in the professional sources were also confident in the media sources and vice versa. The top three trusted sources were scientists (75.7%, 806/1,065 confident/strongly confident), health professionals/doctors (75.5%, 804/1,065), and national food safety agencies/governments (65.3%, 695/1,065), while

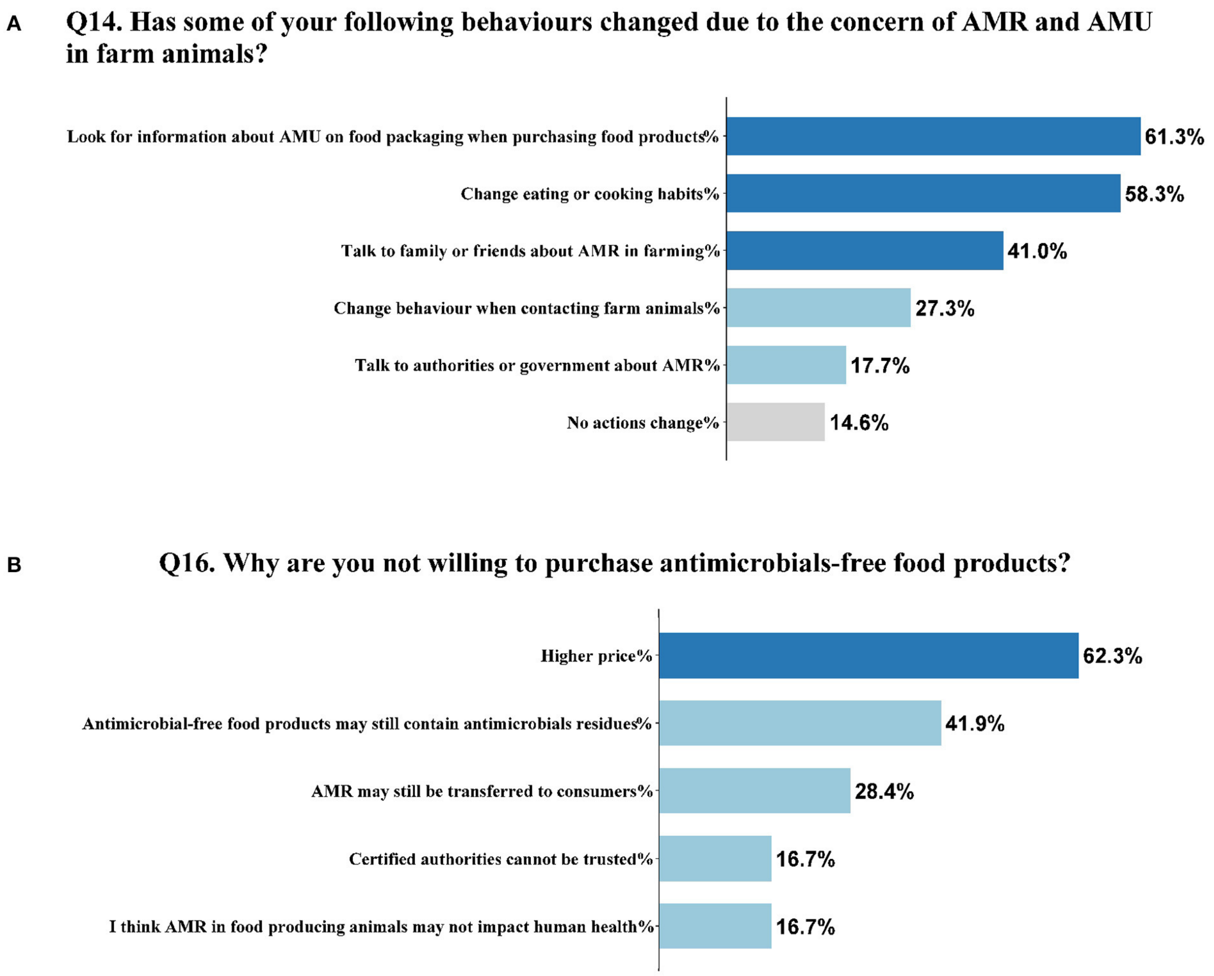


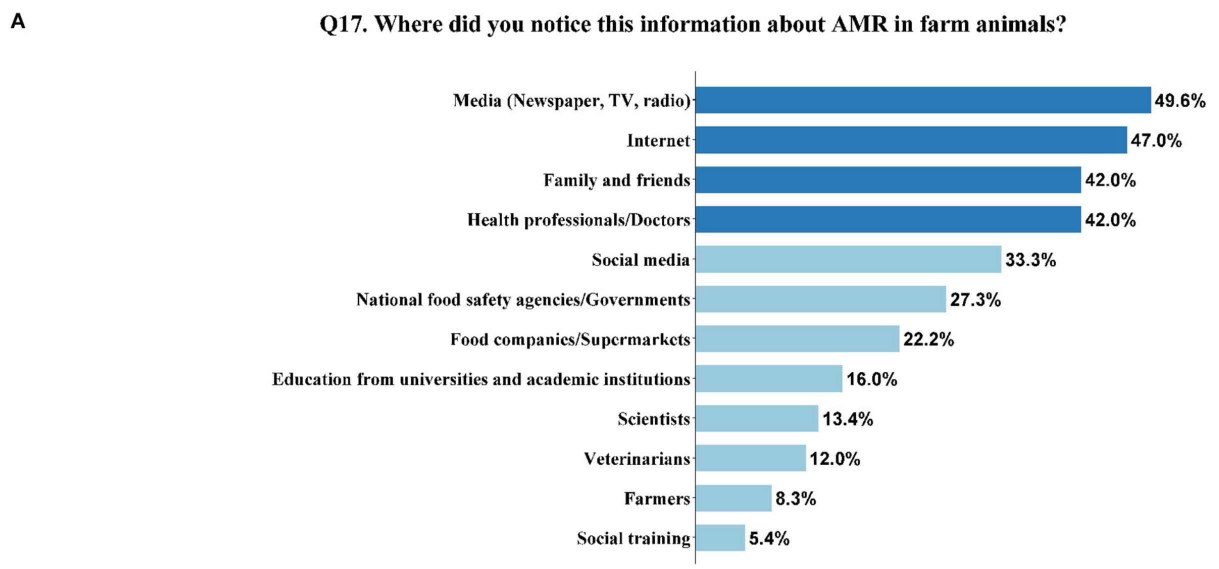
FIGURE 3
Behavioral changes, and the reasons why consumers were not willing to pay extra for antimicrobials-free food products. **(A)** Behavioral changes due to the concern of AMR and AMU in farm animals (N = 1065). **(B)** The reasons why consumers were not willing to pay extra for antimicrobials-free products (N =215).

the most untrusted sources were farmers (26.5%, 282/1,065 strongly unconfident/unconfident). However, 28.9% (308/1,065) of the respondents answered neutral/don't know/not sure about media, Internet, word of mouth, others, and it might be due to the lack of knowledge and awareness of this issue.

Discussion

In this study, consumers were clearly aware of AMR, however, the knowledge of AMU in farming production was not high, which matched the results in the surveys conducted in Europe and Chile (24). We also found that those who were employed full-time, who had completed higher education, and earned higher income, were more likely to be knowledgeable about AMR and AMU in food production. Similar results were published in a previous survey in EU countries (23). In addition, the participants were observed to have insufficient awareness in terms of the related food regulations in China. Although China has taken representative actions to minimize and contain foodborne AMR, e.g., released a national action plan in 2016 (30) and drafted several international regulations (31, 32), our study indicated that it was necessary for the authorized institutions to educate the public, especially those with low levels of education, to improve their awareness and understanding of AMU in food production and the government policy measures limiting the use of antimicrobials.

Previous studies indicated that there were some differences in general concern about AMU in livestock animals as a potential risk to public health from country to country. For instance, most Chilean consumers considered AMU as a potential risk to their health (24), while Dutch consumers did not regard it as an



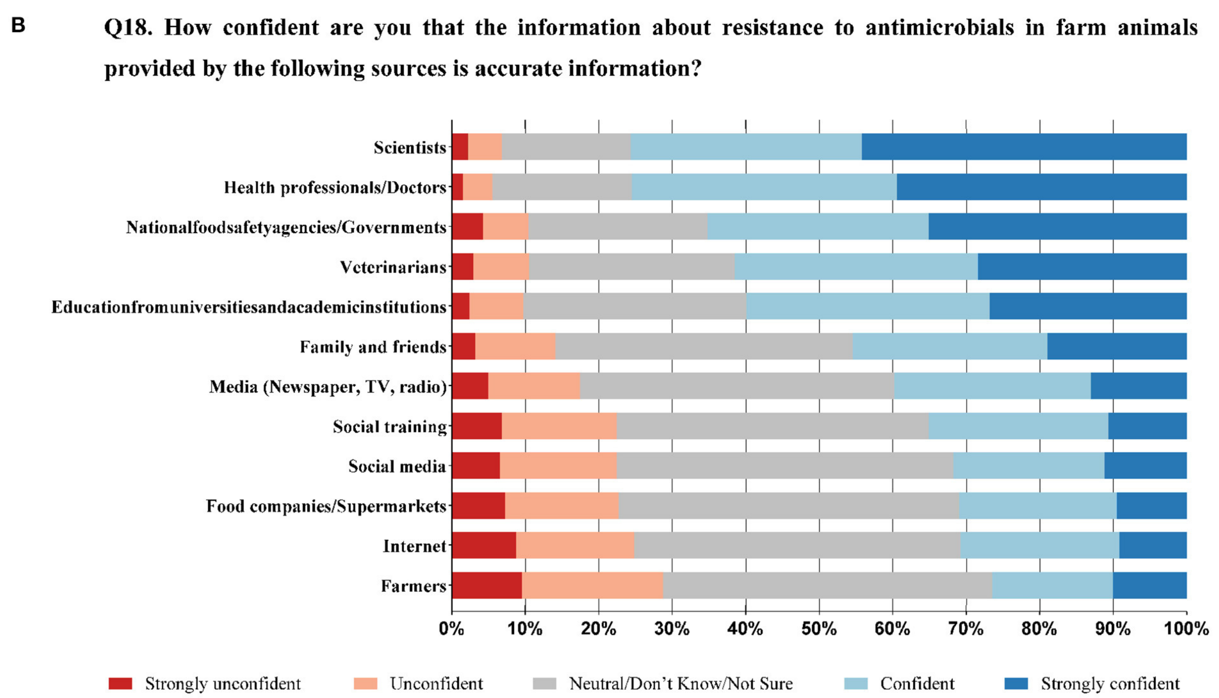


FIGURE 4
Information sources about AMR and AMU in farming **(A)**, and consumers' confidence in information sources **(B)** (N = 1065).

important issue (27). It may be related to the policy regulations and the extent of restrictions enforced by the government. In Netherlands AMU in farm production has been very limited, while Chile still lacks restrictions on this issue. In this study, almost half of the consumers viewed the issues of antimicrobial residues in food products and AMR from live farm animals in China as potential risks to human health. It was found that the middle-aged respondents were more worried about AMU in food production. This population also perceived more that insufficient measures were taken to control the overuse of antimicrobials compared to the young respondents. The respondents with higher income replied with higher concern and perceived more that insufficient measures were taken to control the overuse of antimicrobials than those with lower income. In addition, it suggested that the participants, who were less knowledgeable about AMR and food regulations, were

TABLE 3 The pattern matrix of exploratory factor analysis of information sources.

Information sources	Factor 1	Factor 2
Social media	0.865	0.144
Internet	0.832	0.044
Media (Newspaper, TV, radio)	0.794	0.246
Farmers	0.678	0.286
Social training	0.607	0.323
Food companies/Supermarkets	0.588	0.152
Family and friends	0.508	0.300
Scientists	0.082	0.828
Health professionals/Doctors	0.154	0.822
Veterinarians	0.208	0.723
Education from universities and academic institutions	0.298	0.687
National food safety agencies/Governments	0.346	0.673

Principal component analysis was used as the extraction method and Oblimin with Kaiser Normalization as the rotation method. KMO measure of sampling adequacy = 0.889, Bartlett's test of Sphericity *P*-value <0.001.

TABLE 4 Descriptive statistics (mean, standard deviation, and correlation coefficient) for each information source scale.

Scale	Mean ± SD (95%CI)	Spearman correlation r_S	
		a	b
Media, Internet, word of mouth, others[a]	3.2 ± 0.8 (3.1–3.2)	1	
Professionals and authorities[b]	3.9 ± 0.8 (3.9–4.0)	0.494**	1

[a]Mean score of the seven sources, i.e., social media, Internet, media (newspaper, TV, radio), farmers, social training, food companies/supermarkets, family and friends (1 = strongly unconfident, 2 = unconfident, 3 = neutral/don't know/not sure, 4 = confident, 5 = strongly confident).
[b]Mean score of the five sources, i.e., scientists, health professionals/doctors, veterinarians, education from universities and academic institutions, national food safety agencies/governments (1 = strongly disagree, 2 = disagree, 3 = neutral/don't know/not sure, 4 = agree, 5 = strongly agree).
$^{**}P < 0.01$.

less concerned and were less likely to perceive that insufficient measures were taken to limit the overuse of antimicrobials. As China released and enforced legislation limiting AMU only 2 years ago, it may explain insufficient awareness among the public and why they still hold high concerns toward current actions and measures of Chinese government.

In terms of the behavioral changes of consumers, it was discovered in this study that more than half of the participants claimed that they were more likely to look for specific information about AMU on food packaging when they purchased food products. They changed their eating or cooking habits due to the concern of AMR and AMU in farming. This should urge food companies to provide detailed information to the consumers about the antimicrobials and chemicals used during production and certify that drug residues are within policy and regulation limit.

It was identified in previous studies that consumers in the US, Canada, Germany, and Chile were willing to pay a higher price for food products free of antimicrobials, depending on their knowledge and attitude (24, 26, 33). We found that a large proportion of the respondents in China were willing to pay more for antimicrobial-free food products as well. It might be related to the facts that most respondents viewed AMR and AMU as potential risk to their health based on Spearman correlation. On the other hand, only a small part of the respondents were not willing to pay extra. This was mainly due to the higher price and ignorance of the possibility of antimicrobial residues in the products.

In terms of the research on risk communication from the perspective of authorities and food companies, there are three essential and necessary components when communicating information with consumers (34). First, communication must be rapid and accurate, which helps the public to understand well-about a newly released policy or changed regulations. Consumer research suggested that the public was delighted to be educated thoroughly and completely about food safety issues (24). Second, the administrative personnel of authority should be credible and reliable who makes the announcement. They must be independent without any interest in or relationship with the food companies or suppliers. This should increase the trust of consumers. Third, as for food companies, it is essential to evaluate the scientific correctness and effectiveness of food labels with timely updates. The majority of consumers have far less trust in the food industry and the media as reliable sources of information (23). They tended to have higher confidence in the veterinarians, scientists, and government authorities. They also believed that it was critical to get access to clear and reliable information from food providers which should display important information and health concerns on food labels. However, further studies are needed on whether consumer behavior would change even if the food label information is clear and effective (35).

With the aspect of communication and information sources, most respondents obtained information on AMR in farm animals from the media, followed by the Internet and family and friends in this survey although sources from professionals and authorities were considered more accurate. This result was similar to a previous report that the majority of consumers preferred scientists and food safety agencies as the more reliable sources of information compared to the food industry and the media (23). However, it indicated that those who were less confident in the professional sources were also less confident in the media sources and vice versa. It might be related to the lack of knowledge and awareness of this issue resulting in the overall low level of confidence.

This study was the first to investigate the knowledge, and attitudes of Chinese consumers toward AMU in food production, and evaluated their behavioral changes, purchase intention, and confidence in information sources of antimicrobial-free food products. However, it also had limitations. Given the survey method based on an online questionnaire, only participants with access to technology equipment were reached. Furthermore, the samples were imbalanced, e.g., most participants were 18 to 30 years old (60.7%), and 31.5% of respondents were from Zhejiang Province, therefore the answers may be geographically and demographically biased because the participants were not enough to be representative of Chinese consumers as a whole. Nonetheless, this study provides a valuable contribution to the exploratory investigation of knowledge, attitude, and behavior of Chinese consumers. Further research is needed to widen population representation.

Conclusions

This study demonstrated that most Chinese consumers were aware of AMR, however, the knowledge of AMU in farming production was not high. They were observed to have insufficient awareness in terms of the related food regulations in China as well. Almost half of the participants viewed the issues of antimicrobial residues in food products and AMR from live farm animals as potential risks to human health. More than half of the respondents claimed that they had been more likely to look for specific information about AMU on food packaging when they purchased food products, and had changed their eating or cooking habits due to the concern of AMR and AMU in farming. A large proportion of the participants were willing to pay a higher price for antimicrobial-free food products. Most of them obtained information on AMR and AMU in farm animals from the media, whereas information sources from professionals and authorities were considered more accurate and reliable than those from media, the Internet, word of mouth, and others.

The identified evidence in this research highlighted the importance of updated education for the public and effective communication with the consumers, which could help improve foodborne AMR surveillance system along food chain and communication strategies. However, this study was limited to a biased younger population in a more developed province, Zhejiang, in China. Further studies should expand to other populations and regions on AMR and AMU in food production.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Zhejiang University School of Public Health. The patients/participants provided their informed consent to participate in this study.

Author contributions

Study design: QD, XD, YZ, and MY. Collection of data: QD, JG, YZ, and MY. Analysis and interpretation of data: QD, DH, YZ, and MY. Drafting the manuscript: QD, YZ, and MY. All authors have read, revised, and approved the final version of the manuscript.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1015950/full#supplementary-material

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EDITED BY
Yunquan Zhang,
Wuhan University of Science and Technology, China

REVIEWED BY
Cheng-Yang Hu,
Anhui Medical University, China
Fang Fang Zeng,
Jinan University, China

*CORRESPONDENCE
Qun Xu
xuqun@ibms.cams.cn

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Residential greenness attenuated association of long-term air pollution exposure with elevated blood pressure: Findings from polluted areas in Northern China

Yayuan Mei[1,2], Jiaxin Zhao[1,2], Quan Zhou[1,2], Meiduo Zhao[1,2], Jing Xu[1,2], Yanbing Li[1,2], Kai Li[1,2] and Qun Xu[1,2]*

[1]Department of Epidemiology and Biostatistics, Institute of Basic Medical Sciences Chinese Academy of Medical Sciences, School of Basic Medicine Peking Union Medical College, Beijing, China, [2]Center of Environmental and Health Sciences, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

Background: Evidence on the hypertensive effects of long-term air pollutants exposure are mixed, and the joint hypertensive effects of air pollutants are also unclear. Sparse evidence exists regarding the modifying role of residential greenness in such effects.

Methods: A cross-sectional study was conducted in typically air-polluted areas in northern China. Particulate matter with diameter $<1\,\mu m$ (PM_1), particulate matter with diameter $<2.5\,\mu m$ ($PM_{2.5}$), particulate matter with diameter $<10\,\mu m$ (PM_{10}), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), and ozone (O_3) were predicted by space–time extremely randomized trees model. We used the Normalized Difference Vegetation Index (NDVI) to reflect residential green space. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were examined. We also calculated the pulse pressure (PP) and mean arterial pressure (MAP). Generalized additive model and quantile g-computation were, respectively, conducted to investigate individual and joint effects of air pollutants on blood pressure. Furthermore, beneficial effect of NDVI and its modification effect were explored.

Results: Long-term air pollutants exposure was associated with elevated DBP and MAP. Specifically, we found a 10-$\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, and SO_2 were associated with 2.36% (95% CI: 0.97, 3.76), 1.51% (95% CI: 0.70, 2.34), and 3.54% (95% CI: 1.55, 5.56) increase in DBP; a 10-$\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, and SO_2 were associated with 1.84% (95% CI: 0.74, 2.96), 1.17% (95% CI: 0.52, 1.83), and 2.43% (95% CI: 0.71, 4.18) increase in MAP. Air pollutants mixture (one quantile increase) was positively associated with increased values of DBP (8.22%, 95% CI: 5.49, 11.02) and MAP (4.15%, 95% CI: 2.05, 6.30), respectively. These identified harmful effect of air pollutants mainly occurred among these lived with low NDVI values. And participants aged ≥50 years were more susceptible to the harmful effect of $PM_{2.5}$ and PM_{10} compared to younger adults.

Conclusions: Our study indicated the harmful effect of long-term exposure to air pollutants and these effects may be modified by living within higher green space place. These evidence suggest increasing residential greenness and air pollution control may have simultaneous effect on decreasing the risk of hypertension.

KEYWORDS

air pollution, blood pressure, cross-sectional study, mixture, residential greenness

Introduction

High blood pressure has been reported to play a vital role in a broad spectrum of renal and cardiovascular disease (CVD) and is one of the leading causes for the global burden of disease (1, 2). High systolic blood pressure is also regarded as the top risk factors for CVD, especially for the Chinese population (3). In recent years, the blood pressure levels has been reported to have increased in developing country population, which may related to the life style shift and the irritation of environmental toxic factors (4).

Concurrently, air pollution is pointed to be the largest global environmental threat to human health (5). Mechanistic evidence shows that air pollution exposure may induce the production of pro-inflammatory mediators and oxidative stress products, cause autonomic nervous imbalance, lead to abnormal DNA methylation status, and trigger endothelial dysfunction (6–10), which are also the underlying pathophysiological pathways of hypertension. Therefore, air pollution has been speculated to contribute to the development of high blood pressure. In the past decades, studies have explored the association between air pollutants exposure and blood pressure indicators (11–15).

However, current evidence regarding the hypertensive effect of air pollutants are mixed with some found positive associations (11, 13), some reported non-significant associations (16), and others showed reversed results (14). For example, Du et al., conducted a study among 23,256 participants aged 18–74 years found that an interquartile range increase in $PM_{2.5}$ (16.1 $\mu g/m^3$) was associated with 0.49 mmHg (95% CI: 0.22, 0.77) increase in diastolic blood pressure (DBP) (13). While another study reported an inversed association between $PM_{2.5}$ exposure and DBP with effect estimate of −0.46 (95% CI: −0.68, −0.24) (14). Furthermore, previous study mainly focused on the effect of $PM_{2.5}$, PM_{10}, and NO_2 on blood pressure (5). Evidence on the hypertensive effects of long-term exposure to PM_1 and SO_2 are scarce. Moreover, in the real world scenario, people are simultaneously exposed to various air pollutants, which puts a need to explore the joint effect of the general air pollutants. However, the joint hypertensive effects of air pollutants mixture are currently lacked. Finally, most previous studies were conducted in developed counties or general areas (5). Studies conducted in typically air polluted areas were scarce (17). For example, the Beijing-Tianjin-Hebei (BTH) area in China, where air pollution has been increasingly severe associated with related industrialization and urbanization (18). According to the "2019 Bulletin on the State of China's Ecological Environment" (19), the annual average of $PM_{2.5}$, PM_{10}, O_3, SO_2, and NO_2 in 2019 were 57, 100, 196, 15, 40 $\mu g/m^3$, respectively, all of which (except SO_2) exceed the primary standard levels. Meanwhile, the BTH area has severe high hypertension prevalence. For example, the hypertension prevalence in Beijing (35.9%) ranked the top one province-level municipalities in China (20). Hebei also has a prevalence of hypertension with 23.3% higher than the nation level (23.2%) (20). Therefore, current research gap necessities a better understanding about the association between air pollutants exposure and blood pressure, particularly in typically air-polluted areas.

Previous studies have demonstrated the beneficial effect of residential greenness on human health such as birth outcomes (21), cardiovascular health (22), mental health (23) and so on. Recently, studies began to explore the potential benefits of residential greenness on hypertension risk and blood pressure (24, 25). However, existing evidence is limited. Moreover, few studies have explored the modifying role of residential greenness in the association between air pollutants and blood pressure. For example, study generally investigate the separate individual effect of air pollutants or greenness on blood pressure (16).

In this study, a cross-sectional design was adopted to investigate the individual and joint effect of long-term exposure to PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 on blood pressure indicators in two Chinese cities with serious air pollution situations and high hypertension burden. Furthermore, we explored the potential beneficial effect of residential greenness and its modifying role in the air pollutants-blood pressure associations.

Methods

Study design and populations

We collected data from two typically air polluted cities (Beijing and Baoding) located in the BTH region from the northern China. Briefly, a multistage, stratified cluster sampling method was adopted among general population in these two cities between 2018 and 2020. First, to maximize the inter-district gradients of air pollutants, we selected one or two districts within each functional zone through simple cluster sampling, and seven districts were included for further sampling. Second, at least one community from each district was selected on the basis of its surrounding contamination conditions, population stability, and local medical conditions. Third, all permanent residents who provided signed informed consent in these communities were selected as the study sample.

Inclusion criteria were those aged $\geq$ 18 years and living in their community for more than 5 years. Ineligible participants were those with cancer, major cardiovascular diseases, mental disorders, and pregnant women. Meanwhile, participants who could not provide necessary information were excluded. On enrollment, participants completed the survey by a team of professionals. Trained investigators collected information regarding demographic and lifestyle factors and disease status. Qualified physicians were responsible for collecting anthropometric measurements, and certified nurses collected blood samples. All the procedures were in accordance with the standard operating procedures. Participants provided written informed consent prior to study enrollment, and the Institutional Review Board of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences approved this study protocol (No. 029-2015).

Air pollutants assessment

Grid data on particulate matters (PM_1, $PM_{2.5}$, PM_{10}) with the spatial resolution of 1 × 1 km, and gaseous pollutants (NO_2, SO_2, and O_3) with the spatial resolution of 10 × 10 km in our study sites were obtained from the validated ChinaHighAirPollutants (CHAP) dataset, which was developed using machine learning prediction model (26–29). These data sets exhibited high predictive ability for daily measurements, with 10-fold cross-validation root-mean-square error (R^2) values of 14.6 $\mu g/m^3$ (0.77) for PM_1, 5.07 $\mu g/m^3$ (0.94) for $PM_{2.5}$, 24.28 $\mu g/m^3$ (0.86) for PM_{10}, 7.99 $\mu g/m^3$ (0.84) for NO_2, 10.07 $\mu g/m^3$ (0.84) for SO_2, and 17.10 $\mu g/m^3$ (0.87) for O_3. The 1-year average levels of PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3 before the baseline survey year for each participant were calculated on the basis of the geocode of their address to represent their long-term air pollutants exposure.

Residential greenness

We used the Normalized Difference Vegetation Index (NDVI) to reflect the residential surrounding greenness for each participant. NDVI has been widely adopted to investigate the health effects of greenness, with values ranged from −0.2 to +1.0 (30–32). The higher values represented greater vegetation greenness. NDVI is estimated using the land surface reflectance of the visible red (500–650 nm) and near infrared band (700–900 nm). In this study, we adopted the max value of NDVI during a year to indicate the long-term residential greenness exposure, which was obtained from the National Ecosystem Science Data Center, National Science & Technology Infrastructure of China (http://www.nesdc.org.cn) (33). 0.25 miles (about 400 m) has been proposed to be a suitable radius distance to estimate accessible greenness (31). Meanwhile, studies have widely adopted 500 m radius of greenness to explore the effects of greenness on human health (30–32). Therefore, we calculated the mean values of the max NDVI in 500 m circular buffer for participants. We assigned each participants' residential greenness exposure according to their residential location.

Outcome assessment and definition

We measured the blood pressure for each participant according to qualified SOPs. Participants were prohibited from exercising and were told not to consume tea, coffee, tobacco, and alcohol for 30 min before the examination. Briefly, blood pressure was measured with a calibrated mercury sphygmomanometer after a 15-min rest period by qualified physicians. A minimum of three measurements at intervals of >2 min were recorded until the difference between successive measurements was <5 mmHg. The mean values from the last two readings were calculated to determine systolic BP (SBP) and diastolic BP (DBP). Furthermore, we also calculated the pulse pressure (PP) and mean arterial pressure (MAP) using the following equation (34): $PP = SBP - DBP$; $MAP = [(2 \times DBP) + SBP]/3$.

Covariates

Standard questionnaires were used by trained investigators to collect the following covariates data information. Age and sex were extracted from their identification card. Age was treated as a continuous variable. Sex was regarded as a category variable (male/female). Educational attainment was classified as primary school or less, junior or senior high school, or college or higher. For cigarette use, participants were categorized into non-smokers, current smoker, and former smoker. Current smokers were defined as subjects who smoked at least one cigarette per day over the last 6 months; while participants who had ceased smoking more than 6 months prior were considered former smokers. For alcohol consumption, participants were divided into non-drinker, current drinker (who consumed alcohol at least once per week over the previous 6 months), and former drinker (who had ceased drinking more than 6 months prior). Height and weight were measured with participants wearing light clothing and no shoes. BMI was calculated as weight (kg) divided by height (m) squared. Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg or using antihypertensive agents (35), or have been previously diagnosed by doctor. Diabetes was defined as fasting blood glucose ≥7 mmol/L, or physician diagnosed history, or intake of any antidiabetic agents (36, 37). Dyslipidemia was defined as total cholesterol ≥6.22 mmol/L, triglyceride ≥2.26 mmol/L, high-density lipoprotein cholesterol ≤1.04 mmol/L, low-density lipoprotein cholesterol ≥4.1 mmol/L (38), or the use of any antihyperlipidemic agent. Due to the health effect of temperature and relative humidity (39), we also collected daily mean temperature and relative humidity data from the China Meteorological Data Network (http://data.cma.cn/).

Statistical analysis

Mean ± standard deviations (SD) and number (percentage) were presented to describe the continuous and categorical variables, respectively. Pair wise correlations between exposure variables were examined by the spearman's rank correlation test. We employed the generalized additive model to investigate the associations of air pollutants and NDVI with blood pressure indicators, which were log–transformed to increase their conformity to normal distributions of residuals. Percent changes in the outcomes were calculated with per 10 $\mu g/m^3$ and 0.1 unit increase in air pollutants and NDVI, respectively. The equation is $\left[\exp\left(\beta \times \textit{per increasement}\right) - 1\right] \times 100\%$, where the β is the effect estimate. We employed a progressive cofounder adjustment and thus constructed three models. Model 1: we adjusted the minimal adjustment covariates set identified by the direct acyclic graph (DAG) in case of multicollinearity and overadjustment (Figure 1). However, study proposed that covariates that can only influence the exposure or outcome, which cannot identified by DAG, should also be included in the model (40). For example, the BMI, smoking habit, drinking habit, diabetes history, hypertension history, and dyslipidemia history in our study. Moreover, some covariates such as BMI and disease history may act either as confounder, mediator, or collider. Therefore, we further constructed the Model 2 that added smoking and drinking habits based on Model 1. Model 3 (also the core model) was based on Model 2 and further adjusted BMI and disease history. Therefore, we controlled the following covariates in the core model, including age, sex, BMI, ethnicity, educational level, temperature, relative humidity, season, study district, month of blood sample collection, smoking status, drinking habits, and disease history of hypertension, dyslipidemia and diabetes. Air pollutant levels were separately incorporated as a linear term. Age, BMI, temperature, and relative humidity were controlled by smooth terms to account for their potentially nonlinear effects. The month of blood sample collection was included with a smooth term to control for nonmonotonic changes and secular trends in outcomes (41). The study districts were included with a random-effect term. In this study, we mainly focused on the results from the core model.

Quantile g-computation was adopted to explore the joint effect of air pollutants on each blood pressure indicator. The covariates in the quantile g-computation model were the same as the individual effect analysis. This kind of model can get effect estimate with one-quantile increases in the air pollutants mixture. It does not require all exposure variables in the mixture have the same effect direction with the outcome, and thus can capture the nonlinear, nonadditive effects of both individual and mixture of environmental pollutants (42). Meanwhile, this method has been widely used to explore the effects of air pollutants mixture on human health (42, 43). Furthermore, to evaluate the protective effect of residential greenness, we added the NDVI to the mixture model.

We performed stratified analysis by age (<50 or ≥ 50 years), sex (male or female), smoking status (yes or no), and drinking status (yes or no). The differences between strata were significant by calculating 95% CIs as follows:

$$(\beta_1 - \beta_2) \pm 1.96 \times \sqrt{SE_1{}^2 + SE_2{}^2}$$

where β_1 and β_2 are the effect estimates of each stratification and SE_1 and SE_2 are their corresponding standard errors, respectively (37). Furthermore, to test the potential modification effect of residential greenness, we further classified NDVI in to low NDVI group (smaller than median value) and high NDVI group (larger than median value) and further explore the effect of air pollutants on blood pressure. Then, a product interaction term between air pollutants and dichotomous terms for low and high NDVI were included in the model. *P*-values for the product terms were used to test differences association between each group (44).

Several sensitivity analyses were performed to evaluate the robustness of our results, including: (1) using 2-years and 5-years average concentration before the year of health examination as the long-term exposure metrics. Due to the data restriction of PM_1, we adopted the 4-year average levels for PM_1 in the 5-year sensitivity analysis; (2) excluding outliers defined as values out of four standard deviations (SDs) from the mean; (3) restricting analysis to participants without hypertension, diabetes, and dyslipidemia. All analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna Austria). A two sided *P*-value of <0.05 indicate statistical significance.

Results

Table 1 shows the demographic characteristics of the study participants. In this study, 4,235 participants were included in

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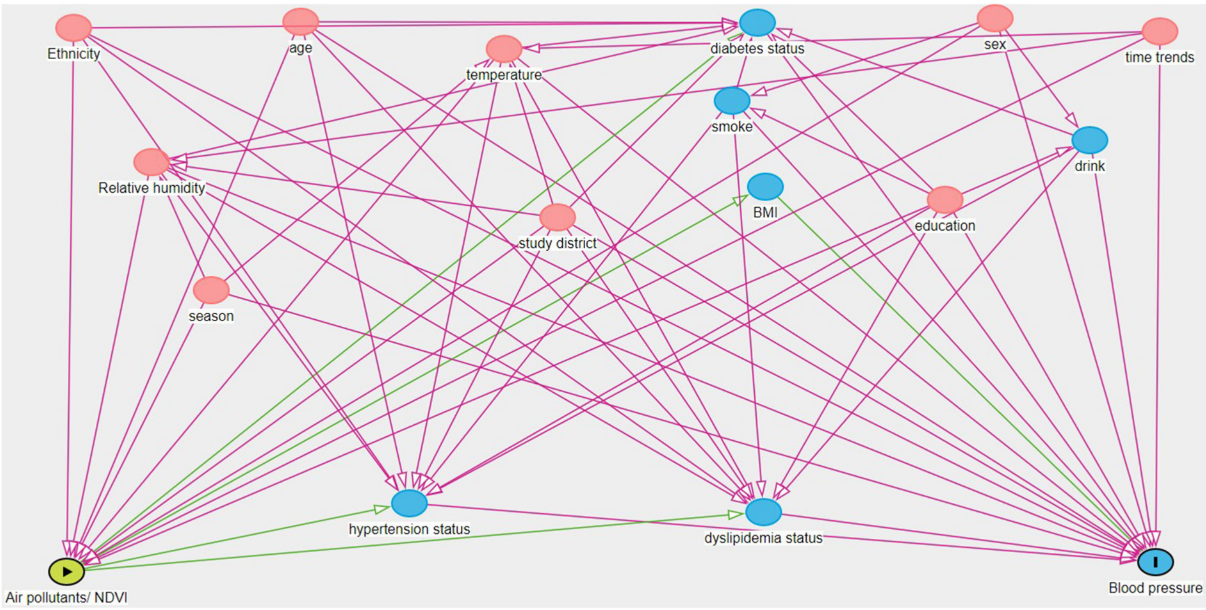

FIGURE 1
Directed acyclic graph (DAG) showing the relationship between exposure variable (the green oval with the triangle) and blood pressure (the blue oval with the line). Covariates with pink ovals are ancestors of exposure and outcome, while variables with blue ovals are ancestors only for the outcome. The minimum adjustment set include age, sex, ethnicity, education, temperature, relative humidity, season, study district, and time trends (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

our analysis. These participants have a mean (SD) age of 54.23 (14.66) years, and the number of men (49.68%) were generally comparable with the number of women (50.32%). About 45.88% of the participants had junior or senior high school educational level. The majority of participants were non-smoker (66.97%) and non-drinker (53.70%). The mean (SD) value of the blood pressure indicators were 134.41 (19.40) mmHg for SBP, 79.48 (11.19) mmHg for DBP, 97.79 (12.59) mmHg for MAP, 54.93 (15.07) mmHg for PP, respectively.

Table 2 presents the distribution of the long-term exposure to each air pollutant and residential greenness. The average (SD) levels of the 1-year exposure were 32.98 (9.51) $\mu g/m^3$ for PM_1, 51.77 (20.56) $\mu g/m^3$ for $PM_{2.5}$, 98.05 (28.02) $\mu g/m^3$ for PM_{10}, 39.08 (7.66) $\mu g/m^3$ for NO_2, 17.15 (7.31) $\mu g/m^3$ for SO_2, and 104.44 (5.50) $\mu g/m^3$ for O_3. The mean levels of particulate matters such as $PM_{2.5}$ and PM_{10} were much higher than the primary standard of annual average for China. O_3 concentrations were also much higher than the latest WHO guidelines. While, the 1-year average concentration of SO_2 and NO_2 did not exceed the Chinese standards.

Supplementary Figure S1 shows the spearman's correlation analysis. Pollutants were strongly correlated with each other correlation coefficients ranging from 0.85 to 0.99. While NDVI was weakly to moderately correlated with air pollutants with correlation coefficients ranging from 0.25 to 0.57.

Figure 2 shows the association between a 10-$\mu g/m^3$ increase in long-term air pollutants exposure and blood pressure indicators. We found that long-term air pollutants exposure was mainly associated with elevated values of DBP and MAP. To be more specific, we found that a 10-$\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, and SO_2 were associated with 2.36% (95% CI: 0.97, 3.76), 1.51% (95% CI: 0.70, 2.34), and 3.54% (95% CI: 1.55, 5.56) increase in DBP. A 10-$\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, and SO_2 were also found to be associated with 1.84% (95% CI: 0.74, 2.96), 1.17% (95% CI: 0.52, 1.83), and 2.43% (95% CI: 0.71, 4.18) increase in MAP. Results from the Model 1 and Model 2 were generally consistent with the results from the core model with similar effect estimate and direction (see Supplementary Table S1 for details).

Supplementary Figure S2 presents the results of the association between 0.1 unit increase in NDVI and blood pressure indicators. No significant associations were found between NDVI and blood pressure indicators. This is consistent with the results from the Model 1 and Model 2, which is presented in Supplementary Table S2.

Figure 3 shows the joint effects of air pollutants mixture on each blood pressure indicator. We found that air pollutants mixture was positively associated with increased values of DBP and MAP. Specifically, one quantile increase in the six air pollutants mixture was associated with 8.22% (95% CI: 5.49, 11.02) and 4.15% (95% CI: 2.05, 6.30) increase in DBP and MAP, respectively. Furthermore, we added the NDVI in the mixture model to test the potential protective effect. As shown in Figure 3, we can see that the effect estimate of air pollutants

TABLE 1 Characteristic information of the participants.

Variables	Mean ± SD or *n* (%)
Demographic characteristics	
No.	4,235
Age, years	54.23 ± 14.66
BMI, kg/m^2	25.30 ± 3.05
Sex	
Male	2,104 (49.68)
Female	2,131 (50.32)
Ethnicity	
Han	4,086 (96.48)
other	149 (3.52)
Education	
Primary school or below	998 (23.57)
Junior or senior high school	1,943 (45.88)
College or higher	1,294 (30.55)
Smoke	
Never	2,836 (66.97)
Current	1,063 (25.10)
Former	336 (7.93)
Drink	
Never	2,274 (53.70)
Current	1,780 (42.03)
Former	181 (4.27)
Hypertension	
Yes	2,074 (48.97)
No	2,161 (51.03)
Diabetes	
Yes	599 (14.14)
No	3,636 (85.86)
Dyslipidemia	
Yes	1,608 (37.97)
No	2,627 (62.03)
Meteorological factors	
Relative humidity (%)	64.77 ± 14.73
Temperature (°C)	20.56 ± 7.50
Blood pressure indicators	
SBP (mmHg)	134.41 ± 19.40
DBP (mmHg)	79.48 ± 11.19
MAP (mmHg)	97.79 ± 12.59
PP (mmHg)	54.93 ± 15.07

BMI, body mass index; SD, standard deviation. SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

mixture on each blood pressure indicator were all became smaller. For example, the effect of air pollutants mixture on MAP became nonsignificant (2.19%, 95% CI: −0.42, 4.88) after adding the NDVI in the model.

We also did stratified analysis by age, sex, smoking habits, and drinking habits (see Tables 3, 4; Supplementary Tables S3–S7 for details). We can see that the stratified results were consistent with the results form the core model. Take the effect of $PM_{2.5}$ and SO_2 for example, we can notice that significant results mainly appeared in DBP and MAP. After the subgroup significant test, we found participants aged ≥50 years are more susceptible to the harmful effect of $PM_{2.5}$ and PM_{10} compared to younger adults. For example, 10-µg/m^3 increase in $PM_{2.5}$ was associated with 0.61% (95% CI: −0.25, 1.47) increase among subjects aged <50 years and 3.09% (95% CI: 1.47, 4.73) increase among participants aged ≥50 years in DBP, respectively. Similarly, 10-µg/m^3 increase in $PM_{2.5}$ was associated with 0.51% (95% CI: 0.01, 1.00) increase among subjects aged <50 years and 2.37% (95% CI: 1.07, 3.68) increase among participants aged ≥50 years in MAP, respectively.

Although we did not find the individual significant protective effect of NDVI on blood pressure indicators, we observed a potential protective role of NDVI in the mixture model. Therefore, NDVI may be an important effect modifier for the air pollutant effect. Thus, we did stratified analysis by dividing the study population into NDVI high exposure group and NDVI low exposure group according to its median value. As shown in Figure 4, we can see that the effect of air pollutants on blood pressure main occurred in low NDVI exposure group. Supplementary Table S8 shows the *P*-values for the interaction term between air pollutants and dichotomous terms for NDVI. The results show that NDVI may interact with air pollutants. Combined with the results of stratified by low or high exposure of NDVI, we found that NDVI may have an interaction effect with $PM_{2.5}$ and SO_2 on the DBP, and with SO_2 on MAP.

Supplementary Figures S3–S6 shows results for the sensitive analysis. We can notice that our results generally remained robust in these sensitive analysis. For example, when we used the 2- and 5-year exposure windows, we observed long-term air pollutants exposure was mainly associated with elevated values of DBP and MAP, which is consistent with the results form the core model. We also found positive associations between long-term PM_1 exposure and increased levels of DBP and MAP in the 5-year sensitive analysis.

Discussion

Mian findings

In this study, we explored the individual and joint effect of air pollutants on blood pressure indicators. We observed positive associations of $PM_{2.5}$, PM_{10}, and SO_2 with DBP and MAP. The joint effect of air pollutants mixture were also on DBP and MAP. Meanwhile, participants aged ≥50 years were more susceptible to the harmful effect of $PM_{2.5}$ and PM_{10} compared to younger adults. Finally, NDVI modified these associations, thus suggesting a protective effect of residential greenness on the harmful air pollutants effects.

TABLE 2 Summary of the residential greenness and 1-year air pollutants exposure of the participants.

Exposure variables	Mean (SD)	Median (IQR)	China standard*	% of > China standard	WHO guideline#	% of > WHO guideline
Air pollutants						
PM_1, μg/m^3	32.98 ± 9.51	31.58 (23.14, 43.77)	None	None	None	None
$PM_{2.5}$, μg/m^3	51.77 ± 20.56	47.25 (31.64, 78.03)	15.00	100.00	5.00	100.00
PM_{10}, μg/m^3	98.05 ± 28.02	99.24 (73.77, 133.37)	40.00	100.00	15.00	100.00
NO_2, μg/m^3	39.08 ± 7.66	39.76 (31.61, 48.32)	40.00	49.99	10.00	100.00
SO_2, μg/m^3	17.15 ± 7.31	12.99 (11.49, 26.79)	20.00	36.32	None	None
O_3, μg/m^3	104.44 ± 5.50	103.25 (99.90, 111.12)	None	None	60.00	100.00
Residential greenness						
NDVI	0.42 ± 0.11	0.41 (0.35, 0.48)	None	None	None	None

SD, standard deviation; Min, minimum; Max, maximum. PM_1, particulate matter with a diameter of <1 μm; $PM_{2.5}$, fine particulate matter of <2.5 μm; PM_{10}, particulate matter with a diameter of <10 μm; NO_2, nitrogen dioxide; SO_2, sulfur dioxide; O_3, ozone; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. NDVI, Normalized Difference Vegetation Index.

*Primary standard levels for annual average proposed by China's Ministry of Ecology and Environment.

#Recommended air quality guideline for long-term standard levels (annual average for $PM_{2.5}$, PM_{10}, NO_2; peak season for O_3) by world health organization.

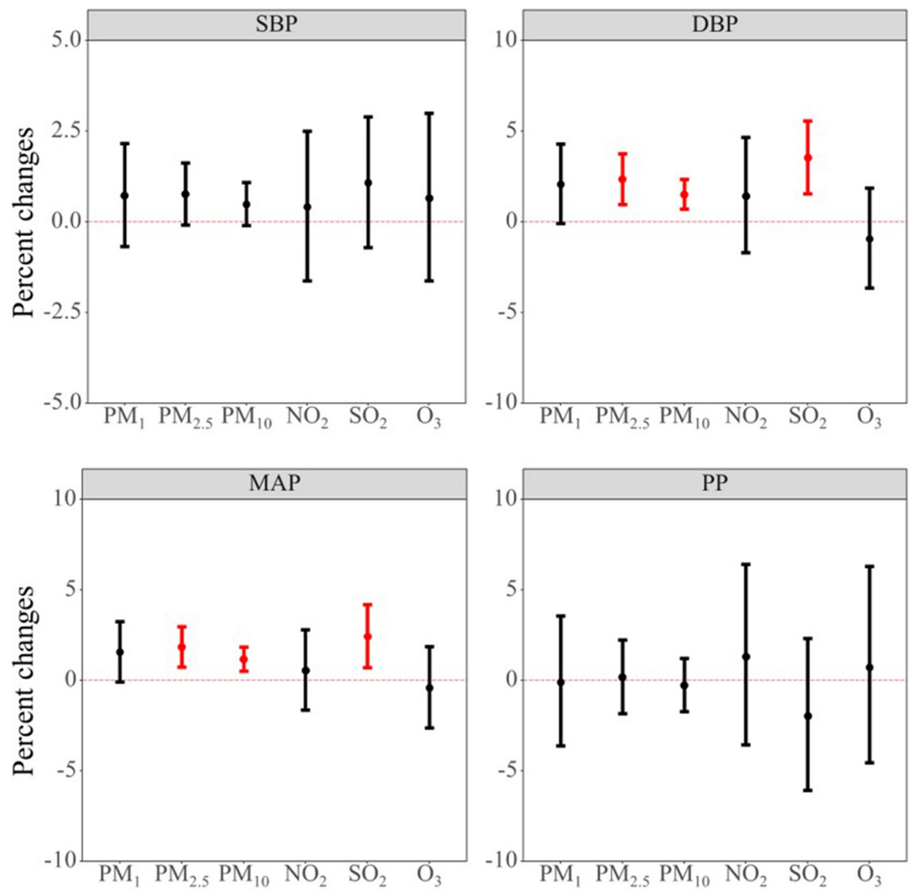

FIGURE 2
Associations between per 10-μg/m^3 increment in air pollutants and blood pressure indicators. Abbreviations: PM1, particulate matter with a diameter of <1 μm; $PM_{2.5}$, fine particulate matter of <2.5 μm; PM_{10}, particulate matter with a diameter of <10 μm; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; O_3, ozone; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

Compared with previous studies

SBP has been a better predictor for risk compared to DBP, and has become the most common form for hypertension given its nature of increasing with age and the aging societies (45). In our study, we found no significant associations between any air pollutants and SBP. Previous studies regarding the effect of long-term air pollutants exposure on SBP were mixed. For example, a cross-sectional study with 23,256 participants aged 18–74 years from communities in China found that an interquartile range increase in $PM_{2.5}$ (16.1 $\mu g/m^3$), PM_{10} (19.3 $\mu g/m^3$), NO_2 (19.8 $\mu g/m^3$), and SO_2 (3.9 $\mu g/m^3$) with associated with 1.86 mmHg (95% CI: 1.50, 2.22), 0.64 mmHg (95% CI: 0.26, 1.03), 0.57 mmHg (95% CI: 0.10, 1.05), and 1.74 mmHg (95% CI: 1.40, 2.09) changes in SBP, respectively (13). Another study conducted among 24,845 participants aged 18–74 years from 33 communities in China reported that a 10-$\mu g/m^3$ increase in PM_1 was associated with 0.57 mmHg (95% CI: 0.31, 0.83) increase in SBP (46). However, a study conducted among 1,432 participants aged 12 years reported no significant association between long-term air pollutants exposure and SBP (47). Similarly, a cross-sectional study in 27,752 residents aged > 65 years showed that none of the long-term air pollutants ($PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_x, NO_2) exposure were associated with SBP (48). The seemingly contrary results from these studies may come from the heterogeneity in study design, study population characteristics, long-term exposure window definition and so on. Nevertheless, results from a comprehensive meta-analysis regarding the global association between air pollution and blood pressure were consistent with ours. This meta-analysis indicated non-significant associations of long-term air pollutants ($PM_{2.5}$, PM_{10}, $PM_{2.5-10}$, NO_x, NO_2, O_3) exposure with SBP (5).

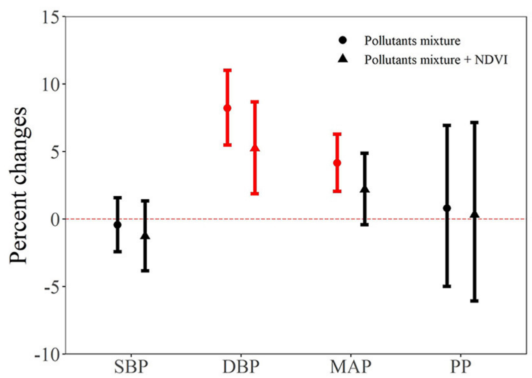

FIGURE 3
The joint effect of air pollutants on blood pressure indicators. NDVI, Normalized Difference Vegetation Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

DBP has traditionally been regarded as the most vital component of blood pressure and the primary aim of antihypertensive therapy (45). In our study, we found that a 10-$\mu g/m^3$ increase in long-term $PM_{2.5}$ and PM_{10} exposure were associated with 2.36% (95% CI: 0.97, 3.76) and 1.51% (95% CI: 0.70, 2.34) increase in DBP, respectively. Previous evidence were generally consistent with our findings. For example, a study conducted among 12,665 participants aged 50 years and older found that each 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated 1.04 mmHg (95% CI: 0.31, 1.78) changes in DBP (49). Another study also found such positive associations (50). Also, a study among 24,845 adults in 11 districts in China found that an interquartile

TABLE 3 Stratified analysis of the association between 10-$\mu g/m^3$ increase in $PM_{2.5}$ and blood pressure indicators by potential modifiers.

Stratification factors	**Percent changes (95% CI)**			
	SBP	**DBP**	**MAP**	**PP**
Age				
<50	0.43 (−0.09, 0.95)	0.61 (−0.25, 1.47)	**0.51 (0.01, 1.00)**	0.97 (−0.14, 2.08)
≥50	**1.11 (0.00, 2.22)**	**3.09 (1.47, 4.73)***	**2.37 (1.07, 3.68)***	−0.23 (−2.55, 2.15)
Sex				
Male	0.44 (−0.53, 1.41)	**1.76 (0.15, 3.40)**	1.06 (−0.04, 2.17)	−0.30 (−2.84, 2.31)
Female	0.41 (−0.55, 1.38)	**1.58 (0.08, 3.11)**	**1.37 (0.17, 2.58)**	0.41 (−1.64, 2.50)
Smoking				
No	0.58 (−0.37, 1.55)	**2.06 (0.61, 3.54)**	**1.83 (0.65, 3.03)**	0.23 (−1.61, 2.10)
Yes	0.52 (−0.30, 1.35)	1.19 (−0.44, 2.85)	0.75 (−0.23, 1.74)	0.17 (−2.18, 2.57)
Drinking				
No	0.57 (−0.34, 1.48)	**1.51 (0.06, 2.98)**	**1.25 (0.15, 2.36)**	0.67 (−1.22, 2.60)
Yes	0.59 (−0.51, 1.69)	1.28 (−0.15, 2.73)	1.06 (−0.13, 2.27)	−0.13 (−2.95, 2.76)

$PM_{2.5}$, fine particulate matter of <2.5 µm; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. The asterisk indicate there is significant difference between the subgroups; no asterisk indicate there is no significant difference between the subgroups. Bold values indicate the effect estimates were significant.

TABLE 4 Stratified analysis of the association between 10-μg/m^3 increase in SO_2 and blood pressure indicators by potential modifiers.

Stratification factors	Percent changes (95% CI)			
	SBP	DBP	MAP	PP
Age				
<50	1.36 (−0.31, 3.05)	**2.08 (0.19, 4.00)**	**1.83 (0.21, 3.48)**	2.09 (−1.39, 5.70)
≥50	1.72 (−0.5, 4.00)	**5.06 (2.54, 7.64)**	**3.64 (1.45, 5.88)**	−2.74 (−7.44, 2.19)
Sex				
Male	0.57 (−1.61, 2.80)	**3.18 (0.90, 5.51)**	**2.11 (0.19, 4.07)**	−3.98 (−9.15, 1.49)
Female	0.92 (−1.26, 3.16)	**3.23 (0.73, 5.80)**	**2.44 (0.27, 4.66)**	−0.41 (−5.09, 4.50)
Smoking				
No	0.97 (−1.08, 3.05)	**3.44 (1.27, 5.66)**	**2.48 (0.53, 4.46)**	−1.06 (−5.2, 3.26)
Yes	0.95 (−1.15, 3.10)	**3.35 (0.42, 6.37)**	2.11 (−0.04, 4.30)	−3.83 (−9.78, 2.50)
Drinking				
No	1.34 (−0.70, 3.44)	**3.35 (0.95, 5.80)**	**2.53 (0.54, 4.55)**	−0.54 (−5.08, 4.22)
Yes	0.27 (−2.24, 2.83)	**2.57 (0.14, 5.07)**	1.68 (−0.49, 3.90)	−3.71 (−9.37, 2.31)

SO_2, sulfur dioxide; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure. The asterisk indicate there is significant difference between the subgroups; no asterisk indicate there is no significant difference between the subgroups. Bold values indicate the effect estimates were significant.

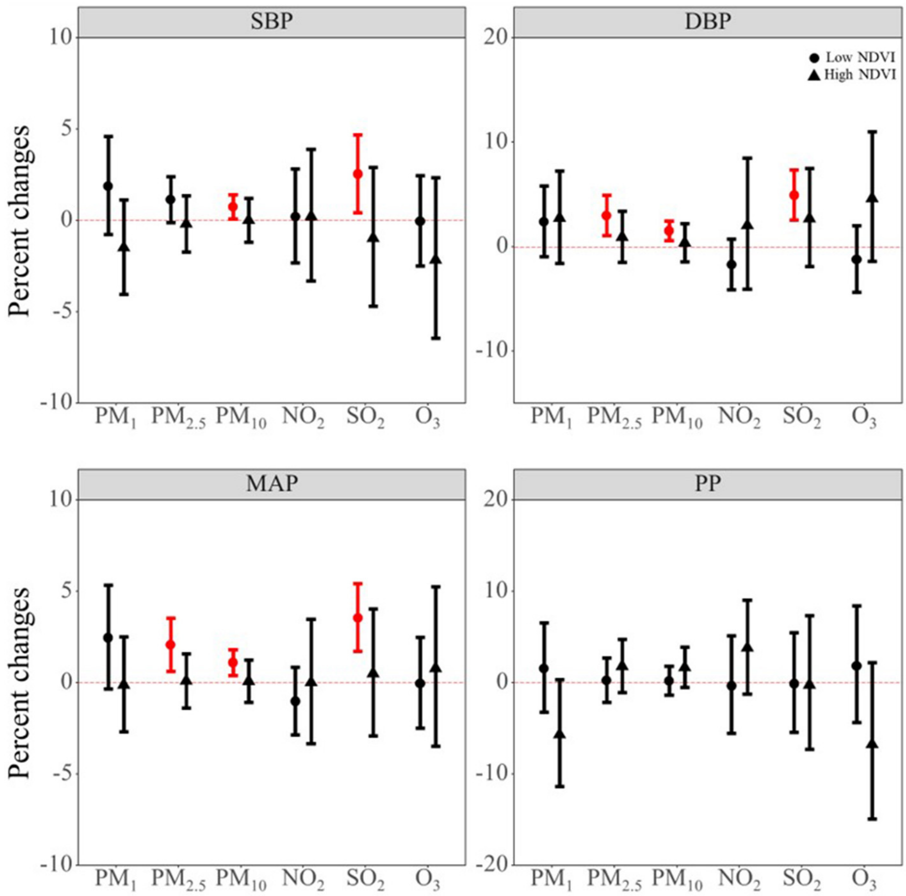

FIGURE 4
The potential modifying effect of NDVI on the association between air pollutants and blood pressure indicators. PM_1, particulate matter with a diameter of <1 μm; $PM_{2.5}$, fine particulate matter of <2.5 μm; PM_{10}, particulate matter with a diameter of <10 μm; NO_2, nitrogen dioxide; SO_2, sulphur dioxide; O_3, ozone; NDVI, Normalized Difference Vegetation Index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure.

range increase in long-term PM_{10} (19 $\mu g/m^3$) exposure was associated 0.32 mmHg increase in DBP (51). All in all, current evidence showed a robust association of long-term exposure to $PM_{2.5}$ and PM_{10} with increased levels of DBP. A comprehensive meta-analysis showed that 10 $\mu g/m^3$ increase in $PM_{2.5}$ and PM_{10} were associated with 0.47 mmHg (95% CI: 0.12, 0.82) and 0.86 mmHg (95% CI: 0.37, 1.35) increase in DBP (5). In our study, we also found that a 10-$\mu g/m^3$ increase in long-term SO_2 exposure was associated with 3.54% (95% CI: 1.55, 5.56) increase in DBP. It is interested that the observed significant results was under the situation that the mean exposure levels of SO_2 (17.15 $\mu g/m^3$) were below the Chinese primary standard levels (20 $\mu g/m^3$). It suggested a more stringent standards for SO_2 in China. Previous studies seldom explored the long-term SO_2 exposure and blood pressure. However, existing evidence are consistent with our findings. For example, a study conducted in 11 Chinese districts involving 24,845 adults reported that each 20 $\mu g/m^3$ increase in SO_2 was associated with 0.31 mmHg (95% CI: 0.10, 0.51) increase in DBP. Previous evidence also showed that short-term SO_2 exposure with positively associated with DBP (5).

MAP is calculated using the SBP and DBP, and it can simultaneously reflect peripheral vascular resistance and cardiac output during a cardiac cycle (52). Meanwhile, this indicator was associated with major cardiovascular events (53, 54). Similar to the results of DBP, we found that a 10-$\mu g/m^3$ increase in $PM_{2.5}$, PM_{10}, and SO_2 were associated with 1.84% (95% CI: 0.74, 2.96), 1.17% (95% CI: 0.52, 1.83), and 2.43% (95% CI: 0.71, 4.18) increase in MAP, respectively. Some of the previous studies are consistent with our findings (11, 55), while some are not (56, 57). For example, Chan et al., analyzed the Sister study data and found significant association of $PM_{2.5}$ with MAP and nonsignificant association of NO_2 with MAP, which supported our findings (11). While Honda et al., conducted a study among older Americans aged ≥57 years did not find significant association between 1-year moving concentrations of $PM_{2.5}$ and MAP (0.32 mmHg, 95%CI: −0.24, 0.88) (56). The heterogeneous results may be due to the air pollutants concentration difference and population characteristic difference. In our study, the mean value of $PM_{2.5}$ were 51.77 $\mu g/m^3$, which is much higher than that of Honda et al., Moreover, the mean age of our study are about 54 years, while the study of Honda et al., has the mean age of about 70 years.

PP can reflect the stiffening of large arteries and is correlated with some cardiovascular risk factors (45). In our study, we did not find any significant associations between air pollutants and PP. Similar to our results, a previous longitudinal study also find non-significant associations of long-term $PM_{2.5}$ and O_3 exposure with increased PP values (14). This is reasonable, because previous study has indicated that although PP can predict cardiovascular events in epidemiological studies, its independent role is hampered by the close correlation between PP and SBP (45). And in our study we also did not find significant results for SBP. Another point should be noted that although previous studies have reported harmful health effect of O_3 (58, 59), we did not found significant association between long-term O_3 exposure and blood pressure in the main analysis. However, we found negative associations between O_3 exposure and DBP and MAP in the 5-year analysis. Previous epidemiological study also found short-term O_3 exposure was associated with decreased levels of blood pressure indicators (60). Similarly, experimental study indicated that O_3 treatment may decrease blood pressure and prevent hypertension progression with the mechanisms of reducing the levels of serum endothelin-1 and ET receptor A mRNA expression (61).

Potential mechanisms

Several potential mechanisms about the air pollutants exposure contributing to the hypertension development or increased blood pressure indicators have been proposed. First, autonomic nervous system may be triggered after air pollutants exposure, and then favor sympathetic over parasympathetic tone, and finally increase blood pressure (9). Second, air pollutants may also induce the creation and circulation of endogenous pro-inflammatory markers and vasculo-active molecules such as endothelin (7, 10) to influence vascular endothelium and then elevate blood pressure levels. Particulate matter contains various constituents including black carbon, metals and so on, which can be inhaled by human. Study has shown that the internal metal exposure were associated with the inflammatory homeostasis disorder (62). Third, air pollution may lead to abnormal DNA methylation status, which has been an explored mechanisms for the effect of air pollutants on blood pressure (6, 63).

Several mechanisms have also been proposed for the underlying effects of residential greenness on blood pressure. Greenness can remove air pollutants (64), which has been reported to be associated with elevated blood pressure both in previous studies and present study (11, 51). Furthermore, greenness can also encourage exercise and further influence participants' obesity status (65), which are strong risk factor for high blood pressure. Lastly, residential greenness may also alleviate personal stress, promote social cohesion, reduce surrounding noise and heat effects, and enrich microbial (66, 67).

Strengths and limitations

Two key strengths of this study were the comprehensive exploration about the individual and joint effect of air pollutants, and the protective effect of residential greenness. Additionally, a series of sensitive analysis indicated that the results of our study are robust.

However, our findings should be interpreted with caution in light of the limitations. First, given the cross-sectional nature of this study, we cannot establish the causal association between air pollutants and blood pressure, thus further well-designed longitudinal studies are warranted to confirm our results. Second, we collected the demographic information and life style from face-to-face interview by qualified questionnaires, which may subject to recall bias. Third, the air pollutants exposure was based on participants' residential location and did not allow for mobility of them, thus may induce measurement error in exposure assessment. However, studies have indicated that this non-differential exposure misclassification might have biased the effects toward null (68, 69). That is to say if we adopted personal exposure levels, the effect estimates would have been higher than the present results of our study. Fourth, due to the accessible of the resources, we only explored the effect of NDVI, which cannot fully represent participants' residential greenness. Fifth, although we have adjusted most possible confounding factors, we cannot rule out confounding bias from unconsidered factors, such as indoor air pollution, noise, traffic factor and so on. Finally, "white coat effect" may occur during the measurement of blood pressure and thus affect our results.

Conclusion

Long-term $PM_{2.5}$, PM_{10}, and SO_2 exposure was associated with elevated levels of DBP and MAP. These associations were modified by greenness indices NDVI. Our study may be useful to policy makers to reduce the burden caused by high blood pressure. Meanwhile, our study indicated the importance to increase green space to protect human from adverse air pollutants effects. Participants aged ≥50 years were more susceptible to the hypertensive effect of $PM_{2.5}$ and PM_{10} compared to younger adults. Nevertheless, given the study limitation, further well-designed longitudinal studies are warranted to better assess causal relationships.

Data availability statement

The datasets presented in this article are not readily available because this dataset is now confidential, but will further available by request to the corresponding author. Requests to access the datasets should be directed to xuqun@ibms.cams.cn.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YM: conceptualization, methodology, software, investigation, validation, writing—original draft, and writing—review and editing. JZ, QZ, YL, and KL: investigation, resources, and validation. MZ and JX: investigation and validation. QX: funding acquisition, writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1019965/full#supplementary-material

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EDITED BY
Ang Li,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

REVIEWED BY
Krittika Bhattacharyya,
University of Calcutta, India
Zilong Zhang,
Sun Yat-sen University, China

*CORRESPONDENCE
Shangcheng Zhou
whzsc2008@hotmail.com

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Time trends in the burden of stroke and subtypes attributable to PM2.5 in China from 1990 to 2019

Huijing Chen, Zhihua Zhou, Zhenglong Li, Shanshan Liang, Jingjing Zhou, Guanyang Zou and Shangcheng Zhou*

School of Public Health and Management, Guangzhou University of Chinese Medicine, Guangzhou, China

Background: Increasing studies have found that PM2.5 has large adverse effects on stroke mortality. We want to investigate the long-term trends in the mortality of stroke attributable to ambient particulate matter pollution and household air pollution to provide evidence facilitating the design of policy.

Methods: The deaths data of stroke and its subtypes attributable to PM2.5 were obtained from the Global Burden of Disease (GBD) 2019, analyzed by Joinpoint regression software and the age-period-cohort (APC) method to assess the magnitude of the trends in mortality and the temporal trends in the mortality rate by age, period, and cohort.

Results: From 1990 to 2019, the age-standardized mortality rate (ASMR) attributable to PM2.5 exposure trended downwards, but the trends of ambient particulate matter pollution and household air pollution were opposite. The trends varied among subtypes, the AAPC of intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage attributable to PM2.5 were 0.7, 2.5, and−3.3%, respectively. The longitudinal age curve of the APC model showed that the mortality rates due to PM2.5 exposure increased with age. The period RRs of ischemic stroke due to ambient particulate matter pollution increased significantly. The cohort RRs of ambient particulate matter pollution increased among those born from 1905 to 1990. The net drifts of all subtypes attributable to PM2.5 were below 0, but owing to the increase of ambient particulate matter pollution, the range of the decline was small. Males had higher net drift values, compared with females.

Conclusions: Ambient particulate matter pollution has become the main type of PM2.5 leading to stroke in China. PM2.5 exposure is more harmful to ischemic stroke, males, and elderly. Chinese government should pay attention to the long-term impact of ambient air pollution on stroke and take effective public health policies and interventions.

KEYWORDS

PM2.5, stroke, Joinpoint regression, age-period-cohort model, ambient particulate matter pollution, household air pollution

Introduction

Stroke is a leading cause of mortality in middle-income countries, especially in China (1). According to GBD 2019, the incident rate of stroke in China reached 276.7 per 100,000 population in 2019, an increase of 86.0% over 1990 (2). Previous studies showed that the disease burden of stroke could be mainly attributable to important environmental and lifestyle risk factors (3, 4).

PM2.5, the particulate matter with an aerodynamic diameter $\leq$2.5 μm, has become one of the three risk factors resulting in more than 1% of DALYs globally (5, 6), causing 8.42 million attributable deaths and the $4.09 trillion of health cost in 2016 (7). PM2.5 exposure includes ambient particulate matter pollution exposure and household air pollution exposure. Ambient particulate matter pollution is defined as annual average daily exposure to outdoor air concentrations of PM2.5, which mainly comes from traffic, factories and household fuel, and household air pollution is defined as individual exposure to PM2.5 due to the use of solid cooking fuel (8). Growing amounts of evidence suggest that ambient particulate matter pollution and household air pollution are closely related to stroke.

A European study showed that for every 5 $\mu g/m^3$ increase in environmental PM2.5 per year, the risk of stroke increased by 19% (9). A prospective cohort study (China-PAR) found that for each increase of 10 $\mu g/m^3$ in ambient PM2.5 concentration, the increased risks of incident stroke, ischemic stroke, and hemorrhagic stroke were 13% (hazard ratio 1.13; 95% confidence interval 1.09 to 1.17), 20% (1.20, 1.15 to 1.25), and 12% (1.12, 1.05 to 1.20), respectively (10). It also has found that household air pollution was related to high blood pressure and escalated mortality of stroke (11, 12).

Owing to economic development and the acceleration of industrialization and urbanization, air pollution has become a global social and environmental issue, especially in developing countries such as China (13–15). Therefore, it is very important to evaluate the stroke burden attributable to PM2.5 exposure in China to advance evidence-informed prevention plans. Several studies are exploring the relationship between stroke burden and PM2.5 exposure (16–19), but few of them focus on estimating the temporal trend and analyzing the independent effects of chronological age, period, and birth cohort of three stroke subtypes burden attributable to ambient particulate matter pollution and household air pollution, respectively.

To address these limitations, we collected data from GBD 2019 to estimate the average annual percent change (AAPC) of stroke and three subcategories of mortality attributable to ambient particulate matter pollution and household air pollution, and analyzed the independent effects by an age-period-cohort (APC) mode. The finding of our study may help public health managers to make evidence-based policies and assess specific interventions.

Materials and methods

Data sources

We extracted the mortality rate of stroke, intracerebral hemorrhage, ischemic stroke, and subarachnoid hemorrhage attributable to PM2.5 in China from 1990 to 2019 from the Global Burden of Disease (GBD) 2019 at GBD Data tool.

The original stroke mortality data were obtained from the Cause of Deaths Reporting System of the Chinese Centers for Disease Control and Prevention (CDC) and Disease Surveillance Points (DSPs) (20). Ischemic stroke is an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. Intracerebral hemorrhage is a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma. Subarachnoid hemorrhage is bleeding into the subarachnoid space. Stroke and each category are identified by International Classification of Diseases (ICD) version 10 (ICD-10): stroke (G45-G46.8, I60-I62, I62.9-I64, I64.1, I65-I69.998, Z82.3), ischemic stroke (G45-G46.8, I63-I63.9, I65-I66.9, I67.2-I67.848, I69.3-I69.4), intracerebral hemorrhage (I61-I62, I62.9, I69.0-I69.298) and subarachnoid hemorrhage (I60-I60.9, I67.0-I67.1) (21).

The mortality rates were age-standardized as follows:

$$ASMRs = \frac{\sum \textit{Age composition of standard group population} \times \textit{Age specific mortality}}{\textit{Age composition of the standard population}}$$

Based on published trials or cohort studies, GBD2019 provides a standardized and comprehensive assessment of the magnitude of risk factor exposure, relative risk, and attributable burden of disease by age, sex, and geographies for specific points in a series of time by using spatiotemporal Gaussian process regression, DisMod-MR 2.1, Bayesian meta-regression method and other alternative methods (5, 22).

In the GBD study, PM2.5 included ambient particulate matter pollution and household air pollution. Ambient particulate matter pollution was defined as the population-weighted annual average mass concentration of outdoor PM2.5 exposure, which was obtained from satellite observations of aerosols in the atmosphere, ground measurements, chemical transport model simulations, population estimates, and land-use data. Exposure to household air pollution (HAP) from solid fuels is estimated from both the proportion of individuals using solid cooking fuels and the level of PM2.5 air pollution exposure. Solid fuels in GBD2019 include coal, wood, charcoal, dung, and agricultural residues (2, 5). The data of household air pollution were obtained from Demographic and Health Surveys (DHS), Living Standards Measurement Surveys (LSMS), Multiple Indicator Cluster Surveys (MICS), and World Health Surveys (WHS), as well as country-specific survey series such as China Monitoring Survey and South Asia General Household Survey (5, 8).

Population attributable fraction (PAF) represents the proportion of related risk that would be reduced if the exposure to a risk factor were reduced to the theoretical minimum exposure level, which is known as the theoretical minimum risk exposure level (TMREL). In GBD 2019, the TMREL of ambient and household air pollution was between 2.4 and 5.9 µg /m^3 (8, 17, 23). The calculation formula for attributable deaths (ADs) is as follows (24): AD = PAF * The number of deaths due to stroke or the subtypes.

The age-standardized rates of PM2.5-ADs, ambient particulate matter pollution -ADs, and household air pollution-ADs were calculated by the world standard population (25). A comprehensive description of the metrics, data sources, and statistical modeling has been reported in GBD 2019 study (5).

Joinpoint regression analysis

In our studies, JoinPoint software (Version 4.9.1.0) was used to calculate the average annual percentage change (AAPC), as well as 95% CIs, which can analyze the magnitude and direction of trends of the mortality rate of stroke and different subtypes over 30 years. The JoinPoint software estimated the mortality data by applying the grid search method with 5 Joinpoints and the Monte Carlo permutation test to optimize the model.

Suppose there is a sequence of observations (x_1, y_1),..., (x_n, y_n), of which, $x_1 \leq ... \leq x_n$, the JoinPoint regression model can be written in log-liner form as

$$E\left[y_i|x_i\right] = e^{\beta_0+\beta_1 x_i+\delta_1(x_i-\Upsilon_1)^+ + \ldots \delta_k(x_i-\Upsilon_k)^+}$$

where y_i represents dependent variable and x_i denotes independent variable for i = 1, 2, ...n; β_0 represents constant parameter; β_1 represents regression coefficient; δ_k represents the regression coefficient of the *kth* piecewise function. When $\left(x_i - \Upsilon_k\right)$ is over 1, $\left(x_i - \Upsilon_k\right)^+ = \left(x_i - \Upsilon_k\right)$, otherwise $\left(x_i - \Upsilon_k\right)^+ = 0$ (26).

Age-period-cohort analysis

It is known that there is collinearity between age, period, and cohort (27). Like previous studies (28, 29), we circumvented this problem by using age-period-cohort (APC) model, which provides a useful parametric framework with complements standard non-parametric descriptive methods, to assess the temporal trends of mortality by age, period, and cohort (30).

The age effect is the age-related physiological and pathological changes, causing epidemiological differences. To assess the age effect, the longitudinal age curve fitted longitudinal age-specific rates, which is relative to the reference cohort adjusted for period deviations. The period effect refers to changes in mortality rate due to human factors, such as the development of diagnosis technology, screening, and early detection, changes in disease definition and registration, treatment improvement, etc. These human factors may affect the disease rate in different periods, resulting in a period effect. The period effect, shown in the period ate ratios (period RRs), refers to changes in disease mortality caused by different human factors, such as the development of disease diagnosis technology, screening, and early detection, changes in disease definition and registration, treatment improvement and the conservation and emission reduction policies introduced by the Chinese government. When RR is over 1, the relative risk of death is higher in this period compared with the reference period, and when RR is below 1,the relative risk of death in this period is lower than that in the reference period. The cohort effects, shown in the cohort rate ratios (cohort RRs), refer to differences in disease mortality rates caused by various lifestyle changes or different exposure to risk factors among generations. Net drift is an overall log-linear trend by calendar period and cohort effects, indicating overall the annual percentage change. Local drift is the log-linear by period and birth cohort for each age group, representing annual percentage changes for each age group (31). Like previous studies (31–33), we also recoded age and period into consecutive 5 years of data. The mortality and population data are arranged into 5-year age groups from 25–29 age-group to 80–84 age-group and 85 plus age-group. Consecutive 5-year periods were defined from 1990–1994 to 2015-2019. Consecutive 5-year cohorts were defined from 1905–1909 to 1985–1989.

APC model can be written in linear regression form as follow (34–36):

$$M = \mu + \alpha_{i*}\text{age} + \beta_{j*}\text{period} + \gamma_{k*}\text{cohort} + \varepsilon \qquad (1)$$

M represents the death rate for age *i* age group during *j* period; α_i denotes age effect of the *i* age group; β_j represents period effect of the *j* period; γ_k denotes cohort effect of the k (k = I + j - 1) birth cohort; µ is intercept or adjusted mean death rate, and ε is the residual or a random error.

This part of the statistical analysis was performed by R statistical software (R version 3.5.1) and the age-period-cohort web tool (https://analysistools.cancer.gov/apc/). $p < 0.05$ was considered significant (17, 37).

Results

The trend in the age-standardized mortality rate of stroke attributable to PM2.5 exposure

Over the past 30 years, the number of deaths increased 1.3 times over, from 637,871 in 1990 to 801,549 in 2019. The ASMR of stroke attributable to PM2.5 decreased among different stroke subtypes, especially for subarachnoid hemorrhage (decreased 6.7% annually).

We further analyzed the ASMRs of stroke attributable to ambient particulate matter pollution and household air pollution. For ambient particulate matter pollution, the number of deaths increased 3.3 times over, from 161,939 in 1990 to 541,796 in 2019. The ASMR of stroke attributable to ambient particulate matter pollution increased by 1% annually, with similar trends observed among both sexes (AAPC: 1.0%; 95% CI: 0.6, 1.5%). Among different stroke subtypes, the ASMR of subarachnoid hemorrhage decreased (AAPC:−3.3%; 95% CI:−3.7,−2.8%), but the ASMR of ischemic stroke (AAPC: 2.5%; 95% CI: 2.0, 2.9%) and intracerebral hemorrhage (AAPC: 0.5%; 95% CI: 0.3, 0.7%) similarly increased from 1990 to 2019.

For household air pollution, the number of deaths decreased from 382, 505 in 1990 to 136,950 in 2019. It also decreased significantly among both sexes (AAPC: −6.6%; 95% CI: – 6.9, −6.3%). The ASMRs of different stroke subtypes attributable to household air pollution were all decreased.

The ASMR due to ambient particulate matter pollution was higher than that due to household air pollution after 2002. For males, the ASMR due to ambient particulate matter pollution was higher than that due to household air pollution after 1999, and for females, the ASMR due to ambient particulate matter pollution was higher than that due to household air pollution after 2005 (Table 1; Figure 1).

The age-period-cohort analysis of the mortality rate of stroke attributable to PM2.5 exposure

For the same birth cohort, the mortality rate of stroke attributable to PM2.5 increased with age. The mortality rate of stroke among males was higher than that among females (Figures 2A,E).

Among different subtypes, for subarachnoid hemorrhage, the mortality rate was lower than others, and it increased with age before 55 and slightly decreased after that. Other subtypes of stroke had increasing trends with age attributable to PM2.5, they trended upwards rapidly after the 55–60 age groups (Figures 2B–D).

In terms of ambient particulate matter pollution and household air pollution, the mortality rates due to ambient particulate matter pollution and household air pollution were low in younger group, but the mortality rate due to ambient particulate matter pollution significantly increased with age among those older groups. Similar changes were observed in males and females (Figures 2A,F).

The period RRs of all stroke subtypes attributable to PM2.5 exposure trended downwards. The downward trend among females was steeper than that among males (Figures 3A,E,F).

In terms of ambient particulate matter pollution, the period RRs of stroke increased from 1990 to 2019. For household air pollution, it trended downwards significantly. Similar trends were observed among those of intracerebral hemorrhage and ischemic stroke. The period RRs of subarachnoid hemorrhage attributable to ambient particulate matter pollution and household air pollution decreased from 1990 to 2019 (Figures 3B–D).

Cohort RRs of all stroke subtypes attributable to PM2.5 exposure decreased among those born from 1905 to 1990. The cohort effects were opposites for ambient particulate matter pollution and household air pollution: for ambient particulate matter pollution, the cohort effects increased, for household air pollution, they declined. Similar trends were observed among both males and females. The downward trend among females was steeper than that among males (Figures 4A,E,F).

In terms of different subtypes, the cohort RRs for household air pollution trended downwards obviously, while for ambient particulate matter pollution, the cohort RRs of the mortality rate of intracerebral hemorrhage and ischemic stroke trended upwards (Figures 4B–D).

The overall net drift values of all stroke subtypes attributable to PM2.5 were below 0 ($P < 0.001$). However, the net drift values of intracerebral hemorrhage and ischemic stroke attributable to ambient particulate matter pollution were above 0 (0.96 and 2.17%, respectively, $P < 0.001$). In terms of sexes, the net drift value of stroke for males was−1.97%, and for females, it was−3.98% ($P < 0.001$). Among different stroke subtypes, males had higher net drift values, compared with females.

The local drift values of stroke decreased by age before the 60-age group and increased after that. Similar changes were observed for ambient particulate matter pollution and household air pollution, while the local drift values of intracerebral hemorrhage decreased by age, and for ischemic stroke, it increased by age (Figure 5).

The detailed results of the APC model regarding the age, period, and cohort effect were shown in Supplementary Tables 1–5.

Discussion

This study provided long-term estimates of the mortality rate of stroke attributable to PM2.5 exposure by sex, age, and stroke subtypes, clarifying the impact of ambient particulate matter pollution and household air pollution changes on stroke by Joinpoint regression and age-period-cohort model in China.

We found that, over 30 years, the number of stroke cases attributable to PM2.5 substantially increased, and the number of deaths attributable to ambient particulate matter pollution accounted for most of it. According to the mortality rate, there is a reduction in the ASMRs of stroke due to PM2.5 from 1990 to 2019, but it also shows the increase in the ASMRs due to ambient particulate matter pollution which was significantly higher than those due to household air pollution after 2002.

TABLE 1 The results by Joinpoint regression analysis on the mortality rate of stroke, intracerebral hemorrhage, ischemic stroke and subarachnoid hemorrhage attributable to PM2.5 exposure from 1990 to 2019.

		PM2.5		Ambient particulate matter pollution		Household air pollution	
		AAPC (%)	95%CI	AAPC (%)	95%CI	AAPC (%)	95%CI
Stroke	Both sexes	−2.5*	(-2.6,−2.3)	1.0*	(0.6,1.5)	−6.6*	(-6.9,−6.3)
	Male	−2.0*	(-2.2,−1.7)	1.1*	(0.6,1.6)	−6.4*	(-6.8,−6.1)
	Female	−3.0*	(-3.3,−2.8)	0.7*	(0.4,1.0)	−6.7*	(-7.1,−6.2)
Intracerebral hemorrhage	Both sexes	−2.8*	(-3.2,−2.5)	0.5*	(0.3,0.7)	−6.7*	(-7.2,−6.3)
	Male	−2.4*	(-2.7,−2.2)	0.6*	(0.1,1.0)	−6.5*	(-6.7,−6.4)
	Female	−3.4*	(-3.7,−3.2)	0.3	(-0.0,0.6)	−6.9*	(-7.3,−6.6)
Ischemic stroke	Both sexes	−0.8*	(-1.1,−0.6)	2.5*	(2.0,2.9)	−5.1*	(-5.5,−4.8)
	Male	−0.5*	(-0.7,−0.2)	2.5*	(2.1,2.9)	−5.2*	(-5.6,−4.8)
	Female	−1.3*	(-1.5,−1.1)	2.4*	(1.8,3.0)	−5.3*	(-5.6,−4.9)
Subarachnoid hemorrhage	Both sexes	−6.7*	(-7.0,−6.3)	−3.3*	(-3.7,−2.8)	−10.5*	(-10.8,−10.1)
	Male	−6.1*	(-6.4,−5.7)	−3.1*	(-3.5,−2.6)	−10.1*	(-10.4,−9.9)
	Female	−7.2*	(-7.6,−6.8)	−3.7*	(-4.1,−3.2)	−10.6*	(-11.0,−10.3)

Statistically significant ($p < 0.05$); AAPC, average annual percent change.

This indicates that ambient particulate matter pollution has replaced household air pollution as the main risk factor of PM2.5 related to stroke. Further reduction in anthropogenic emissions is needed to accelerate the decrease in ambient PM2.5 concentrations, or the burden of stroke attributable to PM2.5 is still severe. Moreover, many rural residents, particularly in western, central, and north-eastern China, still rely heavily on solid fuels, causing uneven household air pollution in the population of China, which should be also called attention to Ma et al. (17).

Both sexes had similar trends in the ASMRs attributable to ambient particulate matter pollution and household air pollution from 1990 to 2019, but the mortality rate of stroke attributable to PM2.5 was higher among males than females. The ASMR attributable to ambient particulate matter pollution among males reached its highest in 2012, and it slightly reduced after that. These findings suggest that PM2.5 exposure had a greater adverse function on the mortality rate of stroke among males, but this effect has been moderated by improvements for both indoor and outdoor pollution in recent years. Another notable aspect is that air pollution is also associated with smoking (38), contributing to the heavier disease burden among males than females.

In subgroup analyses for stroke subtypes, we found that the ASMRs trends of all stroke subtypes attributable to PM2.5 were decreased, but for ambient particulate matter pollution, the ASMRs of ischemic stroke substantially increased. This may be because exposure to ambient particulate matter pollution may induce acceleration of atherosclerosis, alter the vasomotor tone, cause vascular inflammation, and promote blood coagulation, which pathophysiological changes are more likely to provoke ischemic stroke, compared with hemorrhagic stroke (39–41).

We further analyzed the effects of age, period, and cohort on the epidemiological changes in stroke attributable to PM2.5 exposure. We found that the ASMRs of ischemic stroke and intracerebral hemorrhage due to both ambient particulate matter pollution and household air pollution significantly increased after their levels among those 55–60 years, and were low among the younger age groups. A study also estimated that the health cost of stroke attributable to PM2.5 increased faster in the older population than in the younger population (7). Therefore, more policy actions are needed to reduce the stroke burden attributable to PM2.5 concentrations to which elderly individuals are exposed. In addition, the mortality of subarachnoid hemorrhage increased with age before 55 and slightly decreased after that. This finding might be because the ratio of hemorrhagic stroke cases is higher among younger populations overall stroke cases, and hemorrhagic stroke is more preventable (42).

The period RRs attributable to PM2.5 trended downward among all subtypes, but there was still an obvious upward trend for ischemic stroke due to ambient particulate matter pollution, indicating that despite the improvement of air pollution in China, government should formulate an effective policy to prevent the adverse result of ischemic stroke due to ambient particulate matter pollution. The cohort RRs attributable to PM2.5 decreased among those born from 1905 to 1990. But for ambient particulate matter pollution, the cohort RRs trend increased among those born from 1905 to 1990, indicating the younger generations may have a higher risk to get stroke due to ambient particulate matter pollution and we should pay attention to the long-term damage of it.

The overall net values of all stroke subtypes attributable to PM2.5 exposure was−2.72%, but the net drift value of

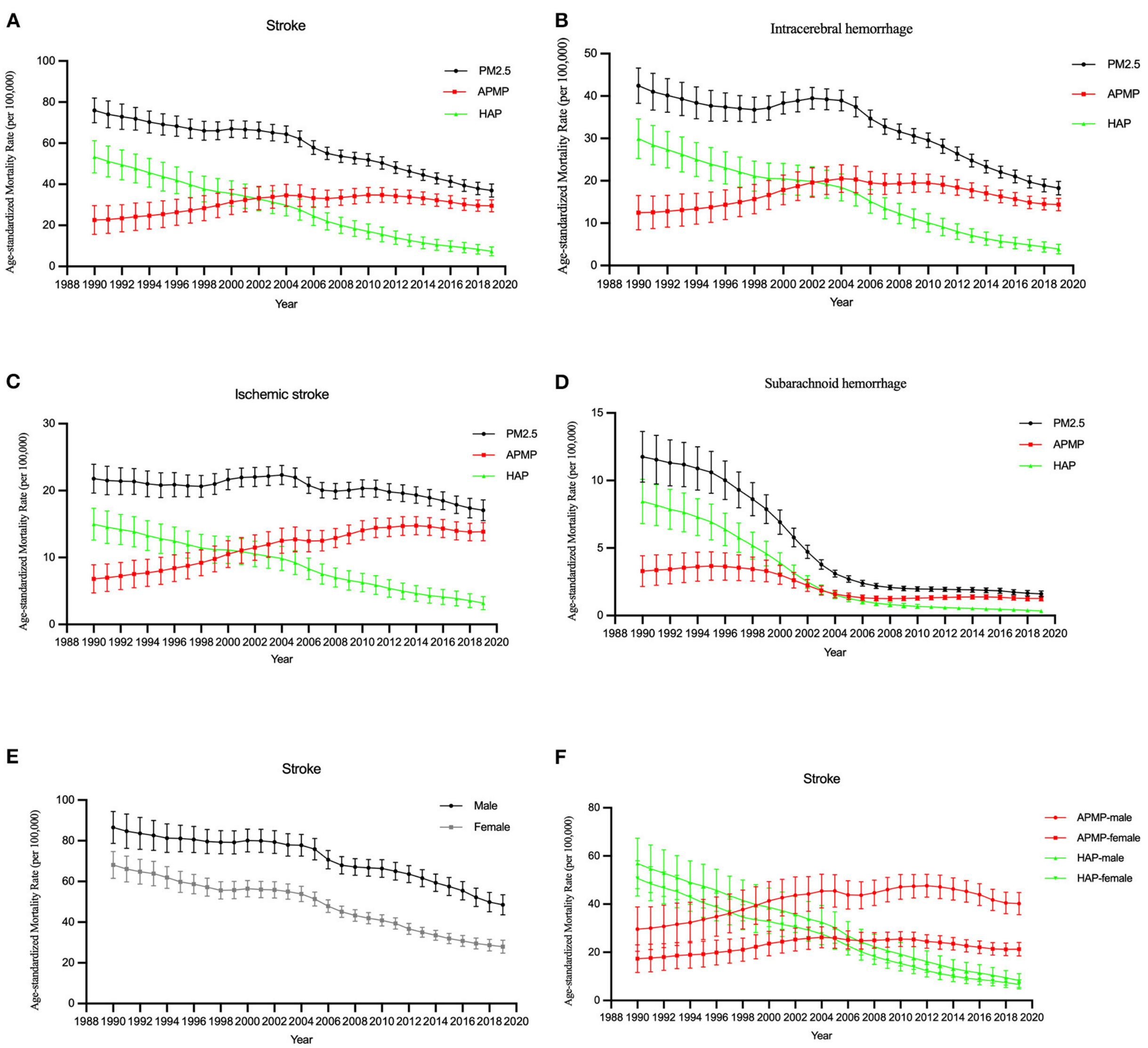

FIGURE 1
The temporal trends in the ASMR of stroke attributable to PM2.5 exposure from 1990 to 2019. **(A–D)** The mortality rate of stroke and subtypes due to PM2.5 exposure, ambient particulate matter pollution, and household air pollution for both sexes. **(E)** The mortality rate of stroke due to PM2.5 exposure by sex. **(F)** The mortality rate of stroke due to ambient particulate matter pollution (APMP) and household air pollution (HAP) by sexes.

ischemic stroke attributable to ambient particulate matter pollution was 2.17%. Considering all results in the local drift value, formulate effective policies for outdoor air pollution attributable to ischemic stroke, males and the elderly might remarkably reduce the risk of stroke from air pollution in the future.

Despite some advancements in this study, there are several limitations. First, although GBD 2019 has modified and adjusted its data sources and collection and evaluation method to improve data quality, it could be difficult to avoid the bias caused by missing data. Second, studies on the relationship between PM2.5 and different types of stroke might be lacking, which led to some mixed results explaining the difference among stroke subtypes (10, 39, 40, 43, 44). Therefore, more studies are needed to improve the reliability of the results through method standardization, increasing sample size, and stratified analysis. Third, in addition to the effects of age, period, cohort, and gender, we should take more factors into account, such as regional differences between North and South in China (45), economic development, and education level.

Conclusion

In summary, ambient air pollution has become the main type of PM2.5 leading to stroke, and its exposure is more

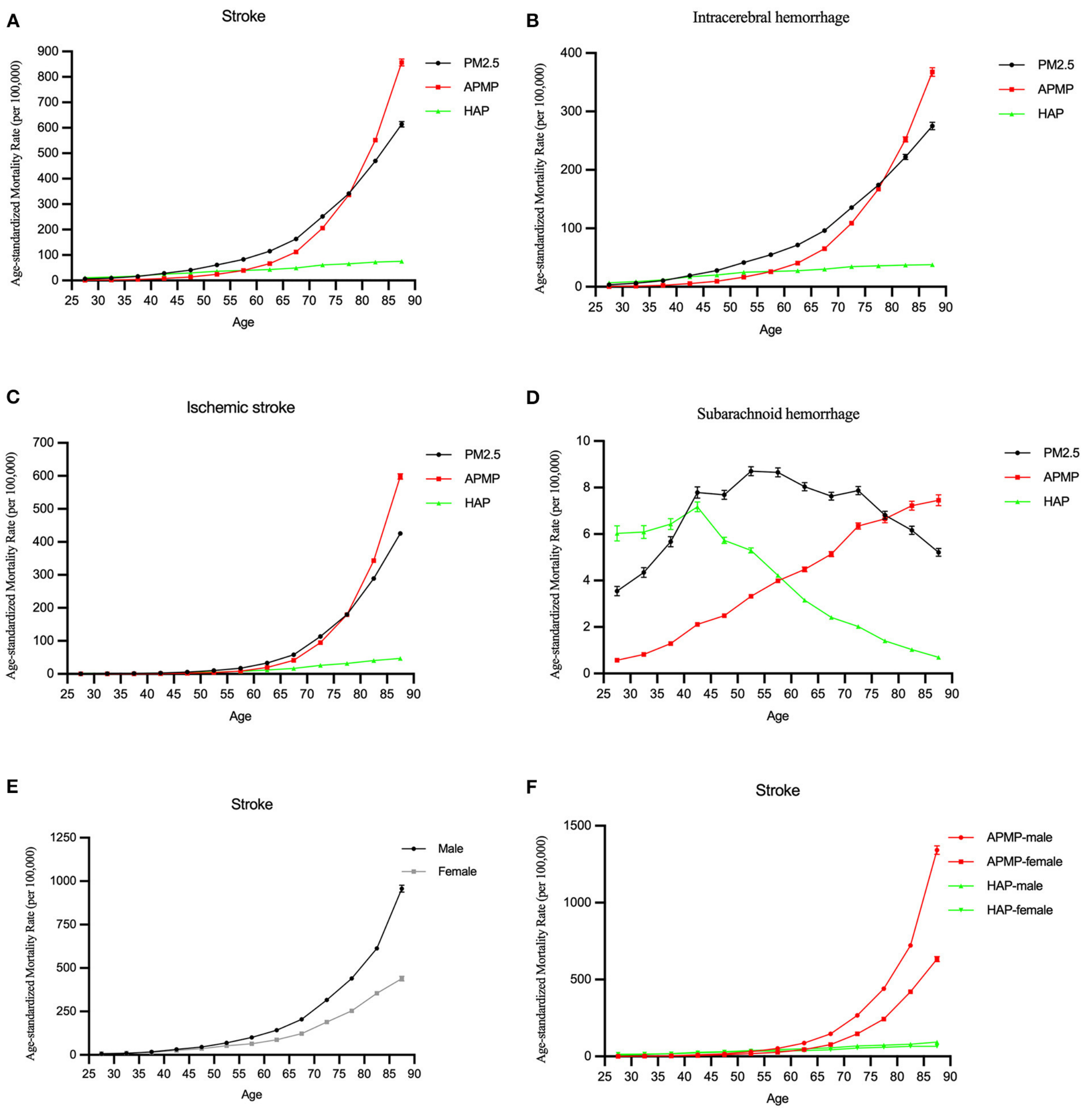

FIGURE 2
The longitudinal age curves of the mortality rate of stroke attributable to PM2.5 exposure from 1990 to 2019. **(A–D)** The longitudinal age curves of stroke and subtypes for both sexes in PM2.5 exposure. **(E)** The longitudinal age curves of stroke by sex in PM2.5 exposure. **(F)** The longitudinal age curves of stroke by sex in ambient particulate matter pollution (APMP) and household air pollution (HAP).

harmful to ischemic stroke, males, and elderly in China. Young generation may have a higher risk to get stroke in the future. To reduce the burden of stroke attributable to PM2.5, Chinese government should pay attention to the impact of outdoor air pollution on stroke and take effective public health policies and interventions to protect the specific population.

Data availability statement

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

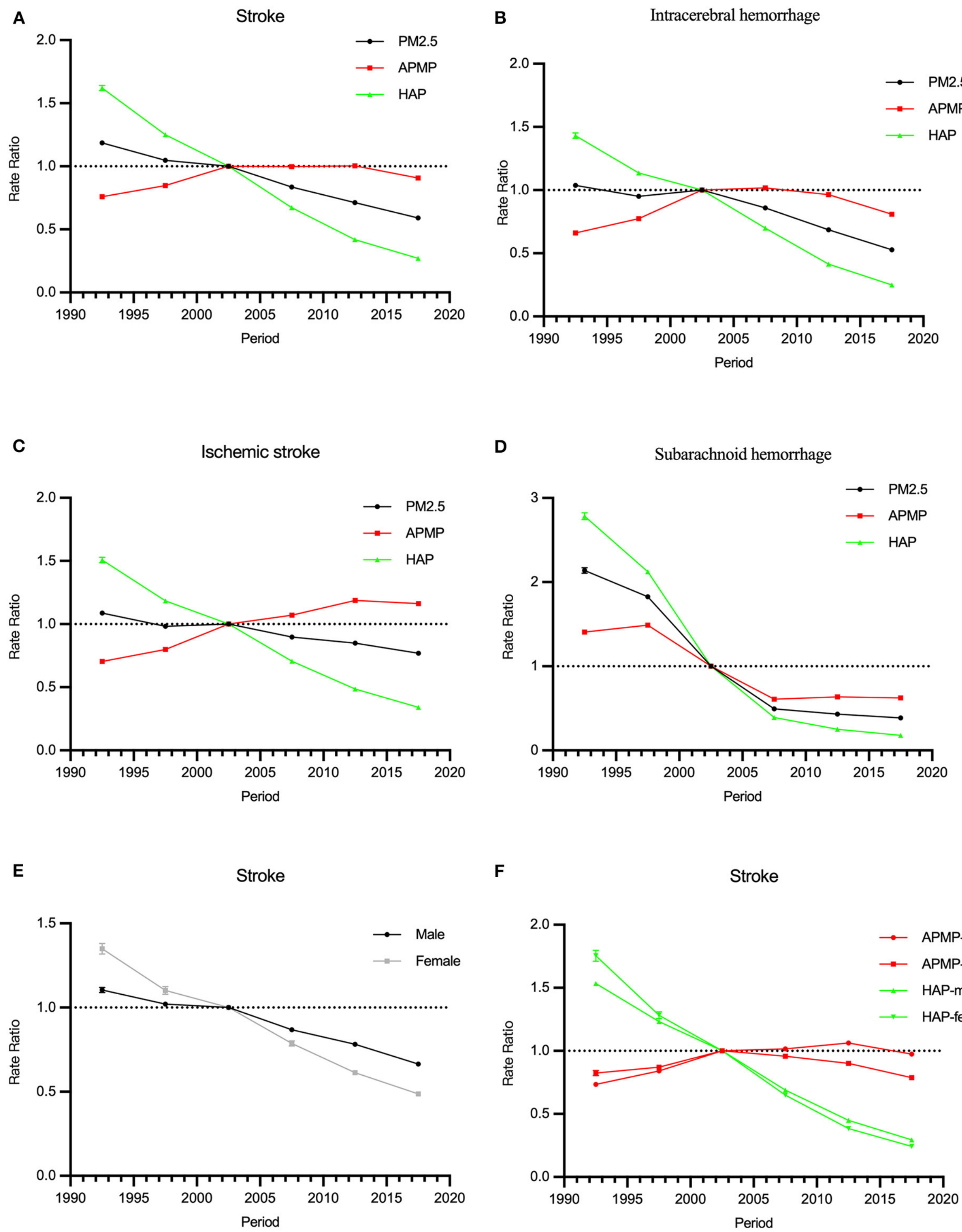

FIGURE 3
The period RRs of the mortality rate of stroke attributable to PM2.5 exposure from 1990 to 2019. **(A–D)** The period RRs of stroke and subtypes for both sexes in PM2.5 exposure. **(E)** The period RRs of stroke by sex in PM2.5 exposure. **(F)** The period RRs of stroke by sex in ambient particulate matter pollution (APMP) and household air pollution (HAP).

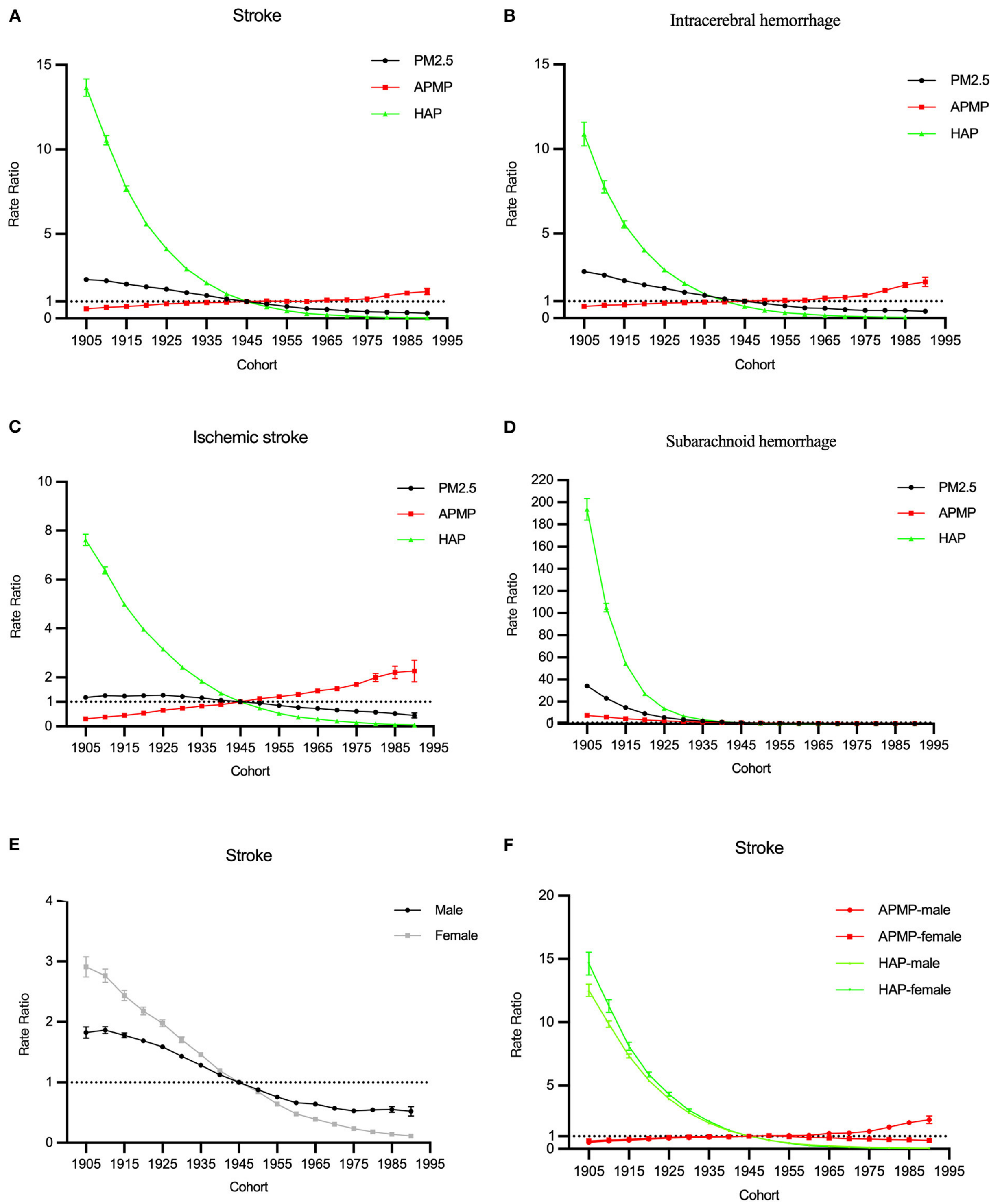

FIGURE 4
The cohort RRs of the mortality rate of stroke attributable to PM2.5 exposure from 1990 to 2019. **(A–D)** The cohort RRs of stroke and subtypes for both sexes in PM2.5 exposure. **(E)** The cohort RRs of stroke by sex in PM2.5 exposure. **(F)** The cohort RRs of stroke by sex in ambient particulate matter pollution (APMP) and household air pollution (HAP).

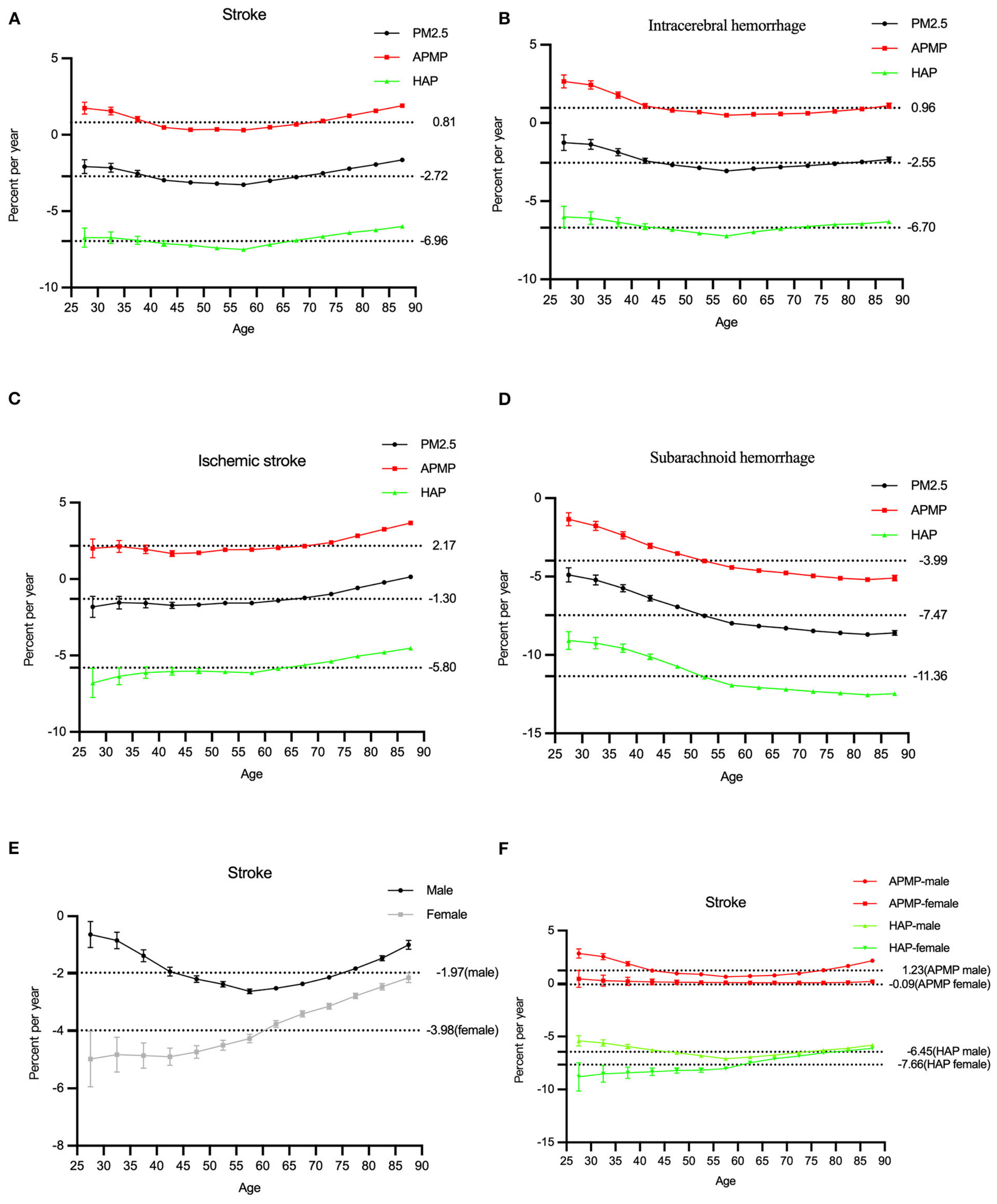

FIGURE 5
The local drifts of the mortality rate of stroke attributable to PM2.5 exposure from 1990 to 2019. **(A–D)** The local drifts of stroke and subtypes for both sexes in PM2.5 exposure. **(E)** The local drifts of stroke by sex in PM2.5 exposure. **(F)** The local drifts of stroke by sex in ambient particulate matter pollution (APMP) and household air pollution (HAP).

Author contributions

HC and ZL wrote the manuscript, with contributions from SZ and GZ. ZZ and SL conducted the data collection. HC and JZ did the analysis. All authors contributed to data interpretation, wrote and revised various parts of the article, and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1026870/full#supplementary-material

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EDITED BY
Yunquan Zhang,
Wuhan University of Science and Technology, China

REVIEWED BY
Xiang Li,
The Chinese University of Hong Kong, China
Yuxiong Chen,
Peking Union Medical College Hospital (CAMS), China

*CORRESPONDENCE
Shaomei Shang
shangshaomei@126.com
Yonghua Hu
yhhu@bjmu.edu.cn

†These authors have contributed equally to this work

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Short-term exposure to ambient fine particulate matter and psoriasis: A time-series analysis in Beijing, China

Junhui Wu[1,2], Hongbo Chen[1,2], Ruotong Yang[2], Huan Yu[2], Shaomei Shang[1*†] and Yonghua Hu[2,3*†]

[1]School of Nursing, Peking University, Beijing, China, [2]Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China, [3]Medical Informatics Center, Peking University, Beijing, China

Background: Ambient fine particulate matter ($PM_{2.5}$) adversely affects human health and has been linked to a variety of skin disorders. However, little is known about the effects of $PM_{2.5}$ on psoriasis.

Methods: The Beijing Medical Claim Data for Employees database recorded 500,266 outpatient visits for psoriasis during 2010–2017. A generalized additive quasi-Poisson model was used to examine the relationship between daily $PM_{2.5}$ concentrations and outpatient visits for psoriasis with stratification by sex, age, and season.

Results: Short-term exposure to $PM_{2.5}$ was associated with outpatient visits for psoriasis-related health concerns. A same-day increase of 10 $\mu g/m^3$ in $PM_{2.5}$ concentrations was associated with a 0.29% (95% confidence interval: 0.26–0.32%) increase in daily outpatient visits for psoriasis. Female and older patients appeared to be more sensitive to the effects of $PM_{2.5}$ ($P < 0.05$).

Conclusions: Short-term elevations in $PM_{2.5}$ concentrations may be associated with exacerbations in psoriasis. Further work is warranted to confirm the findings and elucidate the underlying biological mechanisms.

KEYWORDS

fine particulate matter, outpatient visits, air pollution, psoriasis, time-series study

Background

Psoriasis is a common skin disorder and appears mainly in the form of chronic plaque psoriasis (psoriasis vulgaris) (1). Psoriasis is characterized by erythematous plaques covered by silvery lamellar scales, and common symptoms are pain, itching, and bleeding (2). Globally, psoriasis affects approximately 125 million individuals, and its prevalence is estimated at 3.2–8% (1, 3). The condition exerts significant physical, emotional, and social burdens on patients, including issues such as disfiguration, comorbidities (e.g., cardiovascular disease, psoriatic arthritis, and depression), and reduced ability to work (3, 4). There is no known cure for psoriasis (1), and the periodic recurrence and remission of symptoms consume substantial medical resources, especially in the outpatient department (1, 5). The underlying etiology of psoriasis is unclear, and may be a complex combination of immunological, environmental, and genetic factors that lead to clinically heterogeneous disease (6). Over the past few decades, an apparent upward trend in the prevalence of psoriasis has been observed in developed nations, coinciding with economic development and the accompanying environmental changes (7–10). Furthermore, several studies have reported that environmental factors such as airborne pollution increase the risk for skin disease (6). There is growing concern that air pollution may also have a detrimental effect on psoriasis.

Air pollution is an important and global risk factor for mortality, with an estimated 4.9 million deaths and 147 million years of healthy life lost annually (11). In recent years, multiple studies have reported significant associations between airborne pollution and skin disorders such as eczema, acne, and atopic dermatitis (12–14). However, the relationship between airborne pollution and psoriasis is uncertain. Among air pollutants, particulate matter with an aerodynamic diameter $< 2.5\,\mu m$ ($PM_{2.5}$) has been identified as the greatest threat to human health (15–18), as the small particles can easily penetrate epithelial and endothelial cells, diffusing into blood and lymph circulation (19) and both inducing and exacerbating disease states (20, 21). Levels of $PM_{2.5}$ pollution in China are among the highest worldwide and have been estimated to cause approximately 1 million premature deaths each year (22).

Some epidemiological studies have alluded to a possible link between $PM_{2.5}$ and psoriasis, but not in detail. Previous studies conducted in Korea and Italy were conducted in low-level $PM_{2.5}$ area, and their representation was limited (1, 2, 6, 23). In the present study, we hypothesized that short-term exposure to $PM_{2.5}$ might contribute to the exacerbation of psoriasis. We used a time-series analysis to study the relationship between short-term exposure to $PM_{2.5}$ and outpatient visits for psoriasis in Beijing, China.

Methods

Data collection

We collected daily $PM_{2.5}$ concentrations from reports issued by the United States Embassy air monitoring station for the period between January 1, 2010 and December 31, 2017. These were the only consistent monitoring data we could access because China did not include $PM_{2.5}$ in the air quality standard until 2013. Previous studies that compared $PM_{2.5}$ levels recorded by this source and city-wide $PM_{2.5}$ levels, found similar trends, and this data source has been used in multiple studies (24). The validity and reliability of the data have been demonstrated in detail in previous work (25) and are also described in Appendix S1. Daily mean temperature and relative humidity for the study period were obtained from the Chinese Meteorological Bureau. Personal identifiers and private information for the patients were removed for privacy; therefore, institutional review board approval and patient consent were not required.

Data on outpatient visits for psoriasis from January 1, 2010 to December 31, 2017 were obtained from the Beijing Medical Claim Data for Employees database, which covers all Beijing participants with basic medical insurance and includes all working or retired employees. The database records all medical claim data and basic demographics, date of visit, medications, and clinical diagnosis in Chinese and corresponding International Classification of Disease, 10th Revision codes. We used code L40.001 to identify cases of psoriasis. We only included patients with a primary diagnosis of psoriasis. Patients under 18 years were excluded. Beijing has a permanent population of ∼21 million, of which more than 17.8 million (almost 85%) are included in the claim database. To control for potential residual confounding, we stratified the findings in subsequent analyses.

Statistical analysis

We used a generalized additive quasi-Poisson model to evaluate the relationship between $PM_{2.5}$ concentrations and psoriasis-associated outpatient visits. This model has been widely used and refined for air pollution and health-related time-series studies (26–29). Confounding covariates such as day of the week, public holiday, calendar time, temperature, and relative humidity were added to the main model (30, 31) and used as follows:

$$\begin{aligned} Log\left[E\left(Y_t\right)\right] =\ & \alpha + \beta PM_{2.5} + day\ of\ the\ week \\ & + public\ holiday + s(calendar\ time,\ 7\ per\ year) \\ & + s(temperature, 6) + s(relative\ humidity, 3) \end{aligned}$$

where $E(Y_t)$ refers to the expected number of psoriasis-associated outpatient visits on day t, α represents the model intercept, β denotes the log (relative risk) of morbidity relative to unit increase in $PM_{2.5}$ levels, and s() represents a smoothing based on the penalized splines. Holidays mainly include every weekend and three official traditional festivals. Following the approaches in several relevant studies (32, 33), we selected the degrees of freedom for calendar time, temperature, and relative humidity. To confirm the robustness of our findings, sensitivity analyses were conducted using various degrees of freedom (34).

We applied a penalized cubic regression spline for $PM_{2.5}$ concentration, a widely used approach that can better achieve

Abbreviations: CI, confidence interval; $PM_{2.5}$, particulate matter with an aerodynamic diameter $< 2.5\,\mu m$.

the purpose of evaluating the temporal correlation between $PM_{2.5}$ concentrations and daily outpatient visits for psoriasis (35). Consistent with previous studies, and considering the skin directly exposed to $PM_{2.5}$, we assessed the relationship between $PM_{2.5}$ levels and psoriasis-associated outpatient visits by constructing models with a single-day lag from the current day (lag 0) up to the previous 3 days (lag 1, lag 2, and lag 3), and with 2-day (lag 0–1), 3-day (lag 0–2), and 4-day (lag 0–3) moving average concentrations. To examine effects in subgroups, we stratified the analyses by age (<65 and ≥65 years), sex, and season. The warm season was defined as April to September and the cool season was defined as October to March (36). Z tests were used to assess statistical differences between subgroups (37). The degrees of freedom and parameters set in the main model is consistent with those in subgroup analysis.

All findings are presented as the percentage change and 95% confidence interval in daily psoriasis-associated outpatient visits for each 10-$\mu g/m^3$ increase in ambient $PM_{2.5}$. We used the "mgcv" and "nlme" packages in R 3.2.2 to analyze the data. Percentage change was calculated as (relative risk – 1) × 100. Statistical significance was defined as two-sided $P < 0.05$.

Results

Table 1 lists the characteristics of the psoriasis patients in our study. During the study period (January 1, 2010 to December 31, 2017), a total of 500,266 outpatient visits for psoriasis were identified in the health claims database. More than half (56.93%) of the patients were men; 15.96% of the patients were older than 65 years, and 56.03% of visits occurred in the cool season.

Table 2 summarizes the descriptive statistics for the psoriasis-associated outpatient visits, $PM_{2.5}$ concentrations, and weather conditions. The daily mean number of outpatient visits was 171 (standard deviation: 208). The annual average of $PM_{2.5}$ concentrations was 86.8 $\mu g/m^3$ (standard deviation: 74.3 $\mu g/m^3$), with a maximum of 537.3 $\mu g/m^3$. Figure 1 shows the association of $PM_{2.5}$ concentrations with psoriasis-associated outpatient visits. There was a clear exposure-response association between the same-day (lag 0) daily average concentrations of $PM_{2.5}$ and outpatient visits for psoriasis.

Table 3 presents the estimated relationships between acute elevations in $PM_{2.5}$ concentrations and increases in outpatient visits for psoriasis. A 10-$\mu g/m^3$ increase in $PM_{2.5}$ levels corresponded to an increase of 0.29% (95% confidence interval: 0.26–0.32%) in same-day (lag 0) outpatient visits for psoriasis.

Table 4 lists the subgroup estimates. The association between $PM_{2.5}$ concentrations and psoriasis-associated outpatient visits was greater in women (0.35%, 95% confidence interval: 0.30–0.39%) and in older patients (0.41%, 95% confidence interval: 0.34–0.48%). Sensitivity analyses confirmed these results (Table 5). The changes in degrees of freedom for calendar time (6–9), temperature (5–8), and relative humidity (3–6) did not substantially change the findings, indicating that the association was robust.

TABLE 1 Characteristics of outpatient visits for psoriasis between January 1, 2010 and December 31, 2017 in Beijing, China.

Variable	All year	Cool season	Warm season
Outpatient visits	500,266	280,302 (56.03)	219,964 (43.97)
Sex (%)			
Male (%)	284,815 (56.93)	159,588 (56.93)	125,228 (56.93)
Female (%)	216,299 (43.07)	121,484 (43.07)	94,816 (43.07)
Age (year, %)			
18–64 (%)	420,445 (84.04)	235,302 (83.95)	185,144 (84.17)
≥65 (%)	114,010 (15.96)	64,540 (16.05)	49,471 (15.83)

Discussion

In this citywide time-series analysis, we found significant and positive associations between $PM_{2.5}$ levels and outpatient visits for psoriasis. This introduces fine particulate matter as a factor in psoriasis exacerbation. To our knowledge, this is the first large-scale citywide research in China to comprehensively assess the acute effect of $PM_{2.5}$ on psoriasis-associated outpatient visits. Although previous correlation

TABLE 2 Distribution of daily outpatient visits for psoriasis, fine particulate matter ($PM_{2.5}$) concentrations, and meteorological conditions.

Variable	Mean ± SD	Minimum	Percentile			Maximum	IQR
			25^{th}	50^{th}	75^{th}		
Daily outpatient visits	171 ± 208	7	58	100	256	1,413	198
$PM_{2.5}$ ($\mu g/m^3$)	86.8 ± 74.3	1.0	33.3	66.5	115.0	537.3	81.7
Daily outpatient visits during the cool season	165 ± 213	7	71	87	242	1,413	171
Daily outpatient visits during the warm season	180 ± 201	8	42	122	274	1,139	232
Temperature (°C)	14.6 ± 11.3	−14.3	2.6	15.1	24.0	34.5	21.4
Relative humidity (%)	51.8 ± 20.2	8.0	35.1	52.0	68.1	88.0	33.0

IQR, interquartile range; SD, standard deviation.

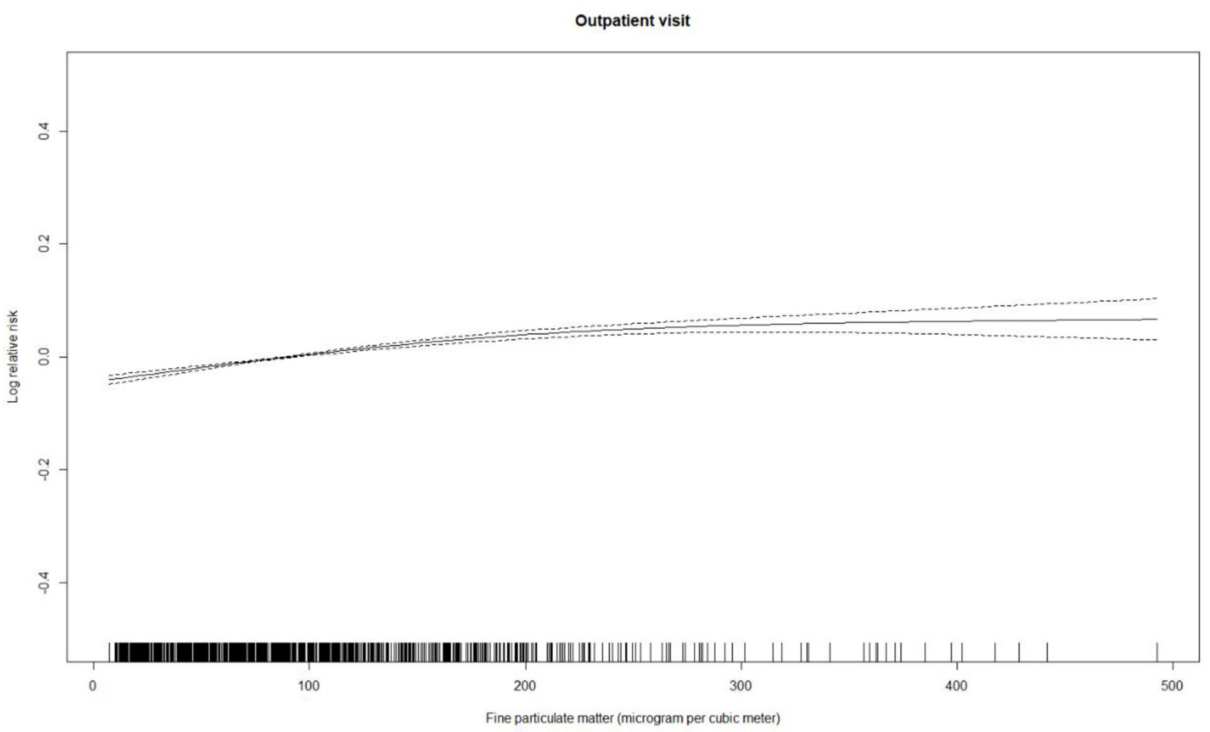

FIGURE 1
Concentration-response curve (solid line) for daily average concentrations of airborne fine particulate matter with three degrees of freedom and the log-transformed relative risk of outpatient visits for psoriasis between January 1, 2010 and December 31, 2017 in Beijing, China. The relative risk is adjusted for temperature, relative humidity, public holiday, and day of the week. Dotted lines represent the 95% confidence intervals.

TABLE 3 Increases in outpatient visits for psoriasis associated with a 10-$\mu g/m^3$ increase in levels of airborne fine particulate matter for various lags.

Lag day	Percentage change	95% confidence interval	*P*
Lag 0 day	0.29	0.26–0.32	<0.001
Lag 1 day	0.02	−0.01–0.05	0.428
Lag 2 day	0.11	0.09–0.14	<0.001
Lag 3 day	0.10	0.08–0.12	<0.001
Lag 0–1 days	0.20	0.17–0.23	<0.001
Lag 0–2 days	0.23	0.19–0.26	<0.001
Lag 0–3 days	0.24	0.21–0.28	<0.001

TABLE 4 Increases in outpatient visits for psoriasis associated with a 10-$\mu g/m^3$ increase in airborne fine particulate matter stratified by sex, age group, and season.

Subgroups	Percentage change	95% confidence interval	*P*	$^a P$
Sex				0.017
Male	0.24	0.20–0.28	<0.001	
Female	0.35	0.30–0.39	<0.001	
Age (year)				0.017
18–64	0.27	0.23–0.30	<0.001	
≥65	0.41	0.34–0.48	<0.001	
Season				0.051
Cool	0.26	0.16–0.36	0.035	
Warm	0.90	0.82–0.98	0.001	

[a] *P*-value was obtained by Z-test for the difference between the two risk estimates derived from subgroup analyses.

studies have explored the association in some low-level $PM_{2.5}$ areas, the results of our study are meaningful for the developing countries with more serious air pollution problem. Our findings provide new evidence that may assist in improving targeted intervention strategies for psoriasis.

In developed and Western nations, regular outpatient visits often require an appointment and treatments may not be available on the same day or at local clinics. Furthermore, as previous studies have indicated, some psoriasis patients present with mild symptoms (1) and do not require immediate medical attention or hospitalization, therefore electing deferred outpatient services. Currently, China lacks a

TABLE 5 Percentage change in same-day (lag 0) outpatient visits for psoriasis associated with a 10-μg/m^3 increase in airborne concentrations of fine particulate matter using various degrees of freedom (*df*) for calendar time, temperature, and relative humidity.

Variable	*df*	Percentage change	95% confidence interval	*P*-value
Calendar time	6	0.29	0.26–0.32	<0.001
	7*	0.24	0.21–0.27	<0.001
	8	0.24	0.20–0.27	<0.001
	9	0.17	0.14–0.20	<0.001
Temperature	5	0.29	0.26–0.32	<0.001
	6*	0.33	0.30–0.36	<0.001
	7	0.31	0.28–0.34	<0.001
	8	0.29	0.26–0.32	<0.001
Relative humidity	3*	0.29	0.26–0.32	<0.001
	4	0.29	0.26–0.32	<0.001
	5	0.29	0.26–0.32	<0.001
	6	0.29	0.26–0.32	<0.001

*The *df* value used in this study model.

general practitioner-based referral system (38). Regular patient visits to the outpatient departments of hospitals do not require an appointment and are made on a first-come, first-served basis (39). In 2014, 95% of hospital visits in China were outpatient visits (39, 40). This is the main manner by which Chinese patients obtain medical advice, and the daily count of outpatient visits is a good indicator by which to evaluate the association of air pollution and psoriasis. We included a citywide outpatient visit dataset to ensure the representativeness and authenticity of our findings.

We found that increases in $PM_{2.5}$ concentrations correlated with outpatient visits for psoriasis. A 10-μg/m^3 increase in $PM_{2.5}$ levels corresponded to a 0.29% increase in same-day outpatient visits. Although the risk is relatively weak, the public health burden is extensive in China because of its large population and considerable air pollution.

To date, only two studies have investigated the effect of $PM_{2.5}$ on psoriasis. A citywide survey in Korea found that every 10 μg/m^3 increase in $PM_{2.5}$ resulted in patient visit increases of 2.71% (95% CI 0.76–4.71; $P < 0.01$) (41). Another observational study with both case-crossover and cross-sectional design conducted in Italy also suggested that exposure to mean $PM_{2.5}$ over 15 μg/m^3 in the 60 days before assessment were associated with a higher risk of psoriasis area and severity index 5 or greater point worsening (adjusted odds ratio, 1.25; 95% CI, 1.0–1.57) (42). Despite some differences in study design and method, the evidence from these two studies strongly supports our study. Multivariate negative binomial regression analysis was conduct in the study of Korea rather than Poisson model because there were over dispersion of data. In addition, the health effects are greater at low-level air pollution area generally. These may account for the larger effect size in Korea. There are a lot of differences between the Italian study and our approach. For the study location, the Italian study was based on hospital data, which could provide a more detailed observation of psoriasis pathological indicators and incorporate more accurate disease outcomes. In addition, based on cohort data, this study could record patients' repeated hospital admissions in detail, which also enabled both case-crossover and cross-sectional design to be carried out. Although there are some differences in method, this study is consistent with our conclusions regarding the association between $PM_{2.5}$ and psoriasis. Further studies with larger cohorts and different settings are needed to corroborate our findings.

Some modifiers of the relationship between $PM_{2.5}$ pollution and psoriasis-associated outpatient visits were considered. In our study, the adverse effects of $PM_{2.5}$ were more pronounced in older patients. Similar findings have been reported for other skin diseases (43, 44) and may reflect age-related differences in inflammatory or immune responses. In addition, older individuals are more vulnerable to high levels of airborne particulate pollution (45). Furthermore, a decline in skin barrier functions associated with aging may lead to increased skin sensitivity to environmental irritants, pathogens, and allergens (46). In the present study, we observed higher estimates in female patients. Duvetorp et al. reported that women with psoriasis were more likely to experience anxiety and depression because of the symptoms, resulting in more frequent hospital visits when the disease worsened (47). From our findings, we recommend that older and female patients with psoriasis reduce their personal skin exposure during periods of severe $PM_{2.5}$ pollution, even though we did not find significant differences in the effect of $PM_{2.5}$ concentrations on psoriasis between seasons. The relationship between season and health effects should be investigated further.

Although our findings suggest that $PM_{2.5}$ pollution is related to psoriasis exacerbations, little is known about the underlying biological mechanisms. Research indicates that multiple mechanisms may mediate the adverse effects of air pollution on skin by influencing skin microflora, activating aromatic hydrocarbon receptors, and inducing inflammatory responses and oxidative stress (48). These mechanisms may be similar in the pathogenesis of psoriasis (6). For example, there is evidence that the adverse effects of polycyclic aromatic hydrocarbons in $PM_{2.5}$ are mediated by activation of the aryl hydrocarbon receptor and may lead to autoimmune conditions (48). Transcriptomic analysis has shown that airborne $PM_{2.5}$ may affect the expression of psoriasis-related genes and pro-inflammatory cytokines and exerts adverse effects on human keratinocytes (49). Moreover, a study in human embryonic stem cells reported that $PM_{2.5}$ can disrupt keratinocyte differentiation and the expression of genes related to inflammation and psoriasis (21). Overall, the mechanism by which $PM_{2.5}$ affects psoriasis requires detailed study.

Our study has some limitations. First, it is an ecological study and individual exposure was not determined. Second, because the information was limited, we did not investigate other potential modifiers, such as comorbidities and nutrition, which may be associated with psoriasis. And different stratification by age may also cause bias, and more studies are needed to further explore the association in different age subgroups. Third, the $PM_{2.5}$ monitoring data were provided only by one source, and the lack of authoritative records of other air pollutants limits our investigation of the independent effects of $PM_{2.5}$, requiring verification of the findings. Fourth, because the lack of recent statistical data related to the incidence of psoriasis in Beijing city, and in our study a same person may have multiple visits, it is difficult to calculate the population attributable fraction accurately, more studies are needed to further explore these issues.

Conclusion

The present study provides robust evidence that short-term elevations in $PM_{2.5}$ levels are related to the risk of psoriasis. Long-term observations, estimates of personal exposure, and consideration of other pollutants and lifestyle factors are required.

Data availability statement

The data analyzed in this study was obtained from private datasets. Requests to access these datasets should be directed to yhhu@bjmu.edu.cn.

Author contributions

JW contributed to the study concept, had full access to all the data in the study, take responsibility for the integrity of the work as a whole, and from inception to published article. RY, HY, JW, and HC contributed to the statistical analysis and tables' development of this article. SS and YH interpreted the findings and drafted the article. All authors contributed to the critical revision of the article for important intellectual content.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1015197/full#supplementary-material

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Blue sky as a protective factor for cardiovascular disease

Haosu Tang[1,2,3†], Congyi Zheng[4†], Xue Cao[4†], Su Wang[1,2,3], Linfeng Zhang[4], Xin Wang[4], Zuo Chen[4], Yuxin Song[4], Chen Chen[4], Yixin Tian[4], Wenping Jiang[5], Gang Huang[1,2,3]* and Zengwu Wang[4]* for the China Hypertension Survey Investigators

[1]State Key Laboratory of Numerical Modeling for Atmospheric Sciences and Geophysical Fluid Dynamics (LASG), Institute of Atmospheric Physics, Chinese Academy of Sciences, Beijing, China, [2]Laboratory for Regional Oceanography and Numerical Modeling, Qingdao National Laboratory for Marine Science and Technology, Qingdao, China, [3]University of Chinese Academy of Sciences, Beijing, China, [4]State Key Laboratory of Cardiovascular Disease, Division of Prevention and Community Health, National Center for Cardiovascular Disease, National Clinical Research Center of Cardiovascular Disease, Fuwai Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China, [5]Key Laboratory of Marine Hazards Forecasting, Ministry of Natural Resources, College of Oceanography, Hohai University, Nanjing, China

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EDITED BY
Ang Li,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

REVIEWED BY
Aung Zaw Zaw Phyo,
Monash University, Australia
Cheng-Yang Hu,
Anhui Medical University, China

*CORRESPONDENCE
Gang Huang
hg@mail.iap.ac.cn
Zengwu Wang
wangzengwu@foxmail.com

†These authors have contributed equally to this work

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Objective: Blue sky has been considered to boost outdoor physical activity and social interaction, ameliorate work pressure and life stress, and enhance people's sense of happiness. However, the direct association between blue sky exposure and cardiovascular disease (CVD) still lacks epidemiological evidence. In this study, we aimed to quantify their relationship via a nationwide prospective cohort in China.

Method: We extracted the baseline data from the China Hypertension Survey (CHS), by enrolling 22,702 participants aged ≥ 35 years without self-reported medical history of CVD from 14 provinces of China between 2012 and 2015 and followed up from 2018 to 2019. A blue day was marked out with no rain, low cloud cover ≤ climatological mean at each station, and visibility at 2 pm ≥ 21.52 km. We calculated the number of blue days at baseline survey year to evaluate the chronic individual blue day exposure. Cox proportional hazards models were employed to calculate the multivariable-adjusted hazard ratio (HR). We implemented subgroup analyses as well to identify potential effect modifications.

Results: A total of 1,096, 993, and 597 incident cases of all-cause mortality, fatal or nonfatal CVD, and stroke occurred during a median follow-up around 5 years, respectively. A 10-day increase in annual blue day exposure was associated with a 3% (95% confidence interval [CI]: 1–6%) and 7% (95% CI: 5–10%) decreased risk of fatal or nonfatal CVD and stroke, respectively. Compared with those exposed to the worst tertile of blue days at baseline, subjects who exposed to the best tertile had a 32% (95% CI: 19–43%) and 43% (95% CI: 29–55%) lower likelihood of developing fatal or nonfatal CVD and stroke, respectively. Negative consistent exposure–response relationships were generally observed between them in the restricted cubic spline model. In the stratified analyses, the cardioprotective effects of blue sky were stronger for females, rural residents, and individuals residing in heavily contaminated areas.

Conclusion: This study indicates that blue sky may serve as an independent environmental protective factor against CVD, and informs future policies on fighting air pollution and protecting the blue sky in China.

KEYWORDS

blue sky, cohort, protective factor, cardiovascular disease, air pollution

Introduction

Cardiovascular disease (CVD), including coronary heart disease (CHD) and stroke, is the leading cause of premature mortality and long-term disability worldwide according to the Global Burden of Disease (GBD) study (1). In recent decades, a growing body of literature have well-documented the behavioral risk factors (unhealthy diet, obesity, cigarette smoking, and alcohol consumption, etc.), socio-economic risk factors (such as poverty), environmental determinants (air pollution, heat wave, and residential greenness, etc.) on the mediation of cardiovascular mortality and morbidity (2). Taking into consideration the increasing numbers of CVD incidence and the epidemiological transition (i.e., from communicable to non-communicable diseases like CVD) occurring rapidly in low- and middle-income countries (LMICs) (3), novel underlying determinants of CVD risk need to be detected, especially in developing countries such as China.

Emerging evidences in recent years suggested that residential blue spaces (coast, lakes, and rivers, etc.) could be beneficial for human health and wellbeing (4–6). An equally important but barely studied blue space is blue sky, which is ubiquitous outdoor during daytime. Blue sky has long been deemed as an indispensable part of natural ecosystem and closely tied with day-to-day lives of people. In China, from "Olympic Blue" (7, 8) to "APEC Blue" (9–11) and "Parade Blue" (12), blue sky drew widespread attention whenever mega national event was held. The number of days with blue sky that people could access dramatically affects the mental and physical health and sense of happiness of people. Up to now, whether and to what extent individual exposure to blue sky might be causally associated with beneficial health outcomes remain a knowledge gap.

During 2013–2017 and 2018–2020, Chinese government launched the first 5-year Air Pollution Prevention and Control Action Plan [APPCAP; (13)] and Three-year Action Plan to Win the Blue-Sky Defense War (14), respectively. As a result, the daily average concentrations of ambient air pollutants observed a rapid decline in China during the last decade (15, 16), together with increments in days with blue sky (17). Hence, the quantitative evaluation of the protective effects of blue sky may also carry potential policy implications and facilitate future cost/health-benefit analysis in China.

In this study, we used a population-based, nationwide, prospective cohort in China and selected three health outcomes (i.e., all-cause mortality, fatal or nonfatal CVD, and fatal or nonfatal stroke) as the endpoints. Our primary objective was to explore whether blue sky is an independent environmental protective factor for CVD, and if any, what is the quantitative relationship between them.

Materials and methods

Study design and population

The China Hypertension Survey (CHS) covered a nationwide representative sample of Chinese population *via* a 4-stage stratified multistage random sampling strategy. Details of the CHS were described in our prior studies (18, 19). In brief, during baseline from October 2012 to December 2015, the CHS surveyed ∼ 500,000 participants aged ≥ 15 years from 31 provinces in China. In this study, 35,000 subjects aged ≥ 35 years from 14 provinces were further randomly selected based on their residential districts' geographical locations (East, Central, or West China) and economic development conditions (20). During follow-up between 2018 and 2019, 30,036 participants who finished the physical examinations during baseline were surveyed once again about all-cause mortality and cardiovascular events through face-to-face interview or through electronic questionnaires or telephone [median follow-up ∼5 years; (21, 22)]. We excluded subjects who possessed self-reported medical history of CVD at baseline ($N = 1,318$), lost during follow-up ($N = 3,518$), and had missing values on important risk factors at baseline year ($N = 2,498$). Eventually, we included 22,702 participants overall in the formal analysis and identified no substantial differences between these two sets of study enrollees (Supplementary Table S1). Among the included subjects, three health outcomes, namely, all-cause mortality, fatal or nonfatal CVD, and fatal or nonfatal stroke were examined during follow-up. Finally, we identified 1,096, 993, and 597 incident cases of all-cause mortality, CVD, and stroke, respectively (Figure 1). This study was approved by the Ethics Committee of Fuwai Hospital (Beijing, China), and each participant offered the written informed consent prior to data collection.

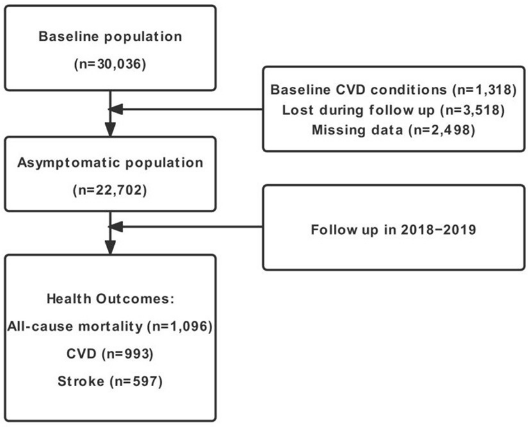

FIGURE 1
Flow diagram of study inclusion. CVD, cardiovascular disease.

Blue day exposure assessment

The current gap in the epidemiological evidence pertaining to the effects of blue sky on CVD primarily originates from lacking in measurement techniques of blue sky. The blue sky could be either defined by ambient air quality from the perspective of environment, or assessed visually *via* cloud cover in the view of meteorology. Thus, it is determined by both environmental and large-scale meteorological conditions (23). For example, blue sky fades to pale when airborne hazes accumulate. Besides, blue sky could not appear in a day with precipitation or high percent of cloud cover even if the ambient air quality is excellent. A day with blue sky could be defined as a blue day, and here we proposed a set of standards to judge whether a day was a blue day. First, a blue day should be sunny, which could be measured by precipitation and low cloud cover. Second, a blue day should possess good air quality, which could be represented by atmospheric visibility.

We extracted observed homogenized daily mean precipitation, low cloud cover, and atmospheric visibility (recorded per day at 2 pm Beijing Time) at 378 ground meteorological stations across China during 1980–2018 after strict quality control (Supplementary Figure S1). Here, we raised three criteria for a blue day as follows: (1) no precipitation (daily precipitation $\leq$ 0.1 mm), (2) low cloud cover $\leq$ 1981–2018 climatology at each station, and (3) atmospheric visibility at 2 pm $\geq$ 21.52 km, which is the mean visibility at all stations during 1980–2018 in China. If a day meets the above three thresholds simultaneously, it would be considered as a blue day. This set of standards could capture almost all well-known blue events in China (APEC Blue, etc.) (24). We calculated the number of blue days at baseline survey year as the measurement of blue day exposure. Therefore, higher value of blue day index indicates more blue day exposure at baseline. We first interpolated the daily meteorological station datasets into 1 $\times$ 1 km grid via Cressman interpolation method. Afterwards, we assigned the address-based blue day exposure of each individual by averaging four grid points' values within its boundary. The impact of the definition of blue day index on the results would be discussed later in the sensitivity analysis sub-section.

Health outcomes

Based on International Classification of Diseases—10th Revision (ICD—10), causes of death and fatal and non-fatal CVD events were coded by well-trained medical staffs at each survey site. These results were further validated *via* death certificates or medical records by the endpoint assessment committee of Fuwai Hospital (Beijing, China). In this study, CVD consisted of stroke (ICD—10 code: I60–I61 and I63–I64), coronary heart disease (I20–I25), chronic heart failure (I50), and deaths owing to CVD (I00–I25, I27–I88, and I95–99). We combined the fatal and nonfatal CVD events into the same category, which provided us relatively more cases to analyze, thereby borrowing us enhanced statistical power. Similarly, the fatal (i.e., ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and unspecified stroke) and nonfatal stroke were combined as well.

Covariates measurement

At baseline, individuals were surveyed about their demographic characteristics, including age, gender, urban/rural residence, ethnicity (Han or ethnic minorities), geographic region (East, Central, or West China), and education level. Besides, the clinical characteristics of participants were collected as well, including smoking status (current, former, or never), alcohol consumption (Yes or No), body mass index (BMI) ($<$ 18 kg/m^2, normal; 18–24 kg/m^2, overweight; and $>$ 24 kg/m^2, obesity), hypertension, hypercholesterolemia, diabetes mellitus, family history of CVD, and CVD medication history.

The annual mean concentrations of ambient fine particulate matter of diameter $\leq$ 2.5 µm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ozone (O_3) at 15 km $\times$ 15 km resolution were derived from assimilations of surface observations from China National Environmental Monitoring Center (25). Aided by the chemical data assimilation system (ChemDAS) developed by the Institute of Atmospheric Physics (Beijing, China), these assimilation products show relatively high consistency with independent observations (R^2 = 0.74–0.86). The baseline ambient air pollutant exposures were assigned based on each participant's residential address. Besides, we obtained annual mean ambient temperature, maximum temperature, relative humidity, and altitude from ∼2419 meteorological stations across China to denote large-scale meteorological conditions and assigned these variables likewise (Supplementary Figure S2). These meteorological datasets were strictly quality controlled by the National Meteorological Information Center (NMIC) of China Meteorological Administration (CMA) (http://data.cma.cn/).

Moreover, annual average years of education, per capita gross domestic product (GDP), and population density across survey counties were extracted from the Data Center for Resources and Environmental Sciences for China (https://www.resdc.cn/) as surrogates to demonstrate socioeconomic statuses. We also derived normalized difference vegetation index (NDVI) and enhanced vegetation index (EVI) with high spatial (1 km × 1 km) and temporal (monthly) resolutions from the moderate resolution imaging spectroradiometer (MODIS) products (MOD13A3, version 6, https://lpdaacsvc.cr.usgs.gov/appeears/), which has been widely used to denote the long-term residential greenness exposure. In addition, we calculated the frequency of extreme heat waves to denote the extent of sun exposure, which is defined as annual number of days when maximum temperature ≥ 90th percentile of 1961–1990 climatology (26). Likewise, we assigned these variables to each participant according to their geocoded residential address.

Statistical analysis

We presented the continuous variables with means ± standard deviation (SD), while the categorical variables with absolute numbers (relative percentages). The between-group comparisons of continuous (categorical) variables were examined *via ANOVA* (χ^2) test. We calculated the incidence rates (per 1,000 person-years) of three health outcomes. Cox proportional hazards models were employed to quantify longitudinal association between blue day exposure and all-cause mortality and cardiovascular events. We interpreted the derived results *via* two methods. First, we used a 10-day increment in the annual blue day exposure. Besides, we categorized the blue day exposure into three categories (worst tertile [≤ 42.0 days/year], middle tertile [42.0–77.4 days/year], best tertile [≥ 77.4 days/year]). Hazard ratios (HRs) were shown with the worst tertile as the reference group. We first applied the change in estimate approaches combined with directed acyclic graphs (DAG) to select the confounders. Finally, we adjusted for the following lists of covariates: (a) In model 1, we adjusted for age, sex, urbanity, ethnicity, geographic region (East, Central, and West), educational level, smoking status, alcohol consumption, and BMI; (b) In model 2, we additionally adjusted for hypertension, hypercholesterolemia, diabetes mellitus, family history of CVD, CVD medication history; (c) In model 3, we additionally adjusted for outdoor $PM_{2.5}$ concentrations and ambient temperature; (d) In model 4, we further adjusted for county-level average years of education, per capita GDP, population density and altitude.

Given the possible nonlinear association between chronic blue day exposure and all-cause mortality and cardiovascular events, we included the restricted cubic spline (RCS) model in our Cox model. The knot number was determined by Akaike information criterion (AIC), while the nonlinear association was examined via the likelihood ratio test. Point estimates and 95% confidence intervals (CIs) reporting as the 2.5th and 97.5th percentiles of the posterior distributions were calculated. Finally, we implemented a series of subgroup analyses, stratified by age (35–59, ≥ 60 years old), sex, urbanity, BMI (< 24, ≥ 24 kg/m^2), outdoor $PM_{2.5}$ concentrations (< 60, ≥ 60 μg/m^3), and individual medical history (i.e., hypertension, hypercholesterolemia, and diabetes mellitus).

To test the robustness of the results in the main analyses, several sensitivity analyses were performed: (a) using another definition of blue day index, which was based on fixed threshold values (22); (b) using another window of blue day exposure (i.e., 3-year mean before baseline year); (c) changing outdoor $PM_{2.5}$ concentration into dichotomous variable given the possible collinearity between blue day index and $PM_{2.5}$; (d) removing participants who died or got disease within the first year after the baseline survey; (e) excluding subjects whose residential address changed during follow-up to evaluate the possible impact of the movement of study participants; (f) excluding subjects who possessed baseline life-limiting chronic diseases (i.e., tumor, kidney disease, chronic obstructive pulmonary disease, and rheumatic immune disease) which could likely be fatal within the next few years; (g) including relative humidity at baseline year additionally as the covariate; (h) including frequency of extreme heat waves additionally as the covariate; (i) including NDVI or EVI additionally as the covariate; (j) including NO_2 or O_3 additionally as the covariate.

The statistical significance was delineated at two-tailed $p < 0.05$. SAS version 9.4 (SAS Institute Inc, Cary, NC) and R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) were used to conduct statistical analyses.

Results

Descriptive statistics

Table 1 demonstrated the descriptive statistics for the enrolled participants at baseline according to blue day exposure tertile. Our CHS cohort included 22,702 entrants, of which 46.3% were males. Among the three groups, participants with higher blue day exposure tended to be less educated and have lower BMI. Moreover, they had a higher prevalence of hypercholesterolemia and family history of CVD, and were less exposed to $PM_{2.5}$ in general.

Figure 2 described the geographical distributions of annual blue days at baseline survey year in China. Vast urban agglomerations in China (Beijing-Tianjin-Hebei region and the

TABLE 1 Baseline characteristics of study participants.

Characteristics	Overall (n = 22,702)	Tertiles of blue days (days/year)			P value
		Worst tertile 3.7–42.0 (n = 7,426)	Middle tertile 42.0–77.4 (n = 6,962)	Best tertile 77.4–122.3 (n = 8,314)	
Age, years	56.1 ± 13.1	56.2 ± 13.4	57.5 ± 12.4	54.9 ± 13.3	<.001
Male	10,505 (46.3)	3,512 (47.3)	2,946 (42.3)	4,047 (48.7)	<.001
Urban	10,130 (44.6)	4,090 (55.1)	2,530 (36.3)	3,510 (42.2)	<.001
Han ethnicity	20,315 (89.5)	7,360 (99.1)	5,342 (76.7)	7,613 (91.6)	<.001
Region					<.001
East	9,263 (40.8)	3,167 (42.6)	2,120 (30.5)	3,976 (47.8)	
Central	9,460 (41.7)	4,259 (57.4)	1,899 (27.3)	3,302 (39.7)	
West	3,979 (17.5)	0 (0)	2,943 (42.2)	1,036 (12.5)	
Education at least middle school	11,109 (48.9)	3,783 (50.9)	3,348 (48.1)	3,978 (47.8)	<.001
Smoking					<.001
Current	5,731 (25.2)	1,878 (25.3)	1,582 (22.7)	2,271 (27.3)	
Former	1,216 (5.4)	313 (4.2)	450 (6.5)	453 (5.4)	
Never	15,755 (69.4)	5,235 (70.5)	4,930 (70.8)	5,590 (67.2)	
Alcohol consumption	6,318 (27.8)	1,893 (25.5)	1,743 (25.0)	2,682 (32.3)	<.001
BMI (kg/m^2)					<.001
Normal	10,213 (45.0)	3,156 (42.5)	2,994 (43.0)	4,063 (48.9)	
Overweight	8,533 (37.6)	2,891 (38.9)	2,663 (38.3)	2,979 (35.8)	
Obesity	3,956 (17.4)	1,379 (18.6)	1,305 (18.7)	1,272 (15.3)	
Hypertension	8,957 (39.5)	2,914 (39.2)	3,044 (43.7)	2,999 (36.1)	<.001
Hypercholesterolemia	7,724 (34.0)	2,221 (29.9)	2,488 (35.7)	3,015 (36.3)	<.001
Diabetes mellitus	2,286 (10.1)	706 (9.5)	840 (12.1)	740 (8.9)	<.001
Family history of CVD	2,621 (11.5)	793 (10.7)	791 (11.4)	1,037 (12.5)	<.001
CVD medication history	4,929 (21.7)	1,577 (21.2)	1,892 (27.2)	1,460 (17.6)	<.001
Ambient temperature, (°C)	24.6 ± 4.3	26.8 ± 2.4	22.2 ± 5.7	24.7 ± 3.1	<.001
$PM_{2.5}$, (µg/m^3)	61.7 ± 22.5	70.8 ± 25.2	59.0 ± 23.9	55.9 ± 15.1	<.001
NO_2, (µg/m^3)	29.3 ± 13.3	33.7 ± 11.1	26.8 ± 18.4	27.4 ± 8.1	<.001
O_3, (µg/m^3)	56.7 ± 10.4	56.7 ± 10.7	57.1 ± 10.8	56.3 ± 9.8	<.001

Numbers are mean ± SD or no. (%). BMI, body mass index; CVD, cardiovascular disease; $PM_{2.5}$, particles with an aerodynamic diameter of ≤ 2.5 µm; NO_2, nitrogen dioxide; O_3, ozone.

Yangtze River Delta, etc.) had relatively few blue days for the period 2012–2015, possibly due to severe air pollution induced by rapid land urbanization and unoptimized energy structure (27). On the other side, Northeast China, Inner Mongolia, North Xinjiang, and Yunnan province had a great many blue days as high as 100 days/year, probably thanks to favorable weather conditions all year round. We further calculated the stratified numbers of baseline annual blue days (Supplementary Table S2). The results showed that rural residents and people living in west China tended to enjoy more blue days than urban counterparts and those in east and central China, respectively. Besides, higher exposure to blue days was generally associated with lower ambient mean temperature. We also noted that lower $PM_{2.5}$ or NO_2 did not necessarily denote more blue day exposure, which could be due to the modification by large-scale meteorological conditions. We calculated the Pearson correlation coefficients between $PM_{2.5}$ or NO_2 and blue day index for all counties/districts, and the correlations are nonsignificant.

Associations of blue sky with health outcomes

At ∼5-year follow-up, the incidence rates of all-cause mortality, fatal or nonfatal CVD, and stroke were 10.49, 9.45, and 5.64 per 1,000 person-years, respectively. In the multivariable-adjusted Cox regression models, a 10-day increase in annual blue day exposure was associated with 3% (95% CI: 1–6%) and 7% (95% CI: 5–10%) lower risks of fatal or nonfatal CVD and stroke, respectively (Table 2). It suggested that blue sky may serve as the protective factor for cardiovascular events. In comparison with those exposed to the worst tertile of blue days at baseline, subjects who exposed to the best tertile had a 32% (95% CI: 19–43%, $p_{trend} < 0.001$) and 43% (95% CI: 29–55%, $p_{trend} < 0.001$) lower likelihood of developing fatal or nonfatal CVDs and strokes, respectively. The association in all-cause mortality was not significant (HR = 1.00, 95% CI: 0.98–1.02). Negative consistent dose-response relationships were observed in blue day exposure and fatal or nonfatal CVD and stroke as well (Figure 3). The associations between blue day exposure and the HRs were L-shaped for CVD ($p_{nonlinearity} < 0.05$) and linear-shaped for stroke ($p_{nonlinearity} = 0.083$).

Figure 4 presented the subgroup analysis results as well as interaction tests to assess the underlying effect modifications. In sex-stratified subgroup, females were inclined to benefit more from blue day exposure than males. When classifying by urbanicity, we found a significant protection effect only in rural residents. Compared with rural residents living in the worst tertile of blue day exposure, those in the best tertile had 60% (95% CI: 46–70%, $p_{interaction} < 0.001$) lower odds of developing CVDs, and 63% (95% CI: 46–74%, $p_{interaction} < 0.001$) fewer strokes. Moreover, a more pronounced protection effect was observed in people living in heavily contaminated areas ($PM_{2.5} \geq 60\ \mu g/m^3$), with 37% (95% CI: 22–49%, $p_{interaction} = 0.005$)

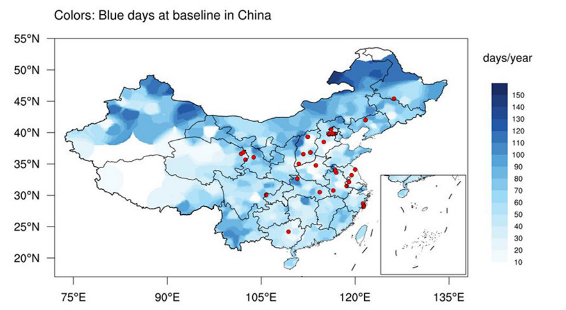

FIGURE 2
The geographical distributions of annual blue days (color, days/year) and 30 China Hypertension Survey sites (red dots) at baseline (2012–2015) in China.

TABLE 2 Hazard ratios (95% CIs) for chronic blue day exposure with all-cause mortality and cardiovascular events.

	Per 10-day increment	Tertiles of blue days			P_{trend}
		Worst tertile	Middle tertile	Best tertile	
All-cause mortality					
No. of cases	1,096	320	347	429	/
Incidence rate[†]	10.49	10.25	10.73	10.50	/
Adjusted Model 1[a]	1.00 (0.98–1.02)	1.00 (ref)	0.89 (0.74–1.06)	0.93 (0.80–1.08)	0.421
Adjusted Model 2[b]	1.00 (0.98–1.02)	1.00 (ref)	0.86 (0.72–1.03)	0.93 (0.80–1.08)	0.455
Adjusted Model 3[c]	1.00 (0.97–1.02)	1.00 (ref)	0.80 (0.66–0.96)	0.85 (0.72–1.00)	0.131
Adjusted Model 4[d]	1.00 (0.98–1.02)	1.00 (ref)	0.84 (0.70–1.00)	0.88 (0.75–1.04)	0.241
CVD (fatal + nonfatal)					
No. of cases	993	305	347	341	/
Incidence rate[†]	9.45	9.73	10.69	8.27	/
Adjusted Model 1[a]	0.98 (0.96–1.00)	1.00 (ref)	1.13 (0.95–1.34)	0.80 (0.68–0.93)	0.002
Adjusted Model 2[b]	0.98 (0.96–1.00)	1.00 (ref)	1.06 (0.90–1.26)	0.78 (0.67–0.92)	0.001
Adjusted Model 3[c]	0.96 (0.94–0.98)	1.00 (ref)	0.91 (0.76–1.10)	0.63 (0.53–0.76)	<.001
Adjusted Model 4[d]	0.97 (0.94–0.99)	1.00 (ref)	0.86 (0.72–1.03)	0.68 (0.57–0.81)	<.001
Stroke (fatal + nonfatal)					
No. of cases	597	192	209	196	/
Incidence rate[†]	5.64	6.09	6.39	4.72	/
Adjusted Model 1[a]	0.95 (0.92–0.97)	1.00 (ref)	1.19 (0.95–1.49)	0.70 (0.57–0.86)	<.001
Adjusted Model 2[b]	0.94 (0.92–0.97)	1.00 (ref)	1.11 (0.89–1.40)	0.69 (0.56–0.84)	<.001
Adjusted Model 3[c]	0.91 (0.88–0.94)	1.00 (ref)	0.93 (0.74–1.17)	0.50 (0.39–0.64)	<.001
Adjusted Model 4[d]	0.93 (0.90–0.95)	1.00 (ref)	0.80 (0.64–1.00)	0.57 (0.45–0.71)	<.001

[†]Incident rate per 1,000 person-years.
CVD, cardiovascular disease.
[a]Model 1: adjusted for age, sex, urbanity, ethnicity, geographic region, educational level, smoking status, alcohol consumption, and BMI.
[b]Model 2: Model 1 + hypertension, hypercholesterolemia, diabetes mellitus, family history of CVD, and CVD medication history.
[c]Model 3: Model 2 + outdoor $PM_{2.5}$ concentrations, and ambient temperature.
[d]Model 4: Model 3 + county-level average years of education, per capita GDP, population density, and altitude.

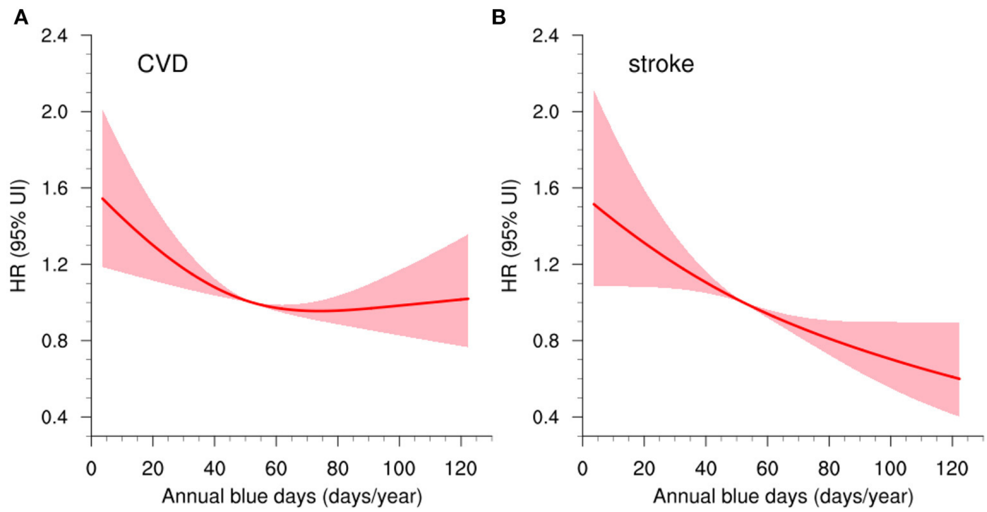

FIGURE 3
Concentration−response curves (red lines) with 95% CIs (shadings) of blue day exposure (days/year) and **(A)** fatal or nonfatal CVD, and **(B)** fatal or nonfatal stroke. CVD, cardiovascular disease.

fewer CVDs and 52% (95% CI: 36–64%, $p_{interaction} < 0.005$) fewer strokes in the best tertile compared with the worst one.

Sensitivity analyses

The results in the main analysis were consistently observed in almost all sensitivity analyses (Supplementary Table S3), implying that different definitions of blue day index, exposure windows, groups of study enrollees, and further adjustments for more underlying covariates did not substantially bias the main conclusions.

Discussion

This population-based nationwide prospective study investigated the relationship between chronic blue day exposure and CVD among individuals aged 35 years and older in China. This cohort investigation found that higher levels of blue day exposure were longitudinally associated with lower risks of cardiovascular incidences, especially in females, rural residents, and people living in heavily contaminated areas. These results robustly hold in the sensitivity analyses. Our work may carry potential societal advantages and public health importance. We highlighted that policies to increase blue sky in China may provide opportunities for better cardiovascular fitness.

In the present study, we observed a slightly stronger cardioprotective effect of blue sky for females. This gender disparity may be partly explained by the hypothesis that women might be more susceptible to the change of external environments (28). Besides, we found that rural residents were more likely to benefit from blue sky than their urban counterparts. It could to some extent be attributed to the outdoor farm work such as the spring planting and autumn harvest by rural residents in China. In that case, they may have more actual contact with blue sky (Supplementary Table S2). In addition, people in heavily contaminated areas were observed to gain more cardiovascular protective benefits of blue sky. This is in accord with guidelines on CVD prevention in clinical practice (29), which indicated that individuals with the highest risk at baseline tend to obtain the most benefits from preventive efforts.

Over recent decades, short- and long-term exposure to air pollutants, as typified by $PM_{2.5}$, are suggested important modifiable risk factors of cardiovascular outcomes (morbidity, mortality and biomarkers) (30–32), and thereby have become an emerging focus field in environmental epidemiology. This study offered a different view to evaluate how the clean air would benefit CVD since the clean air contributes to blue sky. Here, we proposed several potential pathways and mechanistic links by which chronic blue day exposure could lower cardiovascular incidences. First, increased blue day exposures are often tied with lower exposure to ambient air pollutants and better air quality, which are beneficial for cardiovascular health (33–35). Second, people under higher blue day exposure are more willing to enjoy outdoor sports and have contact with natural environment. An extensive number of studies have documented the benefits of physical exercise on elevated cardiovascular fitness through adaptations to the heart and vascular system (36). Recent evidence from cardiovascular cohorts demonstrated that the cardioprotective effects of physical exercise may mediate the traditional or untraditional CVD risk factors. Specifically,

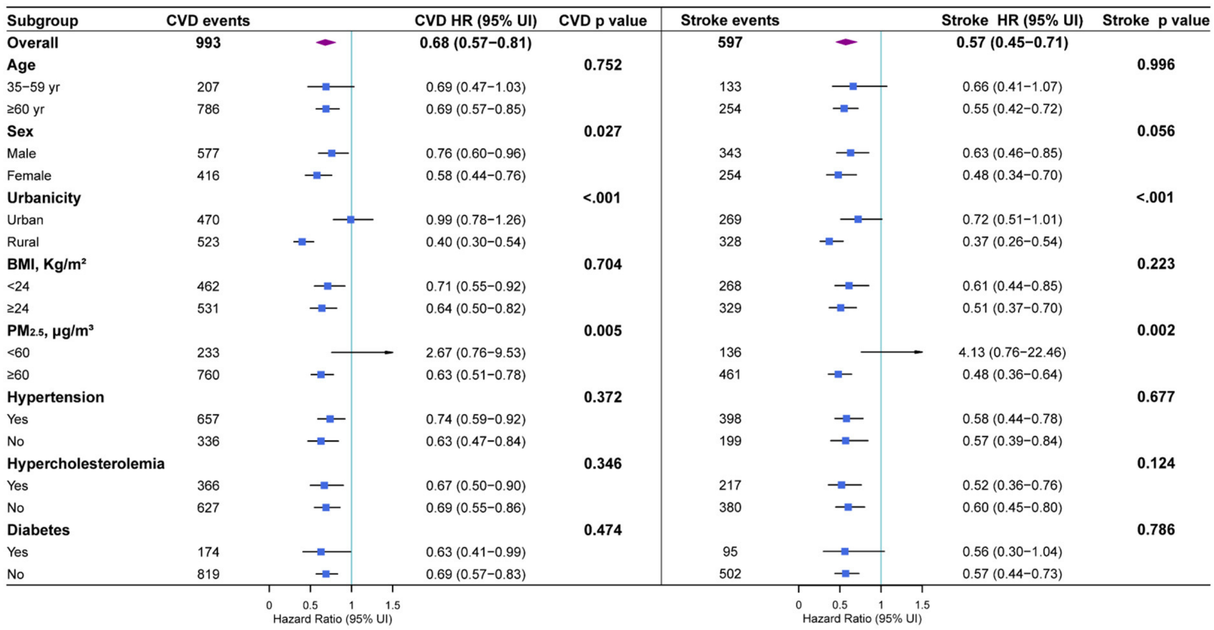

FIGURE 4
Subgroup analyses for full-adjusted hazard ratios (95% CIs) of fatal or nonfatal CVD and stroke with the best tertile compared to the worst tertile in annual blue day exposure.

regular physical activity practice is related to decreased blood pressure and arterial stiffness, increased insulin sensitivity, and a more favorable inflammatory marker profile (37). Thus, enhanced access to blue sky is associated with a better physical quality of life and fewer incidences of non-communicable diseases like CVD (38). Third, blue sky may significantly relieve feelings of anxiety and depression. This psychological recovery will contribute to lower risks of CVD (39). Fourth, blue day exposures would exert a subtle influence on forming social relationships since people are more likely to meet each other in the neighborhood, which may further promote positive outlooks on life as well as active and healthy lifestyles. This boost in social interaction and cohesion would impede the development of CVD (40).

Implications and future research

During the past decade, growing environmental epidemiological studies focused on the blue spaces (lakes, waterways, canals, ponds, coasts, etc.), indicating that living near the coast or inland water bodies may serve as a protective factor for human health including CVD (4–6). In the present study, we attempted to extend the concept of traditional blue spaces and probed the potential relationship between blue sky exposure and CVD. The observations in this study provided a novel line of evidence from existing literatures that how the environment would mediate the burden of CVD. Moreover, we obtained a nationally representative dose–response curve for the blue sky–CVD relationship *via* the RCS model and it could be informative for policymakers to evaluate current progress toward clean air and blue sky, and guide future environmental policy-making and public health advancement in China.

However, owing to the partial nature of our work, it is still too early to provide definitive answer about the beneficial effects of blue sky on human health at this stage. Further studies are required to reveal the relationships between blue sky and other health outcomes and the underlying mechanisms. Besides, it ought to be acknowledged that the definition of blue sky in this study is subjective to some extent given the selection of the three criteria. We would leave such efforts to future studies that could define a more objective blue sky index through technologies such as the satellite remote sensing. Moreover, due to the limited access to observational meteorological, environmental, and human health records, the study region of the present study was confined in China. Future investigations on the potential health benefits of blue skies on world's population living in South Asia, Africa and South America where the air pollution risks are still heavy may be preferable. Furthermore, we have not yet analyzed the respective contribution of air pollution and meteorology/climate to the number of blue days. Additional studies can employ climate model simulations to differentiate the effects of climate from those of air pollution in space and in time (16), which would favor future cost/health-benefit analysis of air pollution reduction programs in China.

Strength and limitations

The major strength of this study is that we identified a potential independent environmental protective factor for CVD, i.e., blue sky. Although blue sky has long been deemed beneficial for cardiovascular health intuitively, here we strived to provide epidemiological evidence and build up their statistical relationship. These results might be instrumental in the attribution of GBD from environmental causes. Besides, we adopted a nationally representative cohort and incorporated a relatively large sample size, which would elevate the statistical power of the findings in this study. Moreover, our study baseline recruitment and follow-up periods were nearly simultaneous with air pollution reduction programs in China that were implemented in 2013–2020, offering the latest high-quality cohort evidence pertaining to the CVD burden associated with the blue sky. Finally, we accounted for a variety of covariates (including demographic, clinical, environmental, and socioeconomic covariates) to adjust for the latent confounding as far as possible.

Despite these advantages, the limitations of the present study also merit consideration. First, the present study was essentially an ecological study, and the discrepancy between individual perception and environmental concentrations (i.e., exposure misclassification) may to some extent bias our results. Second, the limited follow-up period of our CHS cohort (median ∼5 years) may somewhat weaken the statistical power of our results. Thus, the insignificant association between blue day exposure and all-cause mortality shown in this study does not necessarily mean there is no connection between them and we should treat this result with caution. Future researches of a longer follow-up period would be carried out as our CHS cohort marches forward. Additionally, although we adjusted for the corresponding covariates, a likelihood of residual confounding still exists. For instance, the simple "Yes or No" binary classification may be insufficient to adequately control for stressors related with alcohol consumption. A quantitative classification as (a) no alcohol consumption (never), (b) no alcohol consumption (former), (c) low consumption, and (d) high consumption based on national/international guidelines would be preferable. Therefore, our findings need to be confirmed by future studies in other settings. Last, we cannot rule out the potential confounding biases brought by other covariates such as dietary habits and exercise. These potential mediating, confounding or modifying effects may be important and deserve future studies.

Conclusions

In summary, findings from this study offered nationally representative epidemiological evidence for a significant protective association of long-term blue sky exposure with fatal or nonfatal CVD, adjusting for demographic, clinical, environmental, and socioeconomic covariates. This study provided novel insights on probing the environmental determinants of CVD risk. In tandem with previous studies, our work appeals for the continuous implementation of air quality management in China in the future to further protect the blue sky and promote cardiovascular health.

Data availability statement

The meteorological and environmental datasets used in this study are available from the corresponding author upon request. Requests should be directed to ZW to access the CHS cohort datasets.

Ethics statement

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

Author contributions

HT: conceptualization, methodology, formal analysis, software, visualization, and writing—original draft preparation. XC: methodology, data curation, formal analysis, software, and investigation. CZ: software, investigation, and validation. GH and ZW: conceptualization and funding acquisition. All authors: writing—reviewing and 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.2022.1016853/full#supplementary-material

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EDITED BY
Zhiming Yang,
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Abdul Hanif Khan Yusof Khan,
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Pontifical University of Salamanca, Spain
Tamer M. S. Hifnawy,
Beni-Suef University, Egypt

*CORRESPONDENCE
Marwa Rashad Salem
mr80002000@kasralainy.edu.eg;
mr80002000@cu.edu.eg

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Climate change-related knowledge and attitudes among a sample of the general population in Egypt

Marwa Rashad Salem[1]*, Nelly Hegazy[2], Anas Abdullnasser Thabet Mohammed[3], Esraa Mahrous Hassan[4], Mohamed Mohyeldin Saad Abdou[5] and Marwa M. Zein[1]

[1]Department of Public Health and Community Medicine, Faculty of Medicine, Cairo University, Manial, Cairo, Egypt, [2]Department of Public Health and Community Medicine, Faculty of Medicine, Helwan University, Helwan, Egypt, [3]Faculty of Medicine, Cairo University, Cairo, Egypt, [4]Faculty of Medicine, El Menia University, Minya, Egypt, [5]Faculty of Medicine, Emergency Resident, Cairo University, Cairo, Egypt

Introduction: Identifying the public awareness and risk perception regarding climate change, are fundamental preliminary steps in determining gaps and paving the way for awareness campaigns that address climate change causes and counteraction mitigation measures. However, few studies were conducted in Egypt; thus, the researchers conducted the current cross-sectional study among a sample of the Egyptian population to identify general knowledge and perception about climate change and its effects, as well as attitudes toward mitigation measures.

Methods: An exploratory population-based electronic-open survey, was conducted among 527 members of the general population between January and April 2022, using a convenience sampling technique. A pre-tested 2-page (screen) electronic included three sections: sociodemographic characteristics, global warming/climate change-related knowledge, and attitude toward climate change mitigation.

Results: The average global warming knowledge score was 12 ± 3. More than 70% (71.1%) of the participants were knowledgeable (percentage score >70%). Approximately half of the enrolled participants (48.2%) agreed that everyone is vulnerable to the effects of global warming/climate change. More than three-quarters (78.3%) of the participants agreed that carbon emissions from vehicles and industrial methane emissions were the first factors that contributed to climate change, followed by the ozone holes (731%). Global warming/climate change-related knowledge was statistically higher in participants aged of >30 years, married participants, urban residents, highly educated individuals, and employed individuals (p-value ≤ 0.05). Approximately 80% of the participants agreed that responding to the questionnaire drew their attention to the topic of climate change and its effects. More than two-thirds of those polled agreed that increasing public transportation use could help mitigate the effects of climate change/global warming, followed by the materials used and the direction of construction.

Conclusion: More than two-thirds of the participants were knowledgeable regarding climate change. Social media and the internet were the main sources of information. However, participants need to get the information in a different way that could help in changing their attitude positively toward the issue of climate change mitigation. The current study recommends the need for various initiatives that work should be launched.

KEYWORDS

climate change, general population, Egypt, knowledge, attitudes

Introduction

Climate change (CC) is an unavoidable issue that poses a significant risk to human health on a global scale (1). Between 2030 and 2050, CC is expected to cause an additional 250,000 deaths per year due to starvation, malaria, diarrhea, and heat stress. By 2030, it is anticipated that direct health harm expenses will range from $2 to $4 billion annually (2). The areas least equipped to manage without support to plan and respond will be those with limited health infrastructure, which will largely be found in developing countries (2).

Despite its low contribution to greenhouse gas emissions, Africa is considered the most vulnerable continent to the impacts of CC (3). CC has resulted in rising temperatures, rising sea levels, changes in precipitation patterns, and more extreme weather events. All of these new changes in Africa endanger human health, food, and water security and impede socioeconomic development (4).

According to reports from the Intergovernmental Panel on Climate Change, Egypt, as a developing country and part of Africa, is recognized as highly vulnerable to CC impacts due to its geographical location and reliance on climate-sensitive economic sectors (5, 6). Egypt was ranked 107th out of 181 countries in the 2019 ND-GAIN Index, which informs the public sector about their vulnerabilities and readiness to deal with CC and its impacts and to prioritize their efforts and investments (7). Egypt is now facing waves of heavy rainfall, rising sea levels, and the risk of flooding coastal areas such as Alexandria, as well as a large area of the Nile Delta_ Egypt's most cultivated land_ which could have an adverse impact on national food security and result in economic loss (8). A study conducted in 2014, has anticipated that the continuing trend of decreasing agricultural production, malnutrition, hazardous health effects of particulate matter, and heat stress, combined with a subsequent decline in tourism revenues, will result in a substantial economic loss, estimated to reach 2–6%of Egypt's future gross domestic product (9).

Previous research has examined the perceptions of climate risks in either the developed or developing world to better understand the effects of CC on community health (10, 11). Another study revealed that public perceptions of CC and its impact on health may inform policies to deal with CC-related health challenges (12). A recent study conducted among the general population in Bangladesh revealed that the knowledge of CC was average and education was the most influential factor in understanding CC and its impact on health (13).

Identifying public awareness and risk perception regarding CC are critical preliminary steps in determining the gaps and paving the way for awareness campaigns that address CC causes, counteraction, and mitigation measures. However, few studies have been conducted in Egypt; thus, the researchers conducted the current exploratory cross-sectional study among a sample of the Egyptian populationto identify general knowledge and perception about CC and its effects, as well as attitudes toward mitigation measures. The study results can provide the foundation to develop community-based awareness campaigns, draw attention to the causes, indicators, and broad hazards of CC, and advocate for the urgent need to support strict governmental policies to combat it. Egypt has entered a golden age with the launch of the National Climate Change Strategy 2050, which prioritizes Egyptians' quality of life and seeks to serve as a road map to achieving the updated Egypt Vision 2030 (14).

Materials and methods

Study design

The current study is an exploratory population-based electronic-open survey that was conducted among a convenient sample of the general population during the study duration from January 2022 to April 2022. The research was presented following the Checklist for Reporting Results of Internet E Surveys (CHERRIES) guidelines (15).

Sample size and sampling technique

The sample size was calculated using the following formula, n = required sample size, = 1.96, P = prevalence of the outcome (54%), based on a study conducted in Bangladesh in which the majority of the participants (54.2 %) had some knowledge of CC

(13), E = margin of error; 0.05. Assuming a 25% non-response rate, a sample of 478 participants was required.

The inclusion criteria of participants were as follows: (i) being an Egyptian resident, (ii) being adults (≥18 years old), and (iii) and willing to participate.

Data collection tools and techniques

A pre-tested 2-page (screen) electronic questionnaire was used to collect data from the study participants. It was divided into three sections:

1. Sociodemographic characteristics: age in years, gender, education, occupation (working or not), the field of study (biology, medicine, public health, others), marital status, and place of residence.
2. The knowledge of study participants regarding global warming and CC and related consequences was composed of 15 questions. The questions were formatted in closed-ended with yes, no, and do not know options.
3. Attitude toward efforts to combat CC: composed of six questions. The questions were formatted with close-ended agree, disagree, and neutral options.
4. Multiple options formats were used to obtain knowledge on factors contributing to CC and sources of knowledge about CC and global warming.

The questionnaire was adapted from previously published literature (16–20) (see Supplementary File I). Two language experts translated the questions into Arabic and then back-translated them into English by another two independent language experts.

Because of the COVID-19 critical situation to achieve social distance, the researchers used an online data collection method. A Google form was created, and participants were invited to fill it out and submit it. The researchers distributed the questionnaire link to groups on Facebook and WhatsApp. A pilot test was conducted with 10% of the calculated sample size (not included in the study) to assess the clarity of the questions. Two questions were deleted due to non-specific responses. The questionnaire's content was validated by four faculty members who are Public Health experts, and the necessary changes were made. Cronbach's alpha coefficient of 0.879 confirmed the reliability of the Knowledge and Risk Perception of CC and the global warming questionnaire.

Statistical analysis

The researchers used SPSS (Statistical Package for Social Science) version 26.0 (IBM, SPSS, USA) for statistical analysis. Categorical variables were expressed as proportions and percentages. Quantitative variables were examined for normality. Quantitative variables were expressed using mean, standard deviation, median, and interquartile range (IQR); the researchers used the Chi-Square test of significance for comparison. A *P*-value of 0.05 or less was considered significant.

Knowledge question responses were coded 1 for yes responses and 0 for no and don't know responses. The 15 questions responses were added and the score percentage was calculated.

The knowledge percent score was grouped as knowledgeable ≥70%, not knowledgeable <70% following Jamshidi et al., (21), and the individual scores were aggregated and grouped into five categories to indicate the overall knowledge level of respondents: not very knowledgeable (0–1), low knowledge

TABLE 1 Baseline characteristics of the study participants (N = 527).

Variables	*N*	%
Gender		
Male	184	34.9
Female	343	65.1
Marital status		
Married	125	23.7
Not married	402	76.3
Residence		
Urban	316	60.0
Rural	211	40.0
Education		
Read and write	3	0.6
Secondary school	89	16.9
Higher education	435	82.5
Occupation		
Not Working	349	66.2
Working	178	33.8
Is your study or occupation within the field of natural sciences (biology, medicine, public health)		
Yes	319	60.5
No	208	39.5
Have you attended any training courses or workshops on climate change or global warming and its effects during the past 12 months		
Yes	30	5.7
No	497	94.3
Have you heard of the terms global warming/climate change?		
Yes	479	90.9
No	18	3.4
Don't know	30	5.7

(2–4), average Knowledge (5), knowledgeable (6–7), very knowledgeable (8–10) (22).

Ethical considerations

The National Cancer Institute Cairo University Ethical Review Committee revised and approved the study protocol. The Ethical committee of the faculty of Medicine, Cairo University. All the included participants were treated according to the Helsinki Declaration of biomedical ethics. Before data collection, study participants electronically signed an informed consent after being informed about the purpose of the study and the significance of the online form. Participants were informed that the survey was anonymous and that participation was entirely voluntary. Data confidentiality was maintained throughout the study, and completed forms were accessed only by the investigators.

Results

The questionnaire was opened 531 times and received 527 responses, with a response rate of 99.2%. The study participants ranged in age from 18 to 71 years old, with a mean age of 26 ± 8.

Approximately two thirds 65% of the participants were females, more than three-quarters (76.3%) were not married, and 60% of the enrolled participants lived in urban areas.

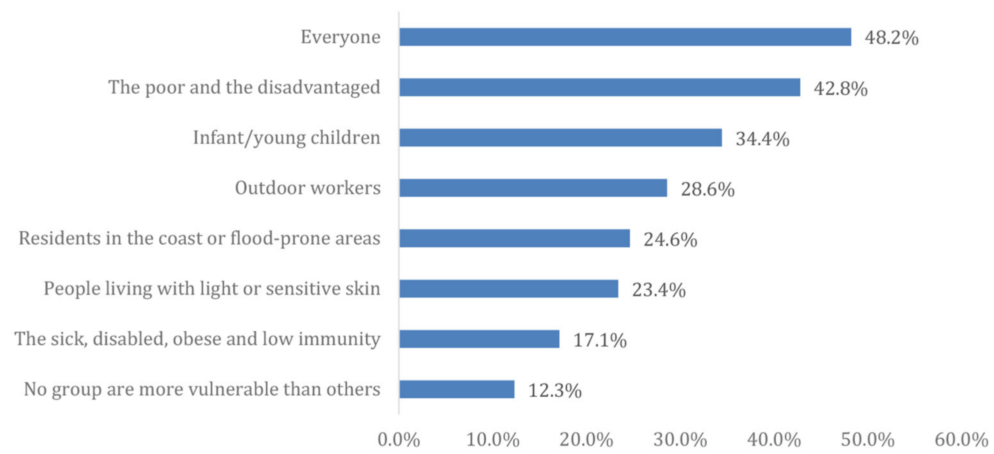

FIGURE 1
More vulnerable people to the effects of global warming/ climate change.

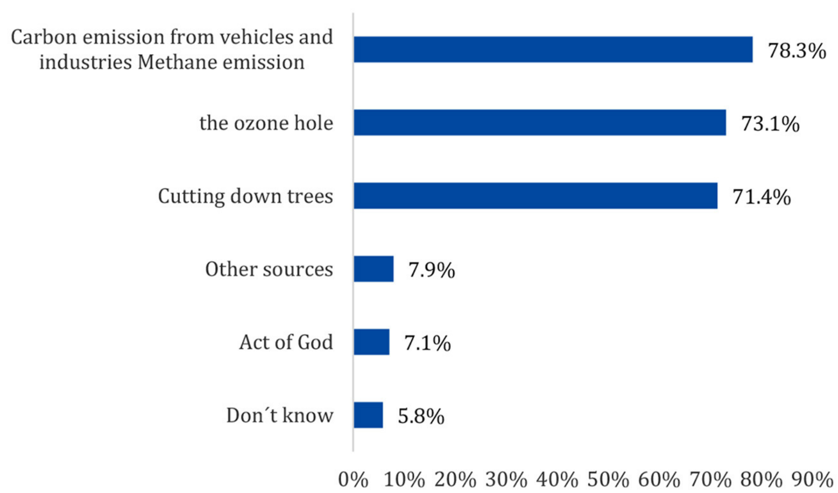

FIGURE 2
Factors contribute to climate change as reported by the enrolled participants.

TABLE 2 Percent distribution of study participants by climate change/global warming knowledge.

Knowledge questions	Yes *N* %	No *N* %	Don't know *N* %
Does global warming have an impact on human health	457 (95.4)	20 (4.2)	2 (0.4)
Climate change			
Increases the incidence of floods	390 (81.4)	75 (15.7)	14 (2.9)
Increases the water shortage problem	368 (76.8)	91 (19.0)	20 (4.2)
Is increasing the rate of glacier melting	445 (92.9)	24 (5.0)	10 (2.1)
Increases the possibility of extreme heat waves	454 (94.8)	18 (3.8)	7 (1.5)
Increases the likelihood of extreme cold	398 (83.1)	69 (14.4)	12 (2.5)
Increases the spread of diseases that are transmitted from one person to another such as gastroenteritis	352 (73.5)	102 (21.3)	25 (5.2)
Increases the prevalence of malnutrition diseases	293 (61.2)	163 (34.0)	23 (4.8)
Increases the likelihood of non-communicable diseases such as lung diseases such as asthma and respiratory problems	360 (75.2)	93 (19.4)	26 (5.4)
Affects mental health and increases anxiety and depression	337 (70.4)	125 (26.1)	17 (3.5)
Can impede health institutions to perform their role during severe cold spells or extreme heat	375 (78.3)	91 (19.0)	13 (2.7)
Displaces people and increases the number of refugees	354 (73.9)	112 (23.4)	13 (2.7)
Developed countries contribute more to climate change	344 (71.8)	123 (25.7)	12 (2.5)
Developing countries are more vulnerable to the effects of climate change	363 (75.8)	104 (21.7)	12 (2.5)
Climate change will be more severe in the future	410 (85.6)	50 (10.4)	19 (4.0)

TABLE 3 Climate change/global warming knowledge score and knowledge percent score ($n = 478$).

Knowledge score mean ± sd, median (IQR)		12 ± 3		13 (10–14)
Knowledge percent score mean ± sd, median (IQR)		79.5± 19.2		86.7 (66.7–93.3)
Knowledge grouping	Knowledgeable (≥70%)		340 (71.1)	
	Not knowledgeable (<70%)		138 (28.9)	
Level of knowledge	Not very knowledgeable (0%–20%)		5 (1.0)	
	Low knowledge (20%–40%)		13 (2.7)	
	Average knowledge (40%–60%)		35 (7.3)	
	Knowledgeable (60%–80%)		130 (27.2)	
	Very knowledgeable (80%–100%)		295 (61.7)	

The majority (82.5%) were highly educated, and more than two-thirds (66.2%) were not working. Most participants hadn't attended any training courses or workshops on CC or global warming during the past 12 months as displayed in Table 1.

The detailed correct answer to the 15 climate change and global warming knowledge questions was illustrated in Table 2. More than two thirds of the participants were knowledgeable about all the items concerned with the dangerous effects of climate change. The highest percentage was for increasing the possibility of extreme weather such as heat waves and extreme cold, ice melting, the incidence of floods, and that climate change will be more severe in the future. The least correct answer was for the following statement: Global worming increases the prevalence of malnutrition as reported by (61.2%) of the enrolled participants.

As shown in Figure 1, approximately half (48.2%) of the enrolled participants agreed that everyone is vulnerable to the effects of global warming/CC.

Figure 2 depicts the factors contributing to CC; more than three-quarters (78.3%) of the participants agreed that carbon emissions from vehicles and industrial methane emissions were the first factors contributing to CC, followed by the ozone hole (73.1%).

Table 3 demonstrates the climate change/global warming knowledge score; the mean knowledge score was 12 ± 3, with a median score of 13 points (IQR 10, 14). The mean knowledge percent score was 79.5 ± 19.2, with a median of 86.7 (IQR 66.7, 93.3). More than three quarters (71.1%) of the participants were knowledgeable.

As shown in Figure 3 more than 70% of the participants depend mainly on the internet and social media as primary sources of information on climate change/global warming.

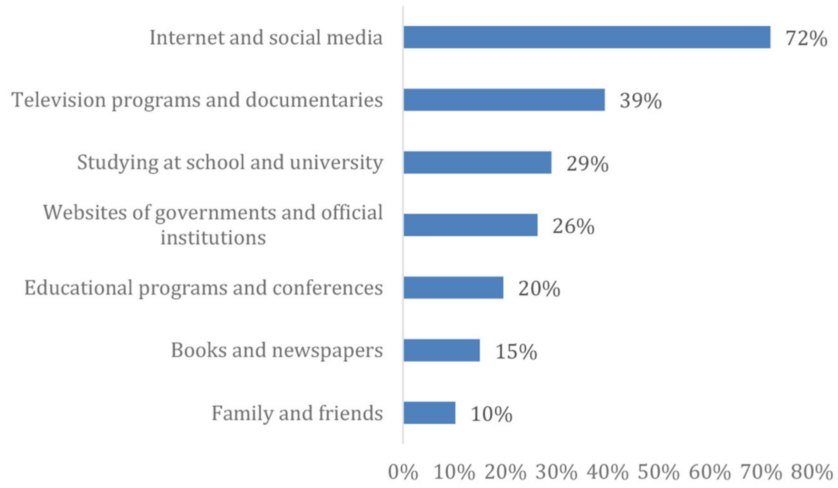

FIGURE 3
Percent distribution of the enrolled participants by source of knowledge.

As shown in Table 4, global warming/climate change-related knowledge was statistically higher in participants aged >30 years, married, urban residents, highly educated, and employed (p-value ≤ 0.05).

Figure 4 depicts some mitigation measures, which revealed that more than two-thirds of the enrolled participants agreed that increasing public transportation use could reduce the effects of climate change/global warming, followed by the materials used and the construction direction.

Figure 5 illustrates that most of the respondents agreed on providing incentives to enterprises that succeed in reducing greenhouse gas emissions and inventing low carbon intensive options as a mitigation measure to combat global warming. Approximately 80% of participants agreed that answering the questionnaire drew their attention to the topic of CC and its effects, and more than 60% of the participants would like to learn more about it.

Discussion

According to the current study's findings, 70% of the participants were knowledgeable about the issue of CC and its effects. These results were based on similar studies conducted in other countries, which revealed that more than 80% of the respondents were aware of the problem of CC and its consequences (17, 23). However, the research results contrast with studies conducted in Saudi Arabia, Turkey, and Kenya, which revealed a low level of knowledge about CC among participants (24–26). Notably, more than 75% of the participants were university graduates, with more than two-thirds of them having a field of study or occupation related to natural sciences, which have a significant association with high knowledge scores (27). These findings have shed light on the critical role of education in the issue of CC and the importance of incorporating it, as well as the urgent measures that should be implemented to mitigate its damaging consequences in the school and college curriculum (26–28).

More than two-thirds of the participants were well-versed in all aspects of CC's perilous consequences. The highest percentage predicted that extreme weather such as heat waves and extreme cold, ice melting, flood frequency, and CC will be more severe in the future (17). However, there is a gap in knowledge about who could be more affected by CC, which needs to be addressed. Less than half of the participants polled agreed that CC affects everyone, but certain groups could be more vulnerable than others (29).

Regarding the knowledge of the main causes of CC as an essential step in risk perception, approximately three-quarters of the participants chose carbon emissions from vehicles and industries, followed by the ozone hole, which increases the amounts of UV radiation reaching the Earth, and finally, deforestation. Only 7% of the voters chose an act of God. These findings are consistent with the results of studies conducted in Egypt, Saudi Arabia, and Oman (24, 30, 31). However, in a study conducted in Ghana, more than one-third of the respondents stated that deforestation is the primary cause of CC; interestingly, a small percentages of participants referred to carbon emissions as the cause of CC, with nearly similar votes given to an act of God (23).

Additionally, more than two-thirds of participants are optimistic about CC mitigation measures. Nearly two-thirds of

TABLE 4 Global warming/climate change level of knowledge with sociodemographic characteristics of the participants ($n = 478$).

Variables		Knowledgeable (>70%)	Not knowledgeable (<70%)	*P*-value
Age group	18–30	233 (65.8)	121 (34.2)	<0.001*
	31–40	77 (88.5)	10 (11.5)	
	>40	30 (81.1)	7 (18.9)	
Gender	Male	119 (69.2)	53 (30.8)	0.482
	Female	221 (72.2)	85 (27.8)	
Marital status	Married	97 (81.5)	22 (18.5)	0.004*
	Not married	243 (67.7)	116 (32.3)	
Residence	Urban	237 (76.9)	71 (23.1)	<0.001*
	Rural	103 (60.6)	67 (39.4)	
Education	Read and write	1 (100.0)	0 (0.0)	<0.001*
	Secondary school	21 (38.9)	33 (61.1)	
	Higher education (university and postgraduates)	318 (75.2)	105 (24.8)	
Occupation	Not working	207 (67.2)	101 (32.8)	0.011*
	Working	133 (78.2)	37 (21.8)	
Your study or occupation within the field of natural sciences (biology, medicine, public health)	Yes	236 (76.1)	74 (23.9)	0.001*
	No	104 (61.9)	64 (38.1)	
Have you attended any training courses or workshops on climate change or global warming and its effects during the past 12 months	Yes	18 (64.3)	10 (35.7)	0.410
	No	322 (71.6)	128 (28.4)	

*Statistically significant.

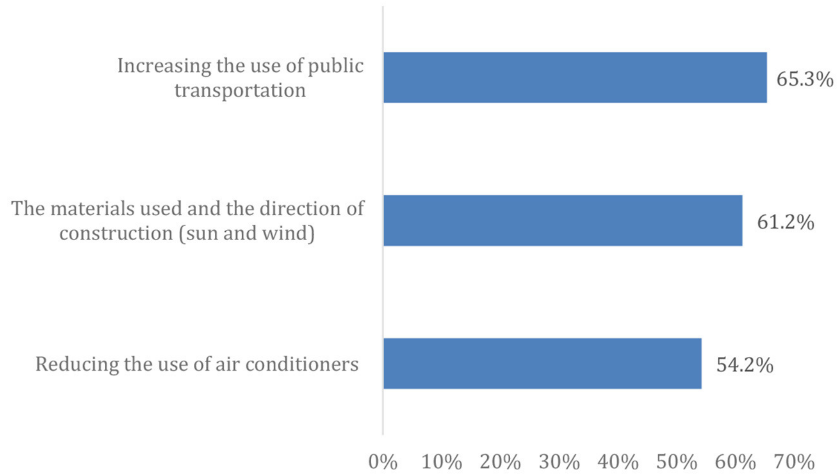

FIGURE 4
Positive attitude toward some factors that can contribute to reducing the impact of climate change.

participants supported the recommended mitigation measures, and the majority supported the idea of providing incentives to enterprises that succeed in reducing greenhouse gas emissions and developing low carbon-intensive alternatives. However, an important consideration should be noted while interpreting these findings that this study was conducted

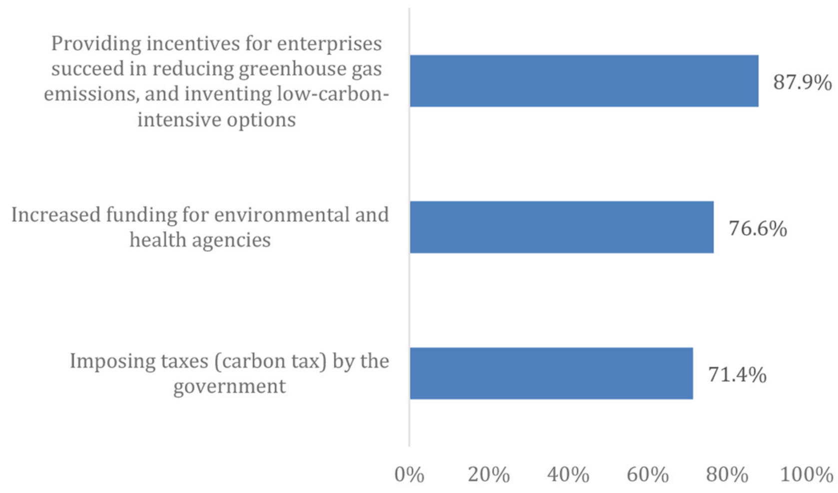

FIGURE 5
Positive attitude toward mitigation measures to reduce global warming.

during the COVID-19 pandemic, which had a significant impact on the perceptions of CC. The detrimental social and economic disruption associated with the COVID-19 pandemic, as well as the significant loss of human life, have attracted people's attention to the interactions between human activities and the environment. Furthermore, pandemic control measures have included mobility restrictions and subsequent behavioral changes, such as working from home and reducing international travel, which consequently have been associated with temporary improvements in air quality and reductions in CO_2 emissions in the environment (32). These circumstances have contributed to raising public awareness of the role of human activities in CC and encouraging a favorable attitude toward urgent policies to combat CC (33). Nonetheless, the public must be more motivated to protect their environment and work hard to restore it to its natural state and conserve its resources. This was evident in the results of a recent Egyptian study, in which climate change/global warming was ranked fifth regarding its significant impact on public life, and sixth regarding its importance to participants (28).

Different sources of information have various degrees of credibility, power of dissemination, and effect on the population. This plays a crucial role in raising public awareness regarding various issues and results in discrepancies in knowledge scores among di fferent populations. This study identified social media and the internet, followed by television programms and documentaries, as the primary sources of information for approximately three-quarters of the participants. Obtaining knowledge from schools or universities was prominent among only one-third of the participants (23). In a study conducted in Oman, TV channels, both international and local, were identified as the primary source, followed by school curricula, and lastly, social media and the internet (27). In a case study conducted in Egypt, most respondents stated that they trusted the information received mainly from scientists and environmental organizations, while approximately one-third relied on the media, such as TV and radio or governmental bodies (28).

The younger generation is our future. They will live longer and will be more vulnerable to the hazardous effects of CC. The next generation has the right to save the environment, preserve natural resources, and work on their efficient use. Consequently, climate literacy is a fundamental step. Consequently, cooperation with the ministry of education will be vital in integrating environmental topics into school and college curricula, considering their ages, to build a new generation highly aware of their environment, with strong values and attitudes, who are more knowledgeable about the required actions to save the environment, adapt to CC and be compatible with achieving the sustainable development goals and aligned with the updated Egypt Vision 2030 (33, 34).

Conclusion

More than two-thirds of the participants were knowledgeable regarding CC. Social media and the internet were the main sources of information. However, participants need to get the information in a different way that could help in changing their attitude positively toward the issue of CC mitigation. The current study recommends the need for various initiatives that work in harmony to combat CC, such as educational campaigns, training workshops, and studies, which take advantage of the prominence of social media, the internet, and television channels for announcing and disseminating valid and credible information and promoting positive change in behavior.

Study limitations

The current study findings should be viewed in light of the following limitations: The observational nature of the study. It was conducted to explore the situation in this new area of inquiry. It was not used to infer causal relationships. And due to the COVID-19 critical situation to achieve social distance, the researchers used the online data collection method. Consequently, the researchers do recommend conducting further studies using face to face interview using a probability sampling technique.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by National Cancer Institute. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MRS conceived the study, contributed to managing the literature searches, and data management. MMSA assisted with the literature search and writing. NH and MZ contributed to data analysis and results writing. AT and EM contributed to data collection and writing. All authors shared in data collection, drafting, approving the final manuscript in the study, contributed to the article, and approved the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1047301/full#supplementary-material

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EDITED BY
Zhiming Yang,
University of Science and Technology Beijing, China

REVIEWED BY
Zhongjun Shao,
Fourth Military Medical University, China
Sasho Stoleski,
Saints Cyril and Methodius University of Skopje, North Macedonia

*CORRESPONDENCE
Yuan Yuan
yuanyuansdu@163.com

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Effects of air pollution on cardiovascular health in patients with type 2 diabetes mellitus: Evidence from a large tertiary hospital in Shandong Province, China

Jitian Zhang[1], Dong Ren[2], Shuo Wang[3], Sha Zhu[4], Kai Qu[5] and Yuan Yuan[1]*

[1]Clinical Nutrition Department, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China, [2]Scientific Research Management Department, Shandong Academy of Macroeconomic Research, Jinan, China, [3]The Center for Economic Research, Shandong University, Jinan, China, [4]Medical Administration Department, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, China, [5]Shandong Provincial Eco-environment Monitoring Center, Jinan, China

Air pollution has posed serious threats to human health. Based on the microdata of a large tertiary hospital in Shandong Province from 2016 to 2021, combined with the macro data such as air quality monitoring data, meteorological data, and city-level regional socio-economic data, this paper empirically tests the impact of air pollution instrumented by thermal inversions on the cardiovascular health of patients with type 2 diabetes mellitus (T2DM) and its group differences. The results show that: (1) Air pollution has a negative impact on the cardiovascular health of patients with T2DM, that is, the cardiovascular health of patients with T2DM will decline in regions with high air pollution; (2) The impact of air pollution on cardiovascular health in T2DM patients is heterogeneous, with males and older patients bearing greater air pollution health losses; (3) From the perspective of the external environment, the negative effects of environmental pollution on patients' health were significantly reduced in areas with higher environmental regulation intensity and better public health conditions, indicating the necessity of strengthening environmental governance and increasing public health expenditure.

KEYWORDS

air pollution, type 2 diabetes mellitus, cardiovascular health, group differences, instrumental variables regression

Introduction

With the development of the economy and the change in environment and lifestyle, the burden of diabetes continues to increase worldwide. The global prevalence of diabetes had reached pandemic proportions with a prevalence of 10.5% (537 million adults) in 2021, and the number of adults with diabetes will continue to rise rapidly and is expected to reach 643 million by 2030 and 783 million by 2045 (1). Cardiovascular disease (CVD) is a major complication in patients with T2DM. Studies have revealed that approximately one in three adults with T2DM had established CVD, and nearly half of all deaths in patients with diabetes could be attributed to CVD (2, 3). Therefore, cardiovascular complications of T2DM have caused serious harm to patients, families, and society.

In recent years, with the acceleration of global industrialization and urbanization, air pollution has become an increasingly prominent problem, which has attracted great attention all over the world. In particular, fine particulate pollution from automobile engines, fireplaces, and coal-fired power plants is easily inhaled, easily enriched with toxic and harmful substances, and widely dispersed. Thus, air pollution affects nearly every organ in the body, causing or contributing to many diseases, such as respiratory diseases, cardiovascular diseases, and even death. The World Health Organization (WHO) warns that all people on the planet are exposed to air pollution levels. The Global Burden of Disease (GBD) study shows that air pollution is the fourth leading risk factor for human mortality. Air pollution is responsible for 9 million deaths worldwide, of which 61.9% are due to CVDs, including ischaemic heart disease (31.7%) and stroke (27.7%) (4). Air pollution is a challenge facing nearly every country in the world. No country, rich or poor, can be immune to air pollution.

Similarly, poor air quality is considered as a major issue in China. Yin et al. (5) estimated the effect of air pollution on deaths, disease burden, and life expectancy across China and its provinces from 1990 to 2017, and found that air pollution remains an important risk factor in China, with 81% living in regions exceeding the WHO Interim Target 1, and 1.24 million deaths in China were attributable to air pollution in 2017, 40.0% of disability-adjusted life-years (DALYs) for chronic obstructive pulmonary disease (COPD) were attributable to air pollution, as were 19.5% for ischaemic heart disease, and 12.8% for stroke. In recent years, the Chinese government has introduced policies, such as the "Action Plan of Air Pollution Prevention and Control," aiming to improve the environment and promote the transformation of the mode of social and economic development. However, does air pollution have a significant impact on cardiovascular health in patients with T2DM? Few scholars have conducted detailed studies. If yes, are there any group differences among different genders and ages? Can government regulation and public health expenditure mitigate or even curb the negative health effects of air pollution? Therefore, it is necessary to quantify the environmental costs of economic policies and to rigorously assess the potential risks to cardiovascular health in patients with T2DM.

The study on the health effects of environmental pollution begins with the health production function proposed by Grossman (6), which describes the relationship between health input and health output. Improving living conditions and sanitation and creating a good environment are considered to be important sources of increasing the health capital stock. This function has become the theoretical basis for mainstream health research in the field of economics. Since then, many scholars have incorporated environmental factors into the health production function and investigated the impact of environmental factors on the health depreciation rate (7–9). Most of the existing studies focus on the field of medicine and public health. Based on micro-individual or non-random samples, epidemiological methods are used to study the dose-response relationship between the concentration of air pollutants and the health of exposed people, and further analyze the impact of air pollution on the health of residents' respiratory system, cardiovascular and cerebrovascular system. For example, a prospective epidemiological study by Hystad et al. (10), based on 157,436 adults aged 35–70 years from 747 communities in 21 high-income, middle-income, and low-income countries, found that an increase of 10 $\mu g/m^3$ in particulate matter less than or equal to 2.5 mm in aerodynamic diameter (PM2.5), cardiovascular events increase by 5%, myocardial infarction increase by 3%, stroke increase by 7%, and CVD mortality increase by 3%. There are few studies on the health effects of air pollution from the perspective of economics. Scholars tend to use quasi-natural experiments to solve the endogenous disturbances of environment and health and evaluate the effects of the environment on health through econometric models. Bayat et al. (11) estimated PM2.5 exposure in 349 communities in Tehran through the Environmental Benefits Mapping and Analysis Program (BenMAP-CE) and used the Global Exposure Mortality Model (GEMM) to estimate the avoidable burden attributable to ambient air pollution in Tehran; the economic and health effects of changes in PM2.5 concentrations were estimated using the value of life-year (VOLY) method. Palma et al. (12) analyzed the causal effect of prenatal exposure to air pollution on neonatal health in Italy in the 2000s by combining detailed information on the mother's residential location from birth certificates with particulate matter less than or equal to 10 mm in aerodynamic diameter (PM10) concentrations from air pollution monitors, and found that an average increase of 10 units of PM10 level would decrease birth weight by about 0.5% and the gestational age by 0.16%; it would increase the prevalence of low birth weight by 22% and of preterm birth by 16%. Maji et al. (13) analyzed the seasonal variation of ground-level O_3 in 338 cities in China during the year 2016 and assessed the city-specific cardiovascular and respiratory disease-related mortality attributable to ozone exposure by the log-linear and linear model, and estimated the city-specific total economic loss in China by the log-linear model. Gu et al. (14) investigated the relationship between air pollution and residents' health by nesting the household registration data of the China Migrant Dynamic Survey in 2014 with city characteristic data and pollution data, and found that the increase in air pollution concentration significantly reduced the health level of residents; after solving the endogenous problems with the instrumental variable (IV)-the ordered probit (OProbit) model, the negative impact of air pollution on residents' health remained significant.

As mentioned above, extensive medical and economic evidence have proved the negative health impacts of exposure to air pollution. Thus, whether environmental regulation and public health services can be used as a breakthrough to recover residents' health losses is a new topic of concern for scholars. Given the short-term effects of environmental policies on health, scholars mainly discuss the effects on health in a relatively short period before and after the implementation of temporary policies. For example, in 2004, the Republic of Ireland implemented a national smoking ban in the workplace. Following the ban implementation, there was a 13% decrease in all-cause mortality, a 26% decrease in ischemic heart disease, a 32% decrease in stroke, and a 38% decrease in COPD within a few weeks (15). For the 2008 Beijing Olympics, the Chinese government imposed factory emissions and travel restrictions from July 1 to September 20. During the implementation period, air pollutant concentrations in Beijing decreased by 62%, resulting in a range of health benefits, including improved lung function in healthy adults and asthmatic adults, a 58% reduction in asthma-related physician visits, lower CVD mortality in women and the elderly, and lower degrees of systemic inflammation among healthy young adults (16). However, the impact of some environmental policies or measures may be lagged after implementation. The implementation of current air pollution prevention policies sometimes has little impact on the environmental quality of the current period, but a large impact on the environmental quality of the next period. Therefore, scholars pay more attention to the long-term health effects of environmental policies. The Clean Air Act, enacted in 1970 and further amended in 1977 and 1990, is the most influential environmental regulation in U.S. history. Since 1990 there has been approximately a 50% decline in emissions of key air pollutants, which also brought dramatic health benefits, 230,000 deaths per year averted from lower concentrations of outdoor PM, 7,100 premature deaths per year averted from lower ozone concentrations, 200,000 fewer acute myocardial infarction cases per year, and 2.4 million asthma exacerbation are prevented each year (17–19). In Western Europe and the European Union, air quality regulations have significantly reduced air pollution and improved small-airway health in adults. Schindler et al. (20) found that from 1991 to 2002, PM10 in Switzerland decreased by 6.2 mg /m^3 on average and was associated with 259 fewer people with regular cough, 179 fewer people with chronic cough or sputum, and 137 fewer people with dyspnea or shortness of breath per 10,000 people in the community. In China, the research on the long-term health effects of environmental policies has just started, and most of the relevant studies are qualitative discussions with relatively little empirical evidence.

To date, health assessment studies on environmental policies are mainly conducted in foreign countries. Most of the studies on the health effects of air pollution in China focus on the fields of medicine and public health and are mainly characterized by statistics. Few studies discuss the health effects of environmental policies from the perspective of economics. To this end, based on the data of T2DM patients from Yi Du Cloud Medical Research Data Platform of Shandong Provincial Hospital Affiliated to Shandong First Medical University, this paper incorporates environmental factors into the health production function to discuss the impact of air pollution on the cardiovascular health of T2DM patients. The main contributions of this paper are as follows. Firstly, compared with medical and public health research, this paper analyzes the effects of air pollution on health from micro and macro dimensions. Secondly, this paper focuses on the effects of air pollution on cardiovascular health in patients with T2DM, which is different from previous studies on the general population. Thirdly, this paper further explores the differential effects of air pollution on cardiovascular effects in T2DM patients of different genders and ages and conducts heterogeneity analysis based on environmental regulations and medical health conditions, which has theoretical and practical implications.

Theoretical background and hypotheses

The effect of air pollution on cardiovascular health in patients with T2DM

In 2021, WHO updated Global Air Quality Guidelines, pointing out that no country met the latest WHO PM2.5 air quality guidelines, suggesting that air pollution poses a major threat to health, and calling on all countries in the world to adopt a "health in all policy" to solve the pollution problem. Theoretically, air pollution can damage the function of the respiratory and circulatory systems and have an obvious negative impact on human health. A large number of medical and epidemiological studies have shown that air pollution (such as sulfur dioxide, atmospheric particulate matter, etc.) is the cause of CVDs in residents (21, 22). However, only a part of the health consequences of environmental pollution can be observed, and current studies have not provided sufficient evidence of the magnitude of the negative health effects. To explore the influence of environmental factors on the occurrence and development of T2DM, this paper included environmental factors in the research scope of health economics to evaluate the effect of air pollution on cardiovascular health in patients with T2DM, which would be the first theoretical hypothesis to be tested in this study:

Hypothesis 1

Air pollution has a negative effect on cardiovascular health in patients with T2DM, controlling for other confounding factors.

The population difference in the effects of air pollution on cardiovascular health in patients with T2DM

Based on the environmental equity theory, environmental pollution and environmental risk exposure have different effects on the health of different social groups. To a large extent, air pollution can have an impact on human cardiovascular health through other systems such as the respiratory system. However, individual differences (characteristics, geographical, economic development level, etc.) can cause environmental iniquity, whether in the same environment or not, the effects of health on groups with different individual characteristics may show heterogeneity. In 2020, China's seventh national census showed that the number of people aged 60 and above reached 264 million, accounting for 18.7 percent of the total population, an increase of 5.44% compared with 2010, indicating a further deepening of population aging. In addition, the worse the air quality, the greater the risk of disease in the elderly, and the lower the health level of the elderly. Honda et al. (23) studied 4,121 people over 57 years old in the United States and found that air pollution may be a key risk factor for abnormal glucose metabolism and diabetes in the elderly. Then, is there also age heterogeneity in the impact of air pollution on cardiovascular health, the main complication in patients with T2DM? Similarly, compared with women, men are more likely to engage in outdoor physical activities and are exposed to air pollution for a longer time, is there gender heterogeneity in the impact of air pollution on cardiovascular health in patients with T2DM? Thus, this paper puts forward Hypothesis2 (H2):

Hypothesis 2

The effects of air pollution on cardiovascular health in patients with T2DM show gender and age differences: male and the elderly bear more environmental losses and greater health risks than female and the young.

The effect of environmental regulation and public health input on health effects of pollution

The externality of environmental public goods may lead to differences in the cost of health damage caused by air pollution among different groups, but previous empirical studies in the field of economics rarely consider this difference. Yang and Zhang (24) estimated the impact of air pollution exposure on household healthcare expenditure by using the China Urban Household Survey (UHS) Database, and showed that a 1% increase in yearly exposure to PM2.5 would lead to a 2.94% increase in household health expenditure. It is estimated that the 13th Five-Year Plan for Ecological and Environmental Protection will reduce annual national medical and health expenditures by 47.36 billion U.S. dollars, accounting for 0.64% of China's gross domestic product (GDP). Giaccherini et al. (25) analyzed the heterogeneous effects of particle pollution on Italian daily hospitalizations and their costs and found that a one standard deviation increase in PM10 leads to additional 0.79 hospitalizations per 100,000 residents, total daily costs represent 0.5% of the total daily health expenditure. However, as an important environmental public good, can strengthening environmental regulation and public health investment reduce the health harm caused by air pollution? This perspective is rarely involved in domestic research. Economic development is bound to damage and affect the environment, and environmental pollution is an important factor affecting people's health. However, economic development also allows the government to invest more funds in public health to improve people's livelihood and health. Therefore, should we follow the old path of "development first, governance later"? Or should we strengthen environmental regulation within the limits of the self-purification of the ecological environment, to minimize the damage to the environment in the process of economic development, and at the same time, we make good use of the economic dividends and increase the investment in public health? In view of this, this paper proposes the following assumptions:

Hypothesis 3

In areas with enhanced environmental regulation and increased public health investment, patients enjoy higher environmental welfare and bear smaller health risks.

Materials and methods

Data sources and processing

In this paper, we combine the microdata of patients with T2DM with the macro data such as air quality monitoring data, meteorological data, and city-level regional socio-economic data, to evaluate the impact of air pollution on the cardiovascular health of patients with T2DM.

Firstly, the health data comes from the Yi Du Cloud Medical Research Data Platform, which collects the data of patients with T2DM admitted to the Endocrinology Department of Shandong Provincial Hospital Affiliated to Shandong First Medical University from 2016 to 2021, including basic information such as age and gender, health behavior information such as smoking, alcoholism, and various medical laboratory indicators, and the prevalence of CVDs, which is considered by scholars to be very detailed data for studying health problems. After matching, a total of 1,446 T2DM patients were enrolled, covering 16 prefecture-level cities in Shandong Province.

Secondly, the air pollution data are derived from the Shandong Provincial Public Data Open Network[1] To accurately obtain the air quality data of the prefecture-level cities where the patients are located, this paper determines the admission dates and prefecture-level cities where the patients with T2DM are located from 2016 to 2021 and selects the observation data of the corresponding monitoring sites. Considering the time lag effect of patient onset, the specific admission date of each patient is backward 1 month, 3 months, and 6 months, and the average value of the corresponding daily air quality data is taken.

Thirdly, the inversion difference intensity data are obtained from the Modern-Era Retrospective Analysis for Research and Applications, Version 2 (MERRA-2) dataset, released by NASA's Global Modeling and Assimilation Office[2]. This dataset records the air temperature data of 42 atmospheric pressure layers (different altitudes have different atmospheric pressures) at a resolution of 0.5° × 0.625° in the unit of the month. This paper, quasi-change the raster data into urban panel data for analysis to meet the high requirements of data quality and precision (26). Specifically, this paper first calculate the average temperature of the atmosphere at 540 and 110 m, respectively and then calculates the difference between them. If the average temperature of the atmosphere at 540 m is higher than that of the atmosphere at 110 m, then the day is a temperature inversion (27).

Finally, since meteorological conditions can also affect the health of patients, it is necessary to control meteorological factors. First,we obtain the original natural meteorological data through the China Surface Climate Data Daily Value Dataset (V3.0)[3], a national meteorological scientific data-sharing service platform. Then, we interpolate the original data into grid data using the Inverse Distance Weighted (IDW) method and calculate the average value in different regions. And last, we acquire multidimensional weather variables including annual average temperature (Temperature), average rainfall (Rainfall), Light hours (Light), and average wind speed (Wind) of the patient's location.

In addition, this paper also collects the economic and social development variables of the prefecture-level cities where the patients are located, including urbanization rate (Urbn), GDP per capita (PGDP), and the number of hospital beds per capita (Beds), which are derived from the China City Statistical Yearbook and the Statistical bulletin of prefecture-level cities.

1 Data source: https://data.sd.gov.cn/portal/index.

2 Raw data on inversion days can be downloaded from NASA's website: https://disc.gsfc.nasa.gov/datasets/M2I6NPANA_5.12.4/summary.

3 Data source: http://data.cma.cn/.

Model setting

The aim of this paper is to empirically examine the effects of air pollution on cardiovascular health in patients with T2DM. As mentioned above, the severity of the disease may vary depending on gender, age, weight, lifestyle, and key medical indicators. Climate change can also lead to imbalances between body functions and climate conditions. At the same time, the regional economic and social development conditions will also affect the physical quality of patients. Therefore, individual characteristics, climatic conditions, and regional development should be taken into account when assessing the severity of the disease. Therefore, the benchmark regression model of this paper is as follows:

$$Diseases_{i,j,t}=\beta_0+\beta_1X_{i,j,t-1}+\gamma I_{i,j,t}+\mu C_{j,t}+\delta D_{j,t}+T_t+S_i+\varepsilon_{i,j,t}$$

In Equation, the subscripts *i, j,* and *t* indicate the individual patient, the region, and the time, respectively; *Diseases* represent the severity of CVD in patients with T2DM; *X* indicates the degree of air pollution, the core explanatory variable of the model, which is represented by the concentration of PM2.5 and PM10 1 month before admission in this paper; *I*, *C* and *D* are control variables, which represent the individual characteristic variable, climate variable and regional economic and social characteristic variable of patients over time, respectively, and γ, μ, and δ are their coefficients, respectively. β_0 is a characteristic variable of individual patients that does not change over time and region, and β_1 is the core explanatory variable coefficient of this paper. In addition to this paper, we also controlled for region and time-fixed effects.

Variable construction

Explained variable: Prevalence of CVD in T2DM patients

In this paper, we collect the disease diagnosis information of patients with T2DM from the Yi Du Cloud Medical Research Data Platform of the Provincial Hospital affiliated to Shandong First Medical University, including whether they had coronary heart disease, myocardial infarction, and hypertension, and add up the prevalence of these three CVDs. "None of the three diseases," "one disease," "two diseases" and "all three diseases" are assigned values 0 to 3, respectively. The higher the value, the more severe the CVD in patients with T2DM. Compared with a single measurement index, this method is more consistent with the reliability and validity of statistics.

TABLE 1 Descriptive statistics ($n = 1,446$).

Variable	Variable description	Mean	Standard	Min	Median	Max
Diseases	Ordinal variable 0–3 (-)	0.8373	0.7460	0.0000	1.0000	3.0000
PM2.5_1	Continuous variable	0.5496	0.2496	0.1407	0.4917	1.6570
PM10_1	Continuous variable	1.0878	0.3927	0.2897	1.0680	2.3447
Individual level variables						
Gender	Male = 0, female = 1	0.4057	0.4912	0.0000	0.0000	1.0000
Age	Continuous variable (year)	57.8283	13.4488	10.5828	59.4099	93.0000
BMI	Continuous variable (kg/m^3)	26.0277	6.8675	13.7000	25.6000	47.7000
Smoking	Yes = 1, No = 0	0.3947	0.4889	0.0000	0.0000	1.0000
Drinking	Yes = 1, No = 0	0.4323	0.4956	0.0000	0.0000	1.0000
FT_3	Continuous variable (pmol/L)	4.3480	1.4857	1.4700	4.3000	30.2500
BUN/Cr	Continuous variable (-)	88.3680	29.5866	21.1300	84.4400	272.7300
Climate variables at the city level						
Temprature	Continuous variable (°C)	13.9190	0.6087	11.4635	13.8529	15.3437
Rainfall	Continuous variable (mm)	794.6238	100.8081	473.7313	828.1262	1100.0000
Light	Continuous variable (h)	2400.0000	144.1834	2000.0000	2400.0000	2900.0000
Wind	Continuous variable (m/s)	2.6993	0.3456	1.7827	2.7399	3.7847
Regional socio-economic characteristic variables						
Urbn	Continuous variable (-)	0.6699	0.0774	0.4736	0.7053	0.7717
PGDP	Continuous variable (RMB 10,000/person)	8.8783	2.7036	3.0028	9.8372	15.6797
Beds	Continuous variable (per thousand person)	6.5385	0.9754	3.7374	6.7614	8.2130

PM2.5_1 and PM10_1 represent PM2.5 and PM10 concentrations 1 month before admission, respectively; In the original data, the unit of PM2.5 and PM10 concentration is $\mu g/m^3$. Considering the magnitude units of other variables, this paper divided the original concentration data by 100 in empirical regression.

Core explanatory variable: Air pollution

Air pollutants are composed of particulate matter and gaseous pollutants. According to the classification of aerodynamic equivalent diameter, particles with aerodynamic equivalent diameter $\leq 100\,\mu m$ are collectively referred to as "total suspended particulate matter" (TSP), and particles with aerodynamic equivalent diameter less than or equal to 10 μm are collectively referred to as "inhalable particulate matter" (PM10). Particulate matter with an aerodynamic equivalent diameter of 2.5 μm or less is called fine particulate matter (PM2.5). Among them, PM2.5 and PM10 are the most intensively studied and extensively monitored. Gaseous pollutants include nitrogen oxides, such as nitrogen dioxide (NO_2) and sulfur dioxide (SO_2). Therefore, the concentration of PM2.5 and PM10 1 month before admission (PM2.5_1 and PM10_1) is selected as the air pollutant variables in the empirical analysis, and the SO_2 concentration 1 month before admission (SO_2_1) is used to conduct the robustness test.

Other control variables

In this paper, we learn from previous studies on health influencing factors and introduce individual characteristics of patients as control variables, such as gender, age, body mass index (BMI), lifestyle habits (whether smoking or drinking), free triiodothyronine (FT3) level and blood urea nitrogen to creatinine ratio (BUN/Cr), to minimize estimation bias due to omitted variables. In addition, we control for city-level climate variables such as Temperature, Rainfall, Light, and Wind, and included city-level regional socio-economic characteristics such as Urbn, PGDP, and Beds. Table 1 shows the descriptive statistics of each variable in this study.

Figure 1 Further depicts the distribution of PM2.5, PM10, and SO_2 concentrations in different months and in different cities. Figure 1A shows that the concentration of air pollutants varies greatly in different months, especially in winter. This is because Shandong Province is located to the north of Qinling Mountains and Huaihe River, and air pollutants will increase significantly during winter heating. Figure 1B shows that the air pollution in Jinan, Zaozhuang, and Dezhou is more serious, while the air quality in Weihai, Qingdao, and Yantai is better. In general, the concentration of air pollutants varies greatly in different months and cities, which meets the needs of empirical analysis.

Results

Benchmark regression

Impact of air quality on cardiovascular health of residents

This paper first estimates the overall impact of air pollution on the cardiovascular health of patients with T2DM

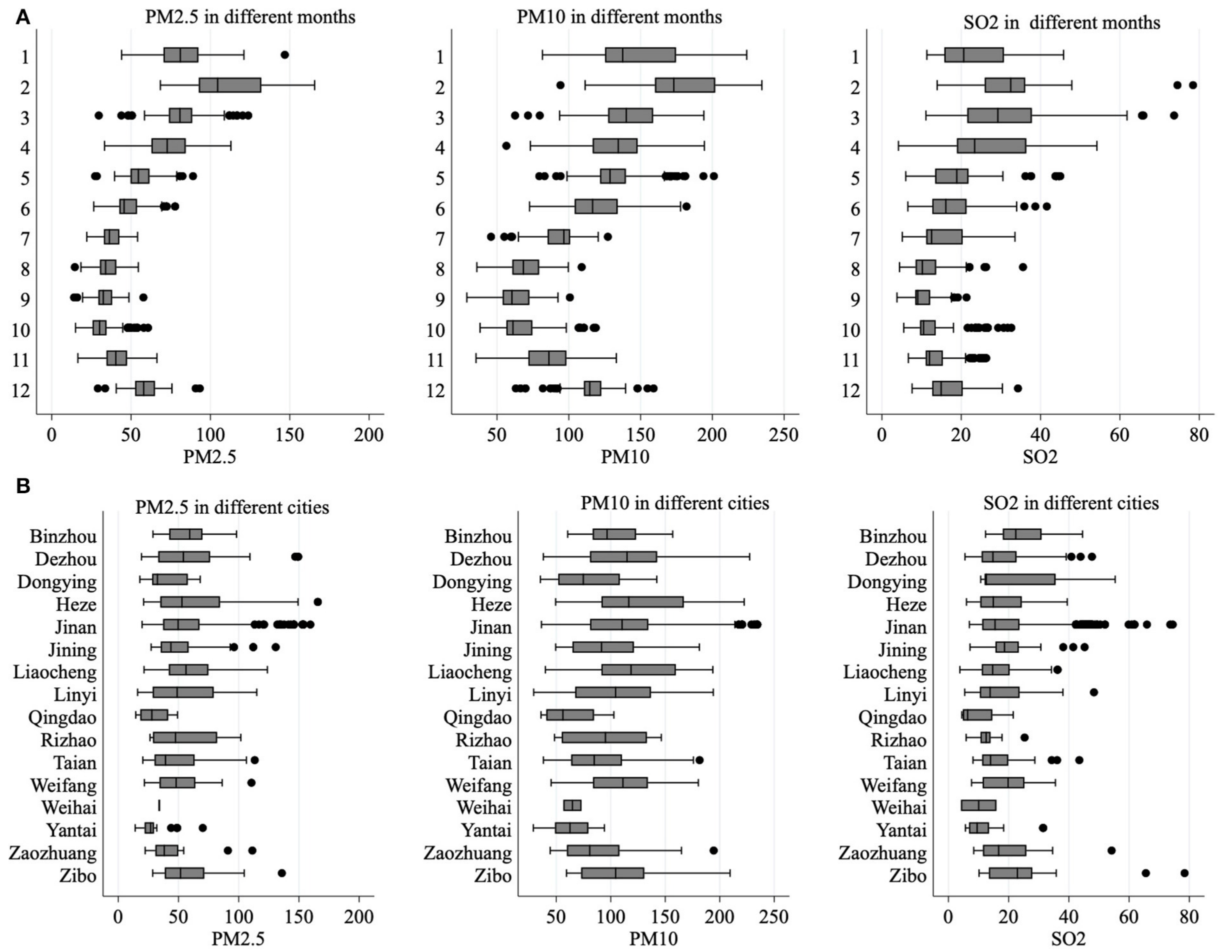

FIGURE 1
(A,B) Air pollution in different months and cities.

according to the model set. Secondly, to reduce the endogenous estimation bias caused by the omitted variables, individual characteristics, regional climate, and economic and social characteristics are gradually controlled. The results are shown in Table 2. In column (1), this paper only adds air pollution variables and individual characteristic variables characterized by PM2.5 and estimates them based on a two-way fixed effect model. The results show that the coefficient of PM2.5_1 is significantly positive at the statistical level of 5%. The results in columns (2)–(3) show that the air pollution variable represented by PM2.5 is always significantly positive at the statistical level of 5% after successively adding climate variables such as Temperature, Rainfall, Light and Wind and regional socioeconomic characteristics variables such as Urbn, PGDP, and Beds. This indicates that the aggravation of air pollution will worsen the severity of CVD in patients with type 2 diabetes. From an economic perspective, for every 1 unit standard deviation increase in PM2.5_1, the severity of the patient's CVD will increase by a 5.58% standard deviation. Similar to the first three columns, control variables are also added in turn in columns (4)–(6). The difference is that PM10 is used to represent the air pollution variable. It can be seen from the results that the variable PM10_1 is always significantly positive at the statistical level of 5%, and hypothesis 1 is verified. For every 1 unit standard deviation increase in PM10_1, the severity of CVD of T2DM patients will increase by 5.70% standard deviation. The conclusion is still stable after changing different pollution indicators. Another interesting finding is that the absolute value of the estimated coefficient of PM2.5_1 is larger than the concentration coefficient of PM2.5_1. This is because PM2.5 is easier to enter the respiratory tract than PM10, which will cause harm to human cardiovascular function.

This paper first adopts the heteroscedasticity robust standard error. However, due to the impact of objective factors such as air pollution in various regions on the cardiovascular health of patients with T2DM in one region, it is bound to

TABLE 2 Benchmark regression results.

Variable	(1)	(2)	(3)	(4)	(5)	(6)
PM2.5_1	0.1601**	0.1594**	0.1668**			
	(0.0807)	(0.0807)	(0.0807)			
	[0.0794]	[0.0794]	[0.0793]			
PM10_1				0.1033**	0.1048**	0.1083**
				(0.0512)	(0.0511)	(0.0511)
				[0.0513]	[0.0513]	[0.0512]
Gender	0.1236**	0.1222**	0.1233**	0.1228**	0.1212**	0.1222**
	(0.0542)	(0.0541)	(0.0542)	(0.0542)	(0.0541)	(0.0542)
Age	0.0193***	0.0195***	0.0196***	0.0194***	0.0196***	0.0197***
	(0.0015)	(0.0015)	(0.0015)	(0.0015)	(0.0015)	(0.0015)
BMI	0.0058	0.0057	0.0059	0.0060	0.0058	0.0060
	(0.0084)	(0.0083)	(0.0083)	(0.0084)	(0.0083)	(0.0083)
Smoking	−0.0226	−0.0187	−0.0176	−0.0232	−0.0193	−0.0183
	(0.0471)	(0.0471)	(0.0471)	(0.0472)	(0.0471)	(0.0472)
Drinking	0.0581	0.0573	0.0598	0.0592	0.0582	0.0607
	(0.0490)	(0.0490)	(0.0492)	(0.0490)	(0.0490)	(0.0492)
FT_3	0.0059	0.0066	0.0067	0.0060	0.0067	0.0069
	(0.0165)	(0.0165)	(0.0164)	(0.0165)	(0.0166)	(0.0165)
BUN/Cr	−0.0020***	−0.0020***	−0.0021***	−0.0021***	−0.0021***	−0.0021***
	(0.0006)	(0.0006)	(0.0006)	(0.0006)	(0.0006)	(0.0006)
Temperature		−0.4868	−0.7673**		−0.5202	−0.7970**
		(0.3329)	(0.3555)		(0.3333)	(0.3567)
Rainfall		0.0043	0.0002		0.0044	0.0002
		(0.0053)	(0.0058)		(0.0053)	(0.0058)
Light		0.0004	0.0005		0.0003	0.0005
		(0.0004)	(0.0004)		(0.0004)	(0.0004)
Wind		−0.5329	−0.5108		−0.5208	−0.5037
		(0.3744)	(0.3915)		(0.3746)	(0.3914)
Urbn			−1.2292			−1.1347
			(2.5958)			(2.5939)
PGDP			−0.0609			−0.0593
			(0.0446)			(0.0446)
Beds			−0.2114**			−0.2113**
			(0.1043)			(0.1046)
constant	−0.4327	6.5522	13.0908**	−0.4643	6.9781	13.4034**
	(0.2830)	(5.0885)	(6.2712)	(0.2867)	(5.0874)	(6.2850)
City FE	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
Year FE	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
N	1,446	1,446	1,446	1,446	1,446	1,446
Adj_R^2	0.1251	0.1252	0.1267	0.1251	0.1253	0.1267

Values in small brackets are heteroscedastic robust standard errors; values in middle brackets are spatially correlated robust standard errors. The *** and ** indicate that the regression results are significant at the 1% and 5% levels, respectively.

be affected by the neighboring regions, which presents the characteristics of mutual correlation. Therefore, the standard error of the regression coefficient may have a spatial correlation, which will affect the estimation result. Therefore, this paper further adopts the calculation method of spatial correlation robust standard error (28), and sets the critical value at 110 km to calculate the robust standard error. According to the results in Table 2, under the robust standard error of spatial correlation, the regression coefficients of PM2.5 concentration level and PM10 concentration level are still significantly positive at least at the level of 5%, and the standard deviation fluctuates slightly, so the results are relatively stable, which proves that air pollution does have a negative impact on the cardiovascular health of patients with T2DM.

Endogenous problem

Although the two-way fixed effect model and the addition of important control variables can partly solve the problem of missing variables that cannot be dealt with by the mixed ordinary least square (OLS) and random effect (RE) models, the problem of missing variables may still exist due to the complexity of the correlation between variables and the limitations of survey data. To solve this problem, this paper refers to the practice of Deschenes et al. (29) and adopts the inverse temperature difference days as the instrumental variable of air pollution to minimize the estimation error caused by endogenous problems and measurement errors. Throughout the existing research, many studies adopt this tool variable. For example, Arceo et al. (30) used the inversion difference days as an instrumental variable to empirically study the impact of air pollution on newborn infant mortality in Mexico; Deschenes et al. (29) used the instrumental variable identification strategy of temperature inversion difference and found that air pollution would lead to the deterioration of BMI and obesity-related indicators.

The selection of inversion days as an instrumental variable is mainly based on correlation and orthogonality (31). The first is a correlation, that is, inverse temperature difference must be related to PM2.5 concentration and PM10 concentration of air pollution. According to the principles of physics, the temperature in the troposphere will drop by 6.5°C every 1,000 m of altitude rise, and it will continue to climb with the airflow in the atmosphere. The suspended particles in the air will dissipate in mid-air with the thinning of the atmosphere. However, under certain conditions, the temperature in the troposphere will also rise with the increase in altitude, or the temperature change rate will be <6.5°C/1,000 m with the increase in ground altitude. This phenomenon is called "inversion." This will cause the suspended particulate matter in the air to sink to the ground due to the obstruction of its longitudinal climb, thus increasing the concentration of PM2.5 and PM10. The suspended particles in the air will dissipate in mid-air with the thinning of the atmosphere. However, under certain conditions, the temperature in the troposphere will also rise with the increase in altitude, or the temperature change rate will be <6.5°C/1,000 m with the increase in ground altitude. This phenomenon is called "inversion." This will cause the suspended particulate matter in the air to sink to the ground due to the obstruction of its longitudinal climb, thus increasing the concentration of PM2.5 and PM10. Previous studies have shown that the "inversion" phenomenon in the troposphere structure is highly correlated with the concentration of PM2.5 and PM10 in air pollution, and this conclusion has been verified by the analytical charts of meteorological observation fields around the world (32). The second is orthogonality, that is, the intensity of inverse temperature difference will affect the severity of CVD, but the latter will not affect the former in turn. This is because "temperature inversion" is a natural weather phenomenon with exogenous impact and randomness, the individual's level of CVD of individuals cannot play a role in it. Although China's economic growth rate and air pollution intensity rose sharply after 2001, the inverse temperature difference intensity did not change significantly, which further confirmed the orthogonality between the two (32). In addition, in order to further avoid the interference of natural environmental factors and economic and social development factors on the regression of instrumental variables in the first stage, the control variables in the benchmark regression are added in this paper.

First of all, this paper studies the relationship between the occurrence of temperature inversion and two air pollutants. In Figure 2, the average pollution level is plotted according to the monthly average inversion days. As shown in the figure, there is a strong positive correlation between inversion days and PM2.5 and PM10 in air pollutants. To further prove the existence of this relationship, in the first stage of the instrumental variable method, this paper takes two air pollutants as explained variables.

From columns (1)–(2) of Table 3, the regression coefficient of the influence of the days when the inversion phenomenon occurs on air pollution has passed the significance test at the level of 1%, which indicates that the inversion phenomenon will indeed worsen the air pollutant index. And all passed the identification deficiency and weak instrumental variable test. From columns (3) to (4) of Table 3, for each increase of 1 unit standard deviation of PM2.5 and PM10 concentrations in air pollutants, the severity of CVD of patients will increase by 24.96 and 19.64%, respectively. The coefficients of all core explanatory variables are larger than those estimated by OLS in Table 2, indicating that endogenous problems will lead to underestimation to a certain extent.

Robust test

Robust test for adjusted variables

First, this paper replaces the core explanatory variables. A 9-year epidemiological cohort study of hypertension covering about 70,000 people in 31 cities in China found that an increase of 10 $\mu g/m^3$ in SO_2 and TSP was associated with an increase of 3.2 and 0.9% in cardiovascular mortality, respectively (33). Moreover, in addition to its own toxicity, SO_2, a gaseous pollutant, can also contribute to the generation of PM2.5 through complex photochemical reactions and form secondary pollution. Therefore, it is reasonable to select SO_2_1 to measure the degree of air pollution and use it to replace PM2.5 and PM10, which can be used as the basis for the robustness test.

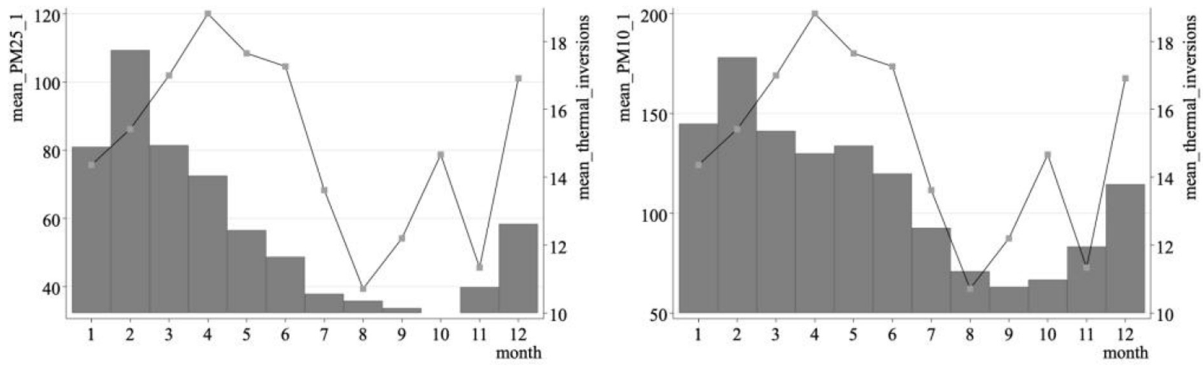

FIGURE 2
The relationship between the number of inversion days per month and air pollution.

Second, this paper extends the time length of core explanatory variables. In the benchmark regression, PM2.5_1 and PM10_1 were respectively used to characterize the degree of air pollution. However, considering that most CVDs are due to long-term exposure to air pollutants, the test period for air pollution before the patient's admission is extended in the robustness test, and the test period for core explanatory variables is extended to 3 months.

The robustness test results of the adjusted variables are shown in columns (1) to (3) of Table 4. Table 4 lists the regression results of replacing the core explanatory variables, prolonging the investigation time of the core explanatory variables, and replacing the explained variables. In columns (1) to (3) of Table 4, the regression coefficients of the core explanatory variables have changed significantly at the sign and significance levels, which further confirms the results and explanations in the benchmark regression. Specifically, from the regression coefficient of air pollution degree in column (1), the air pollution represented by SO_2 worsens the severity of CVD in patients with T2DM, indicating that the change in direction of gaseous pollutants and particulate pollutants and their impact on CVD are similar. The regression results in columns (2)–(3) that when the investigation period of air pollution is extended, the significance of the regression coefficient does not change, but the absolute value of the coefficient decreases, indicating that the influence effect will gradually decrease with time.

Robustness test of transformation regression method

In the benchmark regression in this paper, the explained variable is the CVDs of patients with T2DM. The measurement method is to add the prevalence of coronary heart disease, myocardial infarction, and hypertension to obtain a discrete integer variable, which has internal ranking characteristics. Therefore, it is necessary to use maximum likelihood estimation to estimate the ranking model. Assuming that the random disturbance term obeys the normal distribution, OProbit model is selected for estimation; It is more reasonable to use the ordered logit (OLogit) model if the random disturbance term obeys the logical distribution. In this paper, the OProbit and OLogit models are successively used to estimate the benchmark regression in the robustness test under the two scenarios where PM2.5 and PM10 concentrations are used to measure the air pollution status. From the regression results in columns (4) to (7) of Table 4 whether the Oprobit model or the OLogit model is used, the air pollution variables pass the significance test and the coefficient value is not much different from the benchmark regression, which further confirms the hypothesis that air pollution will worsen the CVD.

Analysis of heterogeneity

Above, this paper estimates the average effect of air pollution on the cardiovascular health of patients with T2DM. It is assumed that all individuals and cities are affected by the same impact. However, the air pollution level among cities is not evenly distributed, and there is heterogeneity among different cities, which may lead to differences in the impact of air pollution on the cardiovascular health of patients with T2DM. Therefore, this paper conducts a sub-sample test on the benchmark model from the perspectives of gender, age, environmental regulation, and medical and health conditions. Considering that the estimator obeys a certain distribution, and its confidence intervals overlap, this paper tests the difference of coefficients between groups. The results are shown in Table 5.

Individual level: Heterogeneity analysis based on individual sex

To investigate whether there is a gender difference in the cardiovascular health of T2DM patients caused by air pollution, this paper conducts group regressions by gender based on

TABLE 3 Effects of air pollution on cardiovascular health [Instrumental variable (IV) estimation model].

Variable	*PM2.5_1* (1)	*PM10_1* (2)	*Diseases* (3)	*Diseases* (4)
Thermal_inversions	0.0088***	0.0176***		
	(0.0012)	(0.0018)		
PM2.5_1			0.7460*	
			(0.4126)	
PM10_1				0.3731*
				(0.2051)
Gender	0.0029	0.0087	0.1173**	0.1162**
	(0.0180)	(0.0275)	(0.0560)	(0.0553)
Age	−0.0006	−0.0016**	0.0199***	0.0201***
	(0.0005)	(0.0007)	(0.0015)	(0.0015)
BMI	0.0005	−0.0002	0.0053	0.0058
	(0.0009)	(0.0014)	(0.0073)	(0.0077)
Smoking	−0.0094	−0.0089	−0.0099	−0.0136
	(0.0164)	(0.0251)	(0.0483)	(0.0477)
Drinking	0.0074	−0.0010	0.0608	0.0667
	(0.0167)	(0.0255)	(0.0503)	(0.0496)
FT_3	−0.0026	−0.0052	0.0076	0.0076
	(0.0043)	(0.0066)	(0.0166)	(0.0169)
BUN/Cr	−0.0002	−0.0001	−0.0019***	−0.0020***
	(0.0002)	(0.0003)	(0.0006)	(0.0006)
Temperature	−0.0612	0.1864	−0.6631*	−0.7782**
	(0.1237)	(0.1891)	(0.3679)	(0.3694)
Rainfall	0.0007	−0.0002	−0.0012	−0.0006
	(0.0020)	(0.0030)	(0.0061)	(0.0059)
Light	−0.0002	−0.0001	0.0006	0.0006
	(0.0001)	(0.0002)	(0.0004)	(0.0004)
Wind	0.0206	−0.0226	−0.4408	−0.4171
	(0.1301)	(0.1989)	(0.4101)	(0.4000)
Urbn	0.6767	0.2069	−1.8908	−1.4624
	(0.8460)	(1.2935)	(2.6759)	(2.6128)
PGDP	−0.0049	−0.0296	−0.0680	−0.0607
	(0.0160)	(0.0245)	(0.0468)	(0.0461)
Beds	0.0330	0.0431	−0.2324**	−0.2238**
	(0.0343)	(0.0524)	(0.1086)	(0.1074)
constant	0.9643	−1.4981		
	(2.1114)	(3.2281)		
Kleibergen-Paap rk LM			63.3930	97.9980
			(0.0000)	(0.0000)
Kleibergen-Paap rk Wald F			73.3980	125.0250
			(16.3800)	(16.3800)
City FE	*YES*	*YES*	*YES*	*YES*
Year FE	*YES*	*YES*	*YES*	*YES*
N	1,446	1,446	1,446	1,446
Adj_R^2	0.1722	0.2187	0.0853	0.1020

The parenthesis content of Kleibergen-Paaprk LM statistic is the *p*-value of the insufficient identification test, the parenthesis content of Kleibergen-Paaprk Wald F statistic is the 10% critical value of the weak identification test, and the rest of the parenthesis content is the heteroskedvariance robust standard error. The ***, ** and * indicate that the regression results are significant at the 1%, 5% and 10% levels, respectively.

benchmark regression. The results show that the regression coefficients of air pollution are all positive, but the effect is not significant in the female group, indicating that air pollution has a greater impact on the cardiovascular health of male patients with T2DM. It may be that compared with women, men are more likely to engage in outdoor labor and are more likely to be exposed to air pollution for a long time, so they are more sensitive to air pollution than women.

Individual level: Heterogeneity analysis based on individual age

To verify whether there is an age difference in the effect of air pollution on the cardiovascular health of patients with T2DM, this paper conducts group regression according to age on the basis of benchmark regression. The population aged 60 and above are classified as the elderly population, and the population under 60 is classified as the young and middle-aged population. The results are shown in Table 6. The results show that the regression coefficients of air pollution are all positive, but the effect is not significant in the young and middle-aged samples, indicating that air pollution has a greater impact on the cardiovascular health of elderly patients with T2DM aged 60 years and above. It may be due to the better physical fitness of young and middle-aged groups, so air pollution has less impact on them. On the contrary, the elderly will experience a certain degree of degradation in various bodily functions and are more susceptible to the effects of air pollution, which can lead to the deterioration of cardiovascular health. In response to the current situation of accelerating aging and worrying residents' health in China, all regions should strengthen residents' attention to the health of the elderly population and reduce the negative effects of air pollution on the health of vulnerable elderly people.

External environment: Heterogeneity analysis based on environmental regulation

To analyze the negative effects of air pollution on the cardiovascular health of patients with T2DM, it is necessary to find a breakthrough to reduce the negative effects of air pollution in combination with the actual situation of China at this stage, to provide more enlightenment for policy formulation. Therefore, this paper considers the perspective of the intensity of government environmental regulation, divides the samples into a low environmental regulation group and high environmental regulation group according to the intensity of urban environmental regulation, and conducts regression in sub-samples. The intensity of environmental regulation is measured by the proportion of local government energy conservation and environmental protection expenditure in GDP. The results are shown in Table 7.

TABLE 4 Robustness test of substitution variables and transformation regression method.

Variable	*Diseases*	*Diseases*	*Diseases*	*OProbit*		*OLogit*	
	(1)	(2)	(3)	(4)	(5)	(6)	(7)
SO_2_1	0.0055**						
	(0.0022)						
PM2.5_3		0.0027***					
		(0.0009)					
PM10_3			0.0014**				
			(0.0006)				
PM2.5_1				0.2704**		0.4489*	
				(0.1299)		(0.2327)	
PM10_1					0.1783**		0.3122**
					(0.0836)		(0.1468)
Gender	0.1208**	0.1218**	0.1223**	0.1987**	0.1968**	0.3237**	0.3201**
	(0.0542)	(0.0542)	(0.0541)	(0.0887)	(0.0887)	(0.1565)	(0.1564)
Age	0.0195***	0.0196***	0.0196***	0.0327***	0.0328***	0.0586***	0.0589***
	(0.0015)	(0.0015)	(0.0015)	(0.0026)	(0.0026)	(0.0061)	(0.0061)
BMI	0.0059	0.0061	0.0062	0.0094	0.0096	0.0598	0.0605
	(0.0083)	(0.0083)	(0.0084)	(0.0124)	(0.0125)	(0.0406)	(0.0405)
Smoking	−0.0190	−0.0194	−0.0182	−0.0315	−0.0327	−0.0763	−0.0763
	(0.0471)	(0.0471)	(0.0472)	(0.0776)	(0.0777)	(0.1346)	(0.1348)
Drinking	0.0581	0.0616	0.0611	0.1164	0.1183	0.1466	0.1474
	(0.0491)	(0.0492)	(0.0493)	(0.0817)	(0.0818)	(0.1486)	(0.1486)
FT_3	0.0063	0.0062	0.0061	0.0111	0.0114	0.0021	0.0021
	(0.0167)	(0.0165)	(0.0165)	(0.0289)	(0.0290)	(0.0469)	(0.0471)
BUN/Cr	−0.0021***	−0.0021***	−0.0021***	−0.0034***	−0.0034***	−0.0053***	−0.0054***
	(0.0006)	(0.0006)	(0.0006)	(0.0010)	(0.0010)	(0.0018)	(0.0018)
Temperature	−0.7491**	−0.7725**	−0.8071**	−1.2442**	−1.2908**	−1.9107*	−2.0048*
	(0.3555)	(0.3558)	(0.3565)	(0.5910)	(0.5927)	(1.0271)	(1.0331)
Rainfall	−0.0003	0.0005	0.0006	−0.0005	−0.0003	−0.0041	−0.0040
	(0.0058)	(0.0058)	(0.0058)	(0.0096)	(0.0096)	(0.0163)	(0.0163)
Light	0.0005	0.0005	0.0005	0.0010	0.0009	0.0014	0.0013
	(0.0004)	(0.0004)	(0.0004)	(0.0007)	(0.0007)	(0.0013)	(0.0013)
Wind	−0.4858	−0.5330	−0.5117	−0.8666	−0.8533	−1.2617	−1.2309
	(0.3931)	(0.3927)	(0.3918)	(0.6384)	(0.6382)	(1.1193)	(1.1190)
Urbn	−1.0490	−1.4515	−1.2914	−1.4655	−1.3159	−1.2328	−0.9006
	(2.5969)	(2.6076)	(2.6019)	(4.4013)	(4.3998)	(7.4775)	(7.4730)
PGDP	−0.0557	−0.0571	−0.0562	−0.0972	−0.0947	−0.1567	−0.1527
	(0.0455)	(0.0447)	(0.0447)	(0.0751)	(0.0752)	(0.1305)	(0.1307)
Beds	−0.2157**	−0.2118**	−0.2092**	−0.3551**	−0.3552**	−0.6775**	−0.6830**
	(0.1050)	(0.1051)	(0.1049)	(0.1726)	(0.1731)	(0.3051)	(0.3063)
constant	12.7562**	13.2245**	13.5515**				
	(6.2599)	(6.2793)	(6.2798)				
City FE	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
Year FE	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*	*YES*
N	1,446	1,446	1,446	1,446	1,446	1,446	1,446
$Adj\_R^2/Pseudo\_R^2$	0.1283	0.1297	0.1272	0.0750	0.0751	0.0792	0.0794

PM2.5_3, PM10_3 and SO_2_3 represent PM2.5, PM10 and SO_2 concentrations 3 months before admission, respectively; Values in parentheses are heteroscedastic robust standard errors; The ***, ** and * indicate that the regression results are significant at the 1%, 5% and 10% levels, respectively.

TABLE 5 Heterogeneity analysis of gender.

Variable	PM2.5_1		PM10_1	
	Male (1)	Female (2)	Male (3)	Female (4)
PM2.5_1	0.2206**	0.0419		
	(0.1026)	(0.1326)		
PM10_1			0.1373**	0.0535
			(0.0654)	(0.0841)
Age	0.0177***	0.0237***	0.0178***	0.0237***
	(0.0018)	(0.0022)	(0.0018)	(0.0022)
BMI	0.0015	0.0338***	0.0017	0.0338***
	(0.0060)	(0.0075)	(0.0060)	(0.0075)
Smoking	−0.0270	0.0019	−0.0281	0.0001
	(0.0502)	(0.1445)	(0.0503)	(0.1446)
Drinking	0.0591	0.0380	0.0607	0.0402
	(0.0524)	(0.1524)	(0.0524)	(0.1520)
FT_3	0.0059	0.0098	0.0065	0.0099
	(0.0174)	(0.0238)	(0.0175)	(0.0239)
BUN/Cr	−0.0018**	−0.0021**	−0.0019**	−0.0021**
	(0.0009)	(0.0009)	(0.0009)	(0.0009)
Temperature	−0.9563**	−0.6278	−0.9926**	−0.6360
	(0.4081)	(0.8524)	(0.4113)	(0.8513)
Rainfall	0.0002	−0.0112	0.0002	−0.0112
	(0.0069)	(0.0105)	(0.0069)	(0.0106)
Light	0.0007	−0.0006	0.0006	−0.0006
	(0.0005)	(0.0009)	(0.0005)	(0.0009)
Wind	−0.2712	−0.6526	−0.2734	−0.6531
	(0.4813)	(0.6908)	(0.4802)	(0.6892)
Urbn	−0.4124	−7.7849*	−0.2654	−7.7822*
	(3.2192)	(4.6603)	(3.2109)	(4.6638)
PGDP	−0.0701	−0.0221	−0.0690	−0.0220
	(0.0555)	(0.0717)	(0.0556)	(0.0722)
Beds	−0.2142*	−0.3305*	−0.2143	−0.3314*
	(0.1295)	(0.1693)	(0.1303)	(0.1693)
constant	14.4091**	19.3941	14.8211**	19.4763
	(7.0019)	(15.8317)	(7.0342)	(15.8175)
City FE	*YES*	*YES*	*YES*	*YES*
Year FE	*YES*	*YES*	*YES*	*YES*
Experience P-value	0.0020	0.0260		
N	864	582	864	582
Adj_R^2	0.0933	0.1641	0.0927	0.1646

Values in parentheses are heteroscedastic robust standard errors. The ***, ** and * indicate that the regression results are significant at the 1%, 5% and 10% levels, respectively.

TABLE 6 Heterogeneity analysis of age.

Variable	PM2.5_1		PM10_1	
	Young and middle-aged (1)	The elderly (2)	Young and middle-aged (3)	The elderly (4)
PM2.5_1	0.0544	0.3175**		
	(0.0976)	(0.1320)		
PM10_1			0.0642	0.1738**
			(0.0612)	(0.0836)
Gender	0.1384**	0.1016	0.1400**	0.0977
	(0.0654)	(0.0859)	(0.0654)	(0.0861)
Age	0.0194***	0.0197***	0.0195***	0.0198***
	(0.0024)	(0.0042)	(0.0024)	(0.0042)
BMI	0.0301***	0.0004	0.0300***	0.0005
	(0.0054)	(0.0058)	(0.0054)	(0.0058)
Smoking	−0.0207	−0.0192	−0.0203	−0.0162
	(0.0570)	(0.0796)	(0.0570)	(0.0797)
Drinking	0.0955	−0.0045	0.0955	−0.0075
	(0.0586)	(0.0839)	(0.0587)	(0.0841)
FT_3	−0.0221**	0.0463	−0.0220**	0.0474
	(0.0087)	(0.0296)	(0.0086)	(0.0294)
BUN/Cr	−0.0018**	−0.0020**	−0.0018**	−0.0021**
	(0.0008)	(0.0009)	(0.0008)	(0.0009)
Temperature	−0.5814	−0.7141	−0.6076	−0.7671
	(0.4290)	(0.6689)	(0.4312)	(0.6769)
Rainfall	0.0017	−0.0037	0.0017	−0.0025
	(0.0078)	(0.0091)	(0.0077)	(0.0091)
Light	0.0008	−0.0001	0.0007	−0.0000
	(0.0005)	(0.0006)	(0.0005)	(0.0006)
Wind	−0.1548	−1.2165*	−0.1435	−1.1639*
	(0.5409)	(0.6345)	(0.5428)	(0.6310)
Urbn	1.2232	−6.7049	1.2594	−6.3999
	(3.0232)	(4.5779)	(3.0208)	(4.6068)
PGDP	−0.0924	0.0115	−0.0912	0.0069
	(0.0568)	(0.0780)	(0.0568)	(0.0782)
Beds	−0.1021	−0.2613	−0.1063	−0.2497
	(0.1235)	(0.1737)	(0.1241)	(0.1744)
constant	6.2627	19.3059*	6.5838	19.4784*
	(7.9174)	(10.9984)	(7.9423)	(11.1190)
City FE	*YES*	*YES*	*YES*	*YES*
Year FE	*YES*	*YES*	*YES*	*YES*
Experience P-value	0.0000		0.0320	
N	716	730	716	730
Adj_R^2	0.0992	0.0368	0.1002	0.0345

Values in parentheses are heteroscedastic robust standard errors. The ***, ** and * indicate that the regression results are significant at the 1%, 5% and 10% levels, respectively.

From the regression results in Table 7, the influence of air pollution on the severity of CVD in patients with T2DM is all positive, but it is more significant in the sample group with low environmental regulation. This paper further observes the coefficient of air particulate pollution in each sub-sample. The results show that from the perspective of PM2.5 concentration,

TABLE 7 Heterogeneity analysis of environmental regulation.

Variable	PM2.5_1		PM10_1	
	Low environmental regulation group	High environmental regulation group	Low environmental regulation group	High environmental regulation group
	(1)	(2)	(3)	(4)
PM2.5_1	0.3799***	0.0796		
	(0.1356)	(0.1015)		
PM10_1			0.1949**	0.0582
			(0.0796)	(0.0678)
Gender	0.0802	0.1278*	0.0759	0.1272*
	(0.0753)	(0.0766)	(0.0757)	(0.0765)
Age	0.0221***	0.0189***	0.0224***	0.0190***
	(0.0020)	(0.0019)	(0.0020)	(0.0019)
BMI	0.0285***	0.0025	0.0296***	0.0025
	(0.0068)	(0.0066)	(0.0068)	(0.0066)
Smoking	−0.1150*	0.0062	−0.1117	0.0051
	(0.0679)	(0.0641)	(0.0682)	(0.0641)
Drinking	0.2011***	−0.0458	0.1975***	−0.0448
	(0.0700)	(0.0677)	(0.0704)	(0.0677)
FT_3	0.0051	0.0110	0.0051	0.0110
	(0.0172)	(0.0238)	(0.0173)	(0.0239)
BUN/Cr	−0.0016**	−0.0024***	−0.0017**	−0.0024***
	(0.0008)	(0.0009)	(0.0008)	(0.0009)
Temperature	−1.7701**	−1.1059	−1.8468**	−1.1005
	(0.8944)	(1.3887)	(0.8916)	(1.3876)
Rainfall	−0.0011	−0.0115	0.0006	−0.0115
	(0.0130)	(0.0136)	(0.0132)	(0.0137)
Light	0.0006	0.0014	0.0007	0.0014
	(0.0009)	(0.0024)	(0.0009)	(0.0024)
Wind	2.7920	1.2570	2.5656	1.2424
	(1.8339)	(0.8540)	(1.8432)	(0.8537)
Urbn	3.6516	−4.5053	3.1506	−4.4762
	(7.9851)	(7.0608)	(7.9717)	(7.0527)
PGDP	0.0072	0.0274	−0.0013	0.0274
	(0.1087)	(0.1275)	(0.1094)	(0.1277)
Beds	−0.3609**	0.2421	−0.3560**	0.2312
	(0.1571)	(0.4825)	(0.1574)	(0.4844)
constant	13.6960	10.8143	15.3991	10.7702
	(16.1330)	(20.6708)	(16.1204)	(20.6311)
City FE	YES	YES	YES	YES
Year FE	YES	YES	YES	YES
Experience P-value	0.0000		0.0100	
N	615	831	615	831
Adj_R^2	0.1662	0.1131	0.1638	0.1132

Values in parentheses are heteroscedastic robust standard errors. The ***, ** and * indicate that the regression results are significant at the 1%, 5% and 10% levels, respectively.

for each unit standard deviation increase, the severity of CVD in the high and low environmental regulation groups will increase by 12.71 and 2.67% standard deviation, respectively. In addition, from the perspective of PM10 concentration, for every standard deviation increase of 1 unit, the severity of CVD in the high and low environmental regulation groups will increase by 10.07 and 3.06% standard deviations, respectively, which indicates that air pollution affects the health of the low environmental regulation groups. The negative effect is greater than that of high environmental regulation groups. It also further proves that the improvement of environmental regulation intensity helps to reduce the negative effect of air pollution on the cardiovascular health of patients with T2DM and proves the necessity of environmental governance. Facing the current situation of air quality deterioration in China, we should pay attention to enhancing the intensity of environmental regulation to curb the negative effects of air pollution.

External environment: Heterogeneity analysis based on medical and health conditions

The average effect of air pollution on cardiovascular health of T2DM patients has been discussed in this paper. However, the current medical and health conditions in China are unevenly distributed, and the ability to avoid environmental negative externalities is obviously different in different medical and health level areas. It is necessary to further study whether there are significant differences in the health effects of air pollution on different groups with different ability to avoid negative environmental externalities. Therefore, according to the level of urban medical and health care, this paper divides the samples into two groups: poor medical conditions and excellent medical conditions and conducts regression analysis by groups. The level of medical and health conditions is measured by the proportion of local government health expenditure in GDP. The results are shown in Table 8.

The regression results in Table 8 show that air pollution, whether expressed in terms of PM2.5 or PM10 concentration, has a negative impact on the cardiovascular health of the sample groups with different air pollution avoidance abilities, but the impact is more significant in the sample group with poor medical and health conditions. This paper further compares the pollution coefficients of groups with poor and good medical and health conditions. It can be found that, from the perspective of PM2.5 concentration, for everyone standard deviation increase of PM2.5 concentration, the severity of CVD in poor and good medical and health conditions will increase by 9.02 and 3.62% standard deviations, respectively. From the point of view of PM10 concentration, the severity of CVD in high and low environmental regulation groups will increase by 10.41 and 2.10% standard deviation, respectively, when the concentration of PM10 increases by 1 standard deviation. This indicates that the negative effect of air pollution on the health of

TABLE 8 Heterogeneity analysis of medical and health conditions.

Variable	*PM*2.5_1		*PM*10_1	
	Poor medical conditions group (1)	Excellent medical conditions group (2)	Poor medical conditions group (3)	Excellent medical conditions group (4)
PM2.5_1	0.2746**	0.1082		
	(0.1293)	(0.1043)		
PM10_1			0.1978***	0.0399
			(0.0748)	(0.0700)
Gender	0.1102	0.1140	0.1082	0.1134
	(0.0751)	(0.0795)	(0.0751)	(0.0793)
Age	0.0217***	0.0192***	0.0219***	0.0192***
	(0.0019)	(0.0020)	(0.0018)	(0.0020)
BMI	0.0314***	0.0012	0.0317***	0.0013
	(0.0063)	(0.0060)	(0.0063)	(0.0060)
Smoking	−0.0193	−0.0251	−0.0184	−0.0274
	(0.0684)	(0.0661)	(0.0683)	(0.0661)
Drinking	0.0286	0.0728	0.0252	0.0754
	(0.0680)	(0.0727)	(0.0680)	(0.0728)
FT_3	0.0106	0.0084	0.0111	0.0084
	(0.0171)	(0.0239)	(0.0171)	(0.0240)
BUN/Cr	−0.0014*	−0.0025***	−0.0014*	−0.0025***
	(0.0008)	(0.0009)	(0.0008)	(0.0009)
Temperature	0.5241	−1.0106*	0.4636	−1.0259*
	(2.1018)	(0.5600)	(2.1573)	(0.5621)
Rainfall	−0.0017	0.0027	−0.0010	0.0028
	(0.0186)	(0.0091)	(0.0190)	(0.0091)
Light	0.0009	0.0007	0.0009	0.0007
	(0.0012)	(0.0005)	(0.0012)	(0.0005)
Wind	2.1320	0.8891	2.1158	0.8230
	(1.5920)	(1.3760)	(1.6338)	(1.3783)
Urbn	13.1026	−0.1984	13.1735	−0.2396
	(21.1146)	(3.2903)	(21.5422)	(3.2889)
PGDP	0.0808	0.0832	0.0790	0.0820
	(0.1774)	(0.0945)	(0.1814)	(0.0946)
Beds	−0.1114	−0.1701	−0.1321	−0.1699
	(0.3325)	(0.2029)	(0.3383)	(0.2033)
constant	−26.1183	10.2580	−25.3603	10.7526
	(25.9033)	(8.9120)	(26.2637)	(8.9178)
City FE	*YES*	*YES*	*YES*	*YES*
Year FE	*YES*	*YES*	*YES*	*YES*
Experience P-value	0.0280		0.0000	
N	702	743	702	743
Adj_R^2	0.1591	0.1078	0.1619	0.1069

Values in parentheses are heteroscedastic robust standard errors. The ***, ** and * indicate that the regression results are significant at the 1%, 5% and 10% levels, respectively.

people in areas with poor medical and health conditions is greater than that of people in areas with good medical and health conditions.

Conclusions and implications

This paper analyzes the impact of air pollution on the cardiovascular health of patients with T2DM and its group differences and makes an empirical test by matching the daily air quality monitoring data of 16 prefecture-level cities of Shandong Provincial Public Data Open Network with the micro-data of the Provincial Hospital affiliated to Shandong First Medical University from 2016 to 2021. The results show that: (1) Air pollution will worsen the CVD of T2DM patients, that is, cardiovascular health declines in people with T2DM as regional air pollution levels rise. Spatial correlation robust standard error is used to solve the spatial spillover effect of air pollution and the inversion phenomenon is used as an instrumental variable to effectively solve the endogenous problem of air pollution. The results still significantly prove the robustness of the research conclusion. (2) From the perspective of individual characteristics, the impact of air pollution on different gender and age groups is different. Compared with women, men are more susceptible to the negative health effects of air pollution, the elderly bear greater health losses from air pollution than the young and middle-aged due to physical degradation. (3) From the external environment, areas with high environmental regulation intensity will significantly reduce the negative impact of air pollution on cardiovascular health, which further illustrates the necessity of environmental governance; The negative effects of air pollution on health can be alleviated in areas with good public health conditions, which indicates that the improvement of public health service conditions can provide a certain barrier for the cardiovascular health of patients with T2DM.

CVD is a leading cause of global mortality and morbidity. Quantitative assessment of the impact of environmental quality on the cardiovascular health of patients with T2DM not only helps to understand the social welfare cost caused by air pollution more comprehensively but also has important implications for environmental governance and the health effect of public health investment. Therefore, the conclusion contains rich policy implications: (1) Policymakers should optimize the economic development mode, take people-oriented as the development purpose, treat the relationship between economy and environment from the perspective of development, no longer follow the old road of "pollution first, treatment later," and must fully consider the impact of economic development on the environment and residents' health. (2) The government should improve the CVD prevention system, increase the publicity of CVD prevention, inform the public, especially men and middle-aged and elderly groups, of the hazards of air pollution, and pay attention to preventing air pollution. (3) Environmental regulation and public health services can be used as a breakthrough to curb the negative impact of air pollution on health. Increasing the intensity of environmental regulation and public health expenditure will effectively reduce the negative impact of air pollution on the cardiovascular health of patients with T2DM and achieve economic-environmental coordinated development.

There are some potential limitations in this paper. First, the health data are collected from a single health care facility, which may limit the generality of the findings. Although Shandong Provincial Hospital Affiliated to Shandong First Medical University is one of the largest tertiary hospitals in Shandong Province, and its endocrinology is national key clinical specialty, the study sample may still be underrepresented, and it is necessary to further expand the sample study in the future to provide evidence. Second, adolescents or children are also vulnerable groups to air pollution, but this was not analyzed due to data availability. Analysis of the specific impact of air pollution for adolescents, children and middle-aged groups should be the direction of further exploration in the future. In addition, air pollution not only affects the cardiovascular health of diabetic patients, but also has a very important effect on individual mental health and economic behavior. The research on these issues is beyond the scope of this paper and needs to be further studied.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Biomedical Research Ethic Committee of Shandong Provincial Hospital (Approval No. SWYX2022472). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

JZ: wringing–original drift, writing–review and editing, methodology, software, formal analysis, and data curation. DR and YY: writing–review and editing, review, and validation. SW: writing–review and editing, conceptualization, methodology, and validation. SZ: conceptualization, supervision, project administration, and funding acquisition. KQ: data curation. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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EDITED BY
Ang Li,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

REVIEWED BY
Chan Lu,
Central South University, China
Arthit Phosri,
Mahidol University, Thailand

*CORRESPONDENCE
Zhuang Cui
zhuangcui@tmu.edu.cn
Wenyi Zhang
zwy0419@126.com

†These authors have contributed equally to this work

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Effect of ambient temperature and other environmental factors on stroke emergency department visits in Beijing: A distributed lag non-linear model

Jinhua Zhao[1†], Yongming Zhang[2†], Ying Ni[1], Junyu He[3,4], Jianping Wang[1], Xuan Li[1], Yuming Guo[5], Changping Li[1], Wenyi Zhang[6]* and Zhuang Cui[1]*

[1]Department of Epidemiology and Biostatistics, School of Public Health, Tianjin Medical University, Tianjin, China, [2]Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, National Clinical Research Center for Respiratory Diseases, Beijing, China, [3]Ocean College, Zhejiang University, Zhoushan, China, [4]Ocean Academy, Zhejiang University, Zhoushan, China, [5]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia, [6]Chinese PLA Center for Disease Control and Prevention, Beijing, China

Background: Most studies have focused on the relationship between ambient temperature and stroke mortality, but studies on the relationship between ambient temperature and stroke occurrence are still limited and inconsistent.

Objective: This study aimed to analyze the effect of ambient temperature and other environmental factors on emergency stroke visits in Beijing.

Methods: Our study utilized stroke visit data from the Beijing Red Cross Emergency Medical Center during 2017–2018, and applied a generalized additive model (GAM) as well as a distributed lag non-linear model (DLNM), respectively, regarding the direct, lagged, and cumulative effects of ambient temperature alone and with correction for other environmental factors on stroke occurrence.

Results: With a total of 26,984 emergency stroke patients in 2017–2018, both cold and hot effects were observed and weakened after correction for other environmental factors. Compared to the reference temperature, in the multi-factor model, extreme cold (−10°C) reached a maximum relative risk (RR) of 1.20 [95% Confidence Interval (CI): 1.09, 1.32] at lag 14 days, and extreme hot (30°C) had a maximum RR of 1.07 (95% CI: 1.04, 1.11) at lag 6 days. The cumulative effect of extreme cold reached a maximum of 2.02 (95% CI: 1.11, 3.67) at lag 0–14 days, whereas the cumulative effect of extreme hot temperature is greatest at lag 0–10 days, but no statistically significant effect was found. In addition, ischemic stroke patients, the elderly, and males were more susceptible to the effects of cold temperature.

Conclusions: There is a non-linear relationship between ambient temperature and stroke occurrence, with cold temperature having a greater and longer-lasting impact than hot temperature.

KEYWORDS

stroke, ambient temperature, environmental factors, generalized additive model, distributed lag non-linear model

Introduction

Stroke is brain tissue damage caused by rupture or blockage of cerebral blood vessels, which is characterized by high morbidity, disability, mortality, and recurrence (1), and it is a major public health concern facing people in China and throughout the world nowadays. The development of stroke is caused by a combination of risk factors, including abnormal metabolic factors, behavioral factors, and environmental factors (2). Global warming, heat waves, and cold waves, as well as increased air pollution, have become more frequent since the beginning of the twenty-first century, the effect of environmental factors on the incidence of stroke has become more and more significant (3). According to the findings of the Global Burden of Disease Study 2019 (GBD), the burden of disease due to non-optimal temperature and environmental particulate pollution accounts for up to 37% of disability-adjusted life years due to stroke (4).

There has been considerable focus on the association between ambient temperature and stroke death (5–7), but in contrast, the risk of morbidity can describe broader health outcomes and medical costs (8). However, the epidemiological evidence that is now available is inconsistent, and the association between ambient temperature and the incidence of stroke has not been sufficiently studied. A comprehensive study has shown an increased risk of cardiovascular hospitalization under cold temperatures and prolonged exposure to very high temperatures (9). Another study found that whereas hot temperatures were protective against stroke incidence, cold temperatures were a risk factor (10). In addition, other studies have shown no significant correlation between stroke admission and ambient temperature (11, 12). Therefore, the relationship between ambient temperature and the incidence of stroke needs to be further clarified.

The results of a large time-series study showed that the total disease burden caused by non-optimal temperatures was more pronounced in the temperate monsoon climate zone of China, yet Beijing, which has a typical temperate monsoon climate, lacks studies on the correlation between ambient temperature and stroke risk (5, 13). To the best of our knowledge, so far, only one study has focused on the attributable risk of stroke hospitalization in Beijing caused by extreme temperatures from 2013 to 2014 (14). However, given the characteristics of the health care system, compared with stroke hospitalization, emergency admission is a better indicator of population response to fluctuations in environmental factors (15). Our study uses stroke emergency data from the largest emergency center in Beijing from 2017 to 2018, which can more reasonably and accurately reflect the association between ambient temperature and stroke risk. It is a repeatable, high-quality latest assessment based on a large population.

Previous studies have found a correlation between other environmental factors and stroke occurrence (16–20), which may modify the relationship between ambient temperature and stroke (21–23); therefore, in our study, we evaluated the effect of ambient temperature alone and then combined the modified effects of multiple environmental factors to consider their effects on stroke occurrence. Since the effect of ambient temperature on stroke incidence is non-linear and lagged (9, 24, 25), we used a distributed lagged non-linear model to analyze stroke emergency department visit data in Beijing from 2017 to 2018, in addition, we explored the effect of temperature and specific environmental factors on stroke by developing a generalized additive model. This analysis could aid public health policies in Beijing in implementing the proper mitigation and adaptation measures.

Materials and methods

Data collection

Daily emergency stroke visits in Beijing from January 2017 to December 2018 were obtained from the Beijing Red Cross Emergency Medical Center. The data included the number of visits, type of stroke diagnosis, gender and age of patients, and stroke subtypes [ischemic stroke (IS) and hemorrhagic stroke (HS)]. The meteorological data and air pollution data for the same period were obtained from the online publication platform of the Chinese

Abbreviations: GAM, Generalized additive model; DLNM, Distributed lagged non-linear model; CI, Confidence Interval; RR, Relative risk; IS, Ischemic stroke; HS, Hemorrhagic stroke; AIC, Akaike information criterion; TV, Temperature variation.

National Environmental Monitoring Center (http://106.37.208.233:20035). The meteorological data include daily mean temperature, daily mean relative humidity, daily mean air pressure, mean wind speed, and daily precipitation, and the air pollution data include daily mean levels of $PM_{2.5}$, PM_{10}, sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO).

Statistical analysis

First, the stroke data were cleaned and organized into daily-scale time series data, and descriptive statistics were used to describe patient characteristics, including gender, age group, and stroke subtype. Time series plot was used to assess the periodicity and long-term trends of stroke visits and daily mean temperatures. Second, because daily stroke incidence for the total population is a low probability event that roughly follows a Poisson distribution, the generalized additive model (GAM) was employed to investigate the association between each environmental element and the frequency of stroke visits.

We then carried out a two-stage analysis. In the first step, we developed a univariate distributed lagged non-linear model (DLNM) of daily mean temperature, combined with GAM to analyze the non-linear relationship, lagged effect, and the cumulative effect of mean temperature on stroke incidence. We established a cross-basis matrix for assessing the two-dimensional relationship between different lag days and mean daily temperature (26), using the natural logarithm of the number of daily stroke visits as the dependent variable and the natural cubic spline function as the basis function for the exposure-response association and the lag-response association, setting the degrees of freedom of the exposure dimension to 6 and the degrees of freedom of the lag dimension to 4 based on previous studies and the results of the generalized deficit pool information minimization criterion (27). According to previous studies, the effect of hot temperature on stroke incidence is within a week, and the cold effect lasts longer. In general, the use of shorter lags may not capture the potential harvest effect of hot temperature, in reference to previous studies, so our study set the maximum lag days to 14 days (28–30). After controlling for day-of-week effects, long term and seasonality, the model we depicted is shown below:

$$Y_t \sim Poisson(\mu_t)$$
$$Log[E(Y_t)] = \alpha + \beta^* Temp_{t,l} + ns(time, 12^*2) + \eta DOW_t \quad (1)$$

where Y_t is the number of stroke visits on day t, α is the intercept, β and η are the regression coefficients, and $Temp_{t,l}$ is the temperature cross basis function established in DLNM, taking into account both the non-linear relationship of ambient temperature and the lag effect from lag 0 (the day of exposure) to lag l, where the maximum value of l is 14 days. *ns* is the natural cubic spline curve, and we used 12 degrees of freedom per year to control for long-term and seasonality, with degrees of freedom chosen with reference to previous research and in accordance with the Akaike information criterion(AIC) minimization (5). DOW_t is the day-of-week effect and is included in the model as a categorical variable. In this study, the ambient temperature was classified as extreme cold (1st percentile of temperature), moderate cold (10th percentile of temperature), moderate hot (90th percentile of temperature), and extreme hot (99th percentile of temperature). The above were compared with reference values to calculate the relative risk (RR) [95% confidence interval (CI)] of emergency stroke visits for different ambient temperature exposures. The above cutoff values for ambient temperature were reasonable choices based on previous studies (14, 31, 32), in addition to which we explored the RR of the single-day lag effect for 14 days at these four ambient temperatures, as well as the RR of the cumulative effect at different ambient temperatures with different lag days, specifically lag 0–3 days, lag 0–7 days, lag 0–10 days, and lag 0–14 days.

In the second stage, in order to comprehensively consider the corrective effects of various environmental factors, we further developed a multi-factor model with ambient temperature as the main variable. In order to avoid multi-collinearity among variables, Spearman test was used to explore the correlation among variables, and factors with correlation coefficients >0.6 were not included in the model at the same time (18). Combined with the GAM results, it was finally determined that daily temperature variation (TV), mean relative humidity, $PM_{2.5}$, SO_2 were included in the multi-factor model, and the model established was as follows:

$$Log[E(Y_t)] = \alpha_1 + \beta_1^* Temp_{t,l} + \beta_2^* TV + ns(RH, 3) + \beta_3^* PM2.5 + \beta_4^* SO_2 + ns(time, 12^*2) + \eta_1 DOW_t \quad (2)$$

In equation (2), α_1 is the intercept, β_1, β_2, β_3, β_4 and η_1 are the regression coefficients, and the parameters in $Temp_{t,l}$ and *time* are set the same as in equation (1). TV, $PM2.5$, and SO_2 are included in the model in a linear relationship according to previous studies (16, 22, 33–35). Mean relative humidity (RH) was used as a natural cubic spline function as a connection with 3 degrees of freedom (9). With reference to previous studies, The median daily temperature was used as a reference value to calculate the RR for different lag days of exposure to the four division point temperatures (14, 36).

TABLE 1 Summary statistics of the number of daily visits and description of environmental factors for stroke and subgroups in Beijing, 2017–2018.

	Mean ± SD	Minimum	P_{25}	Median	P_{75}	Maximum
Daily visits						
Stroke	36.96 ± 9.19	13.00	30.00	37.00	43.00	75.00
IS	23.82 ± 6.95	7.00	19.00	24.00	28.00	50.00
HS	13.15 ± 4.49	2.00	10.00	13.00	16.00	30.00
Age<65	12.96 ± 4.30	3.00	10.00	13.00	16.00	29.00
Age≥65	24.00 ± 6.97	7.00	19.00	24.00	29.00	55.00
Male	21.92 ± 6.20	5.00	18.00	22.00	26.00	42.00
Female	15.04 ± 4.87	3.00	12.00	15.00	18.00	34.00
Meteorological factors						
Mean temperature (°C)	12.07 ± 11.81	−12.00	0.48	13.72	22.97	30.90
TV (°C)	11.87 ± 4.09	2.23	8.70	11.65	14.92	23.80
Air pressure (hPa)	993.76 ± 9.45	974.10	985.50	994.50	1000.83	1019.10
Precipitation (mm)	1.61 ± 6.25	0.00	0.00	0.00	0.00	60.33
Wind speed (m/s)	1.70 ± 0.63	0.47	1.27	1.57	2.00	5.03
Relative humidity (%)	52.76 ± 19.47	14.67	36.33	52.76	70.00	94.67
Air pollution factors						
NO_2 ($\mu g/m^3$)	40.63 ± 19.58	6.00	27.00	36.00	50.00	145.00
SO_2 ($\mu g/m^3$)	5.95 ± 6.45	1.00	2.00	4.00	7.00	81.00
O_2 ($\mu g/m^3$)	61.60 ± 37.77	3.00	33.25	55.00	84.00	181.00
CO ($\mu g/m^3$)	0.87 ± 0.63	0.20	0.50	0.76	1.02	7.28
$PM_{2.5}$ ($\mu g/m^3$)	52.58 ± 49.00	3.00	20.00	40.00	67.75	430.00
PM_{10} ($\mu g/m^3$)	80.92 ± 68.70	0.00	41.00	65.50	99.75	858.00

SD, standard deviation; P_x, xth percentile; IS, ischemic stroke; HS, hemorrhagic stroke; TV, temperature variation.

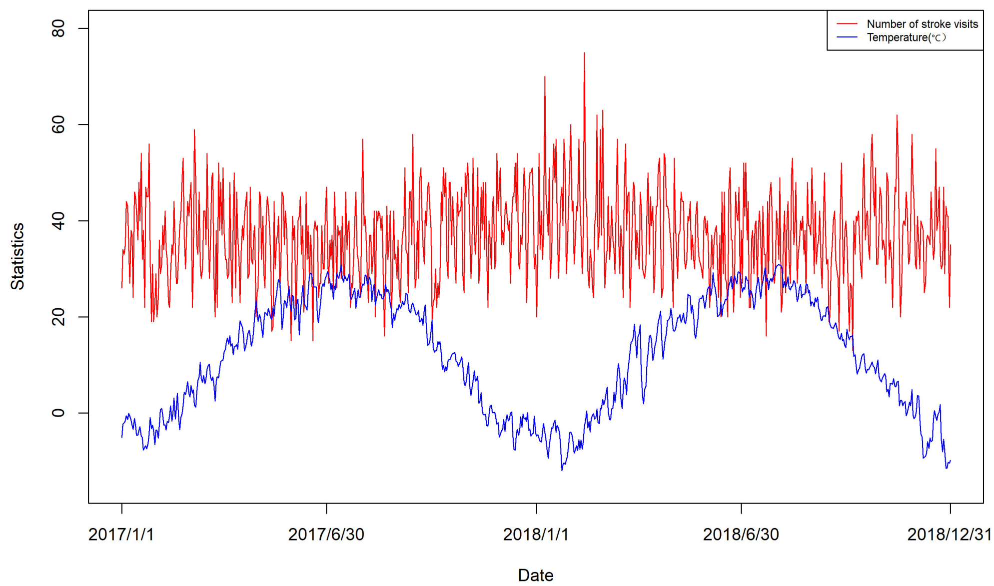

FIGURE 1
Time series distribution of daily number of stroke visits and mean daily temperature in Beijing.

We analyzed the effect of ambient temperature and specific environmental factors on stroke emergency department visits separately by GAM. In addition, subgroup analyses based on a multi-factor model explored the differences between ambient temperature and stroke visits across gender (male and female), age ($<$65 and $\geq$65 years), and stroke subtype populations (IS and HS). To explore the robustness of the multi-factor model, we performed sensitivity analyses by setting the reference temperature to the ambient temperature that provided the lowest risk, as well as varying the degrees of freedom of the exposure dimension from 4 to 8 and the degrees of freedom of the lag dimension from 2 to 6.

The above data analysis and models were done in the "Hmisc," "dlnm," and "mgcv" packages of R software (version 4.1.2). All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Descriptive analysis

Between 2017 and 2018, a total of 26,984 stroke patients were visited, with 17,388 IS patients and 9,596 HS patients. Table 1 shows the number of daily visits for stroke and subgroups, as well as the status of each daily environmental variable during the study period. Non-parametric tests between subgroups showed that the number of stroke visits was statistically significant between each subgroup.

Time series plot and bubble plot of stroke visits and daily mean temperature are displayed in Figure 1 and Supplementary Figure 1 respectively. The plots show that stroke visits follow a cyclical and seasonal pattern, with a trend toward greater numbers in the fall and winter, a negative correlation between stroke visits and ambient temperature, and relatively more visits under extreme ambient temperature exposure.

The GAM results demonstrate a non-linear relationship between meteorological factors such as mean temperature and mean relative humidity and the number of visits, and an approximately linear relationship between TV and most air pollution factors and the number of visits (Supplementary Figures 4, 5).

Single DLNM

Median temperature is used as the reference temperature, the risk of stroke increased with either lower or higher temperatures (Supplementary Figure 2). Supplementary Figure 3 shows the lagged effect of dividing the point temperature based on the reference temperature, the RR for extreme cold (-10°C) and moderate cold (-4°C) reached the maximum on lag 14 with 1.20 (95% CI:1.09, 1.32) and 1.20 (95% CI:1.10, 1.30) respectively, the RR for extreme hot (30°C) and moderate hot (27°C) both reached the maximum on lag 6, at 1.07 (95% CI: 1.04, 1.11) and 1.07 (95% CI: 1.03, 1.11), respectively.

Table 2 shows the cumulative effect of specific temperature on stroke incidence compared with the reference temperature. The RR of cold temperature gradually increased during the cumulative lag 0–14 days, and the RR of hot temperature peaked and then decreased after the cumulative lag 0–10 days. Specifically, extreme cold and moderate cold were 2.09 (95% CI: 1.16, 3.77) and 2.25 (95% CI: 1.33, 3.80) at lag 0–14 days, respectively, and the RR for moderate hot reached a maximum of 1.40 (95% CI: 1.06, 1.84) at lag 0–10 days, but the RR for extreme hot was not statistically significant.

Multi-factor DLNM

The correlation is stronger when the correlation coefficient is >0.6. Strong correlations exist between air pressure and O_3 and ambient temperature. In addition, the correlations between relative humidity and wind speed, $PM_{2.5}$ and PM_{10}, and SO_2 and CO are strong, and covariance occurs if factors with strong correlations are included in the model at the same time (Supplementary Table 1). In this study, we finally combined the GAM results (Supplementary Figures 4, 5) and chose to select the daytime temperature variation, daily average relative humidity, $PM_{2.5}$, and SO_2 to be included in the multi-factor model.

Figure 2 depicts the combined exposure-lag-response effect of mean temperature on the incidence of stroke in the multi-factor model. Compared to the reference temperature, the risk of stroke occurring increases for both cold and hot temperatures. Overall, compared to hot temperatures, cold temperatures had a higher impact and longer lag time. In the multi-factor model, the extreme cold and moderate cold effects were also largest at lag day 14 with RRs of 1.18 (95% CI: 1.07, 1.30) and 1.18 (95% CI: 1.09, 1.28), respectively; the extreme hot and moderate hot had the largest RRs at lag day 6 with RRs of 1.08 (95% CI: 1.04, 1.13) and 1.08 (95% CI: 1.03, 1.13), respectively (Figure 3).

The cumulative effect of cold temperature reached the maximum at lag 0–14 days, with 2.02 (95% CI: 1.11, 3.67) for extreme cold and 2.14 (95% CI: 1.25, 3.64) for moderate cold (Supplementary Table 2). The extreme hot and moderate hot reached the maximum at lag 0–10 days but were not statistically significant (Supplementary Table 2). Compared to the single model, the cumulative effects of specific temperatures at the same lag days were all decreased when controlling for the effects of other environmental factors. We then analyzed the interaction effect of temperature with other specific environmental factors in multi-factor DLNM on stroke visits by GAM (Supplementary Figure 6). The correction effect showed that at a certain ambient temperature, higher TV, higher $PM_{2.5}$

TABLE 2 Cumulative effects of specific temperatures on stroke incidence in single DLNM at a specific lag structure.

	Extreme cold P_1: −10°C	Moderate cold P_{10}: −4°C	Moderate hot P_{90}: 27°C	Extreme hot P_{99}: 30°C
Lag 0–3	0.95	0.93	1.01	0.97
	(0.75, 1.20)	(0.76, 1.14)	(0.87, 1.18)	(0.81, 1.15)
Lag 0–7	1.35	1.27	**1.33***	1.24
	(0.95, 1.91)	(0.93, 1.74)	**(1.06, 1.67)**	(0.97, 1.58)
Lag 0–10	1.39	1.42	**1.40***	1.33
	(0.89, 2.19)	(0.94, 2.13)	**(1.06, 1.84)**	(1.00, 1.77)
Lag 0–14	**2.09***	**2.25***	1.17	1.12
	(1.16, 3.77)	**(1.33, 3.80)**	(0.82, 1.66)	(0.78, 1.62)

*$p < 0.05$ was considered statistically significant and is indicated in bold font.

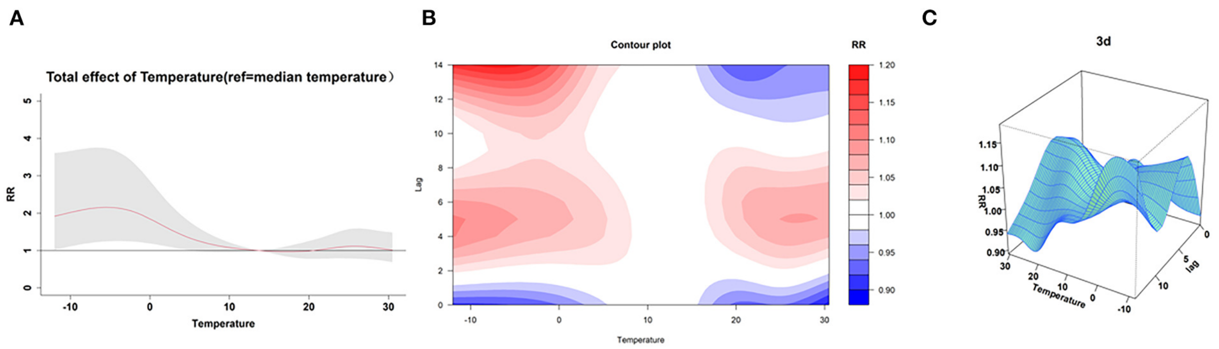

FIGURE 2
The visualization of the lag effect. **(A)** Shows that cold temperature significantly increased the risk of stroke compared to the median temperature. The contour plot **(B)** and 3D plot **(C)** of the lag effect show that the lag effect of cold temperature is strongest on day 14, while the lag effect of hot temperature is strongest on day 5 and day 6.

concentration and lower SO_2 concentration were linked to a higher risk of stroke incidence, while relative humidity showed a obviously negative association with the risk of stroke incidence within a certain interval.

Subgroup analysis

According to Table 3, the cumulative effects of cold temperature in different subgroups all peaked at lags of 0–14 days, and the cumulative effects of hot temperature all peaked at lags of 0–10 days. The risk of stroke was greater in IS than in HS at low temperatures, and the effect of hot temperatures on the onset of HS was greater. Both low and high temperatures were more likely to affect those aged ≥ 65 years than those aged <65 years. Male exposed to high and moderate levels of cold temperature had a higher risk of stroke, with moderate cold exposure having the highest impact on the male at lag 0–14 days, 2.38 (95% CI: 1.19, 4.76). Stroke incidence in female was more affected by extreme cold at lag 0–14 days, 2.11 (95% CI: 0.84, 5.35), but not statistically significant.

Sensitivity analysis

The temperature that provided the lowest risk of stroke visits in this study was 17°C. By re-analyzing in the multi-factor DLNM with 17°C as the reference temperature, the results showed the cumulative-exposure-lag effect of temperature on stroke visits was not found to be significantly altered (See Supplementary Tables 3, 4). The sensitivity analysis is also by changing the degree of freedom of the natural cubic spline function of the lag dimension and the exposure dimension of the cross basis in the DLNM. In the previous analysis, the values were 4 and 6 respectively, which followed the AIC minimization (Supplementary Figure 7). The effect values did not change significantly when we took the lag dimension degrees of freedom from 2 to 6 and the exposure dimension from 4 to 8 (Supplementary Figure 8). These analyses all indicated

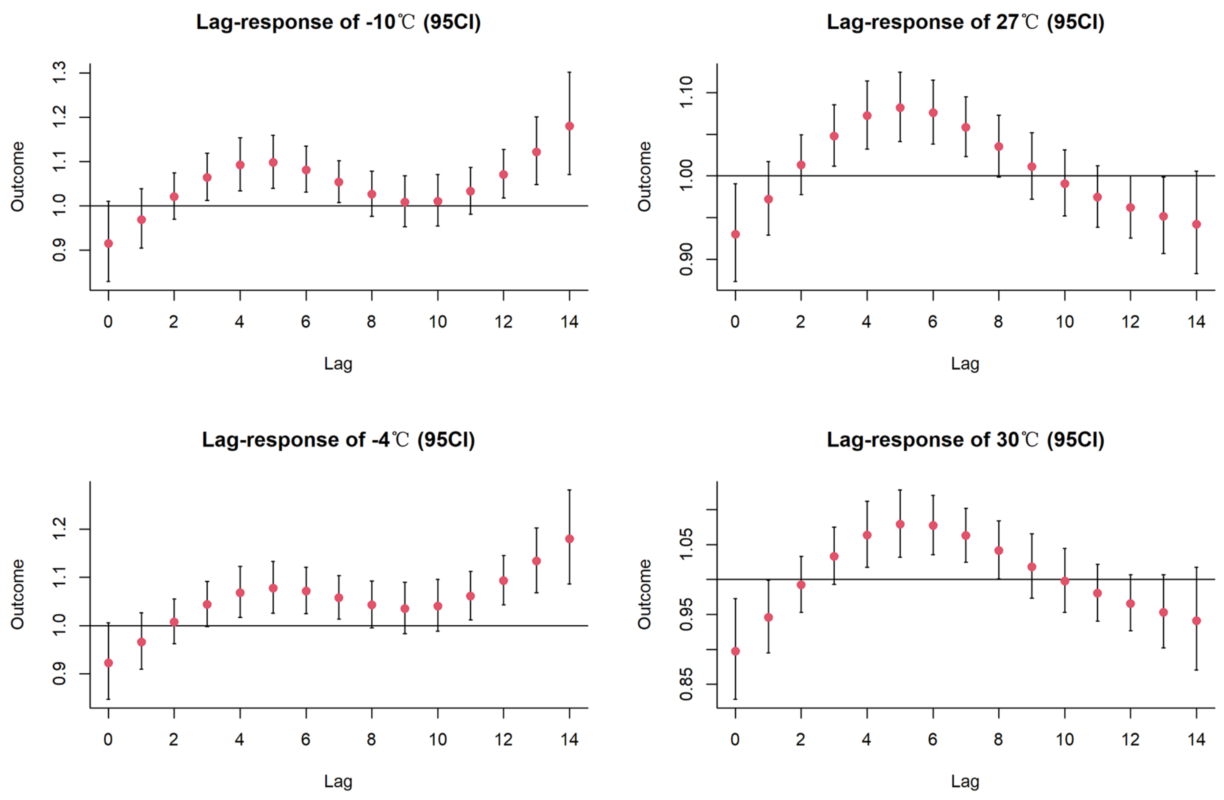

FIGURE 3
The visualization of the lagged effect at specific temperatures.

that the parameters of the DLNM model developed in our study were chosen reasonably and the model fitting results were more robust.

Discussion

As far as we know, this is the first study to use DLNM to explore how daily mean temperature affects emergency stroke visits in Beijing. After a two-stage analysis, we confirmed the direct and lagged effects of cold and hot temperatures on the risk of stroke incidence, and the effect of increased cold temperatures was more significant, but after correction for other environmental factors, we only observed a cumulative effect of cold temperatures on stroke incidence.

Extensive epidemiological evidence suggests that cold and hot exposures show a significant association with the risk of stroke mortality, and a study that combined the acute effects of ambient temperature on stroke mortality in 12 counties in Hubei Province, China, revealed a general inverse J-shaped connection between cold and heat waves and an increase in stroke mortality, with findings that were consistent with those of other research (5, 37–39). The association between ambient temperature and morbidity risk has received less attention in research, yet morbidity risk can reflect more direct productivity loss, patient and healthcare costs than mortality risk. In previous studies from China, a Taiwan study reported that the risk of hospitalization for HS on a cold day was approximately twice that of a warm day (40), and a study from Hong Kong found that a 1°C decrease in mean temperature was associated with a 2.7% increase in stroke admissions in the range of 8.2–31.8°C (41). A study analyzed stroke patients from 67 sentinel hospitals in Guangzhou from 2013–2015 and found that the attributable risk of IS and HS caused by cold temperature were 9.06% and 15.09%, respectively (9). In consistent with the findings above, our data revealed a statistically significant positive correlation between cold temperature and the incidence of stroke. The mechanism of the effect of cold temperature may be due to the fact that cold temperature tends to induce cerebral vasoconstriction, blood pressure fluctuations, and elevated circulatory levels, which may contribute to the occurrence of stroke (9).

After correction for multiple environmental factors in phase 2, both the direct and lagged effects of cold and hot temperatures on stroke risk were attenuated, and the effect of hot temperatures became non-significant, our results broadly agree with those of the one earlier study conducted in Beijing (14), which found

TABLE 3 Cumulative effects of different subgroups on stroke incidence at specific ambient temperatures.

		Extreme cold P_1: −10°C	Moderate cold P_{10}: −4°C	Moderate hot P_{90}: 27°C	Extreme hot P_{99}: 30°C
Stroke type					
IS	Lag 0–3	1.06	0.98	0.96	0.83
		(0.78, 1.42)	(0.75, 1.28)	(0.79, 1.18)	(0.65, 1.04)
	Lag 0–7	1.48	1.31	1.25	1.08
		(0.95, 2.30)	(0.88, 1.96)	(0.94, 1.68)	(0.79, 1.48)
	Lag 0–10	1.60	1.56	1.31	1.15
		(0.90, 2.83)	(0.93, 2.62)	(0.92, 1.86)	(0.79, 1.66)
	Lag 0–14	**2.33***	**2.36***	1.15	0.98
		(1.10,4.92)	**(1.20, 4.62)**	(0.74, 1.80)	(0.62, 1.56)
HS	Lag 0–3	0.82	0.87	0.95	0.97
		(0.55, 1.21)	(0.61, 1.23)	(0.73, 1.24)	(0.71, 1.33)
	Lag 0–7	1.07	1.09	1.29	1.28
		(0.60, 1.92)	(0.65, 1.84)	(0.88, 1.90)	(0.84, 1.95)
	Lag 0–10	1.06	1.11	1.32	1.35
		(0.50, 2.26)	(0.56, 2.18)	(0.83, 2.11)	(0.82, 2.23)
	Lag 0–14	1.56	1.80	1.02	1.15
		(0.58, 4.19)	(0.75, 4.31)	(0.56, 1.85)	(0.61, 2.16)
Age					
<65	Lag 0–3	0.89	0.97	0.88	0.80
		(0.59, 1.33)	(0.68, 1.39)	(0.68, 1.15)	(0.59, 1.10)
	Lag 0–7	1.12	1.31	1.23	1.05
		(0.61, 2.03)	(0.77, 2.25)	(0.83, 1.81)	(0.69, 1,59)
	Lag 0–10	1.02	1.26	1.26	1.04
		(0.47, 2.21)	(0.63, 2.53)	(0.79, 2.02)	(0.63, 1.70)
	Lag 0–14	1.44	1.99	1.16	0.93
		(0.52, 3.99)	(0.81, 4.90)	(0.64, 2.10)	(0.50, 1.74)
≥65	Lag 0–3	1.00	0.92	1.01	0.91
		(0.75, 1.34)	(0.71, 1.19)	(0.83, 1.23)	(0.72, 1.15)
	Lag 0–7	1.43	1.18	1.30	1.20
		(0.93, 2.20)	(0.80, 1.75)	(0.97, 1.74)	(0.88, 1.65)
	Lag 0–10	1.61	1.45	1.36	1.32
		(0.92, 2.83)	(0.87, 2.41)	(0.95, 1.93)	(0.91, 1.91)
	Lag 0–14	**2.39***	**2.22***	1.09	1.09
		(1.15, 5.00)	**(1.15, 4.31)**	(0.70, 1.70)	(0.68, 1.74)
Gender					
Male	Lag 0–3	0.87	0.91	0.97	0.83
		(0.64, 1.19)	(0.69, 1.20)	(0.79, 1.19)	(0.65, 1.06)
	Lag 0–7	1.23	1.22	**1.35***	1.14
		(0.78, 1.95)	(0.80, 1.84)	**(1.00, 1.82)**	(0.82, 1.58)
	Lag 0–10	1.30	1.51	**1.52***	1.26
		(0.72, 2.36)	(0.89, 2.59)	**(1.06, 1.93)**	(0.86, 1.85)
	Lag 0–14	1.94	**2.38***	1.49	1.23
		(0.90, 4.21)	**(1.19, 4.76)**	(0.93, 2.19)	(0.76, 2.03)
Female	Lag 0–3	1.11	0.97	0.94	0.93
		(0.77, 1.60)	(0.70, 1.35)	(0.73, 1.21)	(0.70, 1.25)
	Lag 0–7	1.44	1.23	1.17	1.16
		(0.83, 2.48)	(0.75, 2.01)	(0.81, 1.68)	(0.78, 1.72)

(Continued)

TABLE 1 (Continued)

	Extreme cold P_1: −10°C	Moderate cold P_{10}: −4°C	Moderate hot P_{90}: 27°C	Extreme hot P_{99}: 30°C
Lag 0–10	1.47	1.19	1.08	1.15
	(0.72, 3.00)	(0.62, 2.26)	(0.69, 1.67)	(0.72, 1.83)
Lag 0–14	2.11	1.80	0.73	0.80
	(0.84, 5.35)	(0.78, 4.14)	(0.42, 1.27)	(0.44, 1.43)

*$p < 0.05$ was considered statistically significant and is indicated in bold font.
IS, ischemic stroke; HS, hemorrhagic stroke.

that extreme cold temperature (P_1: −9.6°C) compared with 1.2°C (P_{25}) increased the cumulative RR for IS at lag 0–14 days, The cumulative RR was 0.51 (95 % CI: 0.08–1.10) higher for IS and 0.28 (95 % CI: 0.03–0.59) higher for HS at lag 0–3 days compared with 1.2°C (P_{25}), similarly, this study did not find an effect of hot on stroke incidence. In contrast, our study found a greater RR of cold temperature on IS incidence at lag 0–14 days, and in addition we did not find a significant effect of ambient temperature on HS. Some of the reasons why our study differs from it may be the following, firstly, the lag structure and reference temperature settings of the two studies were different, which led to the difference in the final RR values, secondly, the factors included in the multi-factor model were different, we took into account the effects of TV and SO_2 in addition to relative humidity and $PM_{2.5}$, and the subsequent analysis showed that these factors did interact with ambient temperature. Our study used emergency data rather than hospitalization data, as stroke is an acute and serious condition with rapid incidence and progression, so the use of emergency visits can more accurately and reasonably reflect the risk of stroke due to the corrective effect of environmental factors. According to domestic and international studies related to the effect of ambient temperature on stroke emergency department visits, a study from Japan found that each 1°C drop in ambient temperature increased IS and HS visits by 3.56% and 35.57%, respectively (42), and another study from Turkey also found that lower ambient temperatures increased stroke visits (43). Additionally, a research from Brisbane, Australia, revealed no statistically significant link between high temperatures and admissions for emergency stroke (44), and the results of these studies, which were based on emergency data, were the same as our results.

The lag effect analysis results showed that neither the single-factor model nor the multi-factor model changed the lag days of the maximum effect, with the cold temperature effect being maximum at lag 14 and lag 0–14 days and the hot temperature effect being maximum at lag 6 and lag 0–10 days, indicating that the cold temperature effect persisted over a longer lag period while the hot temperature effect was relatively weak and acted within a shorter period. Similarly, a previous study from Beijing also found that hot temperature effects behave acutely relative to cold temperatures (14). Health care resource allocation and the development of public health interventions can be informed by this lag structure. Preventive measures in the short term can help address the health risk of stroke incidence under the effects of hot temperatures, while long-term protection can target the risk of stroke incidence under the effects of cold temperatures. In addition, this can be used to estimate the cost of health service utilization. Based on our data, we conclude that the relative risk of extreme cold exposure in Beijing in 2017–2018 is lower than that of moderate cold temperatures in emergency department visits for stroke, and we speculate that this finding may be due to the effect of early warning. Public health authorities have previously implemented preventive and protective measures mainly for extreme weather (45), so people are more sensitive to extreme cold temperatures and are more likely to take protective measures, such as going out less, actively adding clothing, and increasing heating, which implies that health problems caused by moderate cold temperatures should receive more attention in the future and public health authorities should further develop defensive measures against moderate cold temperatures.

In the second phase of the analysis, with the analysis in the GAM, we also focused on how ambient temperature and other environmental factors affect the development of stroke. We found that higher TV increases the risk of stroke, following the findings from Bangladesh, which found a 1.00% increase in emergency department visits for cardiovascular disease per 1°C increase in TV (17), with possible underlying mechanisms being unstable changes in ambient temperature can disrupt the body's thermoregulatory balance, thereby reducing the ability to adapt to ambient temperature, and in addition TV is associated with peripheral vasoconstriction, platelet viscosity, and the ability of the immune system to resist infectious agents (46). We observed a positive association between $PM_{2.5}$ and the risk of stroke, which is also consistent with previous studies (18, 47). In our original data, the relative humidity in Beijing was distributed between 60% and 80% for many days, so for this interval, the lower the relative humidity the higher the risk of stroke, a finding that is consistent with previous studies (48, 49). However, we found that SO_2 was negatively associated with stroke incidence, which is contrary to the previous positive findings (47, 50), probably because these studies were on the effect of SO_2 on IS, but we did not investigate the effect of SO_2 on stroke subtypes, perhaps because of the confounding effect between subtypes. In addition, it has been reported that there is no significant relationship between SO_2 and stroke visits (51, 52), so the relationship between SO_2 and stroke or stroke subtypes is not conclusive, and further studies are needed to provide a reasonable and accurate basis.

Subgroup analysis revealed a positive correlation between the effects of low temperature on different subtypes, and no change in the lagged pattern of cold and hot effects, which is consistent with previous findings (9, 14, 40, 41). This is different from previous studies from Taiwan and Hong Kong (40, 41), our study found that the effect of cold temperature on the incidence of IS was greater than that of HS, possibly because both studies were from subtropical monsoon climate regions, whereas Beijing is a typical temperate monsoon climate, and there is a large difference between the mean temperatures of cold and hot months in both, with temperatures generally higher in subtropical monsoon climate regions than in Beijing, it is possible that the association between cold temperatures below a certain threshold on stroke subtypes was not observed. It is also possible that factors such as urban characteristics, air pollution levels, and heating facilities in the north and south may be relevant, but it is certain that there are differences in the effects of ambient temperature on stroke subtypes among each other. The analysis of subgroups of people of different ages and genders showed that the effect of cold temperatures was more significant in the elderly and male population, with an RR of 2.39 and 2.38, respectively, which is in full agreement with the results of a previous study from Guangzhou (9), possible reasons for this result are decreased metabolic levels, reduced thermoregulatory capacity, or co-morbidities in the elderly; the difference between the genders may be due to different hormone levels in males and females, and the fact that males are generally more likely to work outdoors and have more exposure to ambient temperature or other environmental factors (53).

Our study has obvious advantages. First, we applied an advanced statistical method, DLNM can more accurately and comprehensively reflect the effect of ambient temperature on stroke incidence, including quantitative assessment of the lagged effect and the cumulative effect of ambient temperature. Finally, because our data are newer, large-scale emergency department visits, they are a more accurate representation of stroke incidence than inpatient data, and to our knowledge, we are the only study to explore the effect of temperature on stroke emergency department visits in Beijing, which may provide a useful tool for public health research in Beijing. This may not only offer the department of public health a scientific foundation for developing relevant policies, but also provide new ideas for improving hospital emergency room prediction models with temperature as a predictor. Of course, our study has some limitations, as other similar studies are ecological studies and cannot avoid ecological fallacies; there are differences between the exposure levels of the population and the actual exposure of individuals; secondly, due to different geographical characteristics, our findings need to be extrapolated to areas outside Beijing with caution; and finally, because stroke incidence is influenced by socioeconomic conditions, literacy, and other co-morbidities in addition to environmental factors, however, our study did not collect and analyze these possible confounding factors.

Conclusions

In summary, our study shows that there is a significant non-linear relationship between temperature and stroke incidence, with cold temperatures having a stronger and longer-lasting effect on stroke incidence compared with hot temperatures. In addition, larger TV, higher $PM_{2.5}$, and lower relative humidity increased the risk of stroke occurrence. These findings have important public health and clinical implications for the development of stroke control strategies in Beijing under different weather conditions.

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethics statement

This study was approved by the Ethics Committees of Tianjin Medical University (No. TMUhMEC 2021009). Overall aggregated data were used in our study and no information about individual patient privacy was involved in the analysis.

Author contributions

JZ, ZC, and WZ: conceptualization, data curation, investigation, and writing-original draft. YZ: conceptualization, investigation, and writing-original draft. YN: validation and formal analysis. JH, JW, and XL: writing-review & editing. CL and YG: conceptualization and writing-review & editing. ZC and WZ: writing-review & editing and supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1034534/full#supplementary-material

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EDITED BY
Zhiming Yang,
University of Science and Technology Beijing, China

REVIEWED BY
Jitian Zhang,
Shandong Provincial Hospital Affiliated to Shandong First Medical University, China
Kejia Hu,
Zhejiang University, China

*CORRESPONDENCE
Lu Ma
malu@whu.edu.cn

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Association between smoking and hypertension under different $PM_{2.5}$ and green space exposure: A nationwide cross-sectional study

Qihao Chen[1], Xuxi Ma[2], Yan Geng[2], Jingling Liao[3] and Lu Ma[1]*

[1]Department of Biostatistics, School of Public Health, Wuhan University, Wuhan, China,
[2]Department of Global Health, School of Public Health, Wuhan University, Wuhan, China,
[3]Department of Nutrition and Food Hygiene, School of Public Health, Medical College, Wuhan University of Science and Technology, Wuhan, China

Background: Smoking has been widely reported to have a significant relationship with hypertension, but the past description of this relationship has not been uniform. In addition, there has been a lack of research to discuss the impact of environmental exposure on the relationship between smoking and hypertension. Therefore, this study estimates the association between smoking and hypertension in middle aged and elderly people in China under different $PM_{2.5}$ (fine particulate matter) concentrations and the green space exposure conditions.

Methods: Individual sample data from the China Health and Retirement Longitudinal Study in 2018 and the long-term average exposure concentration of fine particles and green space exposure for all participants were used with a multilevel binary logistic mixed effects model. Adjustments were made for sociodemographic characteristics and other health behaviors including drinking, physical activity, and social activity. The normalized difference vegetation index (NDVI) and $PM_{2.5}$ concentration stratification were assigned with the median of the population exposure concentration as the dividing line, and the dual environmental factor stratification was assigned in combination with the two types of environmental exposure. The analysis was also stratified using age groups.

Results: A total of 10,600 participants over the age of 45 were included in the study. The effects of smoking on hypertension were diverse under different environmental exposure conditions. There was a significant relationship between smoking behavior and hypertension in the Low-NDVI group, and the effect value of this relationship was significantly different from that in the High-NDVI group. Furthermore, for respondents exposed to low green spaces and high $PM_{2.5}$ environments at the same time (Low-NDVI/High-$PM_{2.5}$ group), their smoking behavior may lead to an increase in the risk of hypertension. In addition, the risk of hypertension caused by smoking in the middle-aged (45–64) was significant under low green space exposure, but the effect difference between the different age groups was not significant.

Conclusions: The relationship between smoking and hypertension was different under different environmental exposure conditions. Exposure to low green spaces may strengthen the association between smoking and hypertension risk. When participants were exposed to both low green spaces and high $PM_{2.5}$ concentrations, the risk of hypertension caused by smoking was significantly higher than that of those who were exposed to high green spaces and low $PM_{2.5}$ concentrations.

KEYWORDS

smoking, hypertension, $PM_{2.5}$, green space, air pollution

Introduction

Smoking has been widely reported as a risk factor for cardiovascular disease (CVD) (1, 2), while smoking cessation and tobacco consumption control are regarded as important means to prevent CVDs such as hypertension and coronary heart disease (3). Published studies support that atherosclerosis caused by smoking may increase the risk of hypertension (4), and nicotine may lead to a rise in blood pressure (BP) through a variety of biological mechanisms such as symptomatic action and modulation of the renin angiotensin system (5).

Although a significant association between smoking and hypertension is widely recognized, the association strength and the effect description among smokers in previous studies have been inconsistent. For this reason, previous studies have tried to control the confounding factors in the association analysis between smoking and hypertension using the body mass index (BMI), demography, smoking behavior details, and other aspects, but the results obtained were still different. A study on men reported that the relative risk of hypertension of former smokers and current smokers reached 1.08 and 1.15, respectively (6). However, a cross-sectional study conducted only in men also found that there was a more significant relationship between former smokers and hypertension, with an odds ratio (OR) of 1.48 (95 CI%: 1.01, 2.18), while the risk of hypertension in current smokers was not significant (7). A longitudinal population-based study supported that the abdominal obesity population had a higher risk of hypertension due to smoking. The OR of former smokers compared with current smokers was 1.62 (95, CI%: 1.08, 1.41) (8). However, a cross-sectional study in France reported that there was a significant relationship between current smokers and hypertension, and claimed that the BMI was independent of this relationship (9). Zhang et al. also believe that the potential confounding effect from body weight cannot totally explain the inconsistent findings (10). A study conducted in Iran suggested that a significant socioeconomic status (SES)-smoking association may determine increasing blood pressure (11), while another study that examined education, the living area, and other SES factors as covariate controls found that smoking had no significant relationship with hypertension (12).

As an important risk factor related to hypertension, environmental factors, such as air pollution and green space, have been widely associated with hypertension in the field of environmental epidemiology. However, most previous studies on smoking and hypertension lacked the control of environmental exposure. As an important pollutant in the atmosphere, $PM_{2.5}$ has frequently appeared in hypertension risk factor studies (13, 14), and multiple studies have focused on the elderly, supporting the possibility that smoking might lead to an increase in BP (15, 16). In addition, studies regarding long-term exposure to green space have indicated that the odds of hypertension are related to the green space exposure (17), and some studies have claimed that living near green spaces may reduce the risk of hypertension (18, 19). Under the premise that environmental factors have potential effects on hypertension, the lack of control over environmental factors in the analysis may have led to biased effect descriptions.

Therefore, to further explain the relationship between smoking and hypertension, it is necessary to explore the risk difference of smoking on hypertension under complex environmental exposure. The China Health and Retirement Longitudinal Study (CHARLS) used a multilevel binary logistic mixed effects regression to analyze the risk of hypertension caused by smoking under different $PM_{2.5}$ concentrations and green space exposure, attempting to provide a new perspective for the study of hypertension risk factors. In addition, a nationwide study reported that the tobacco dependence of middle-aged people in China was significantly higher than that of the elderly (20). Hence, an age stratified analysis under different environmental conditions is also included in our study.

Materials and methods

Study population

The information of study population was collected from the China Health and Retirement Longitudinal Study (CHARLS). CHARLS aims to collect a set of high-quality micro-data representing families and individuals aged 45 and over in China that provide data support for an analysis of aging of the Chinese population and promote the interdisciplinary research of aging (21). CHARLS covers 150 county-level units (the latest survey resulted in 2018 covering 125 cities), 450 village level units, and nearly 20,000 people in approximately 10,000 households. The CHARLS national baseline survey was conducted in 2011, and three follow-up investigations were repeated in 2013, 2015, and 2018. The datasets are available for researchers after registration and can be obtained on the corresponding website.

It should be noted that the propose of this study is to assess the difference in the impact of smoking on hypertension under different long-term environmental conditions, while according to the Air Pollution Prevention and Control Action Plan proposed by the State Council of China, China included all of the prefecture level cities in the $PM_{2.5}$ measurement on January 1, 2015 (22). Therefore, to obtain complete long-term exposure concentration data of $PM_{2.5}$, CHARLS 2018 conducted from July 2018 to September 2018 was chosen as the data support of this cross-sectional study.

Health data

Individual information on the smoking status, hypertension diagnosis, other health behaviors and demographic data were collected from the China Health and Retirement Longitudinal Study—Baseline Questionnaire, which was one of a series of questionnaires in CHARLS.

Smoking status

For smoking status, respondents were described as "never smoking", "current smoker", and "former smoker". First, for question DA059 ("Have you ever chewed tobacco, smoked a pipe, smoked self-rolled cigarettes, or smoked cigarettes/cigars?"), respondents were divided into never smoking and people with smoking history. Second, according to DA061 ("Do you still have the habit, or have you totally quit?"), people with smoking histories were further divided into "current smoker" and "former smoker", which means that smoking status was described as a categorical variable in this study.

Hypertension diagnosis

The diagnosis basis of hypertension was obtained from DA007 ["Have you been diagnosed with (one of the following chronic diseases) by a doctor?"] that included hypertension, dyslipidemia, diabetes or high blood sugar, cancer or malignant tumor, chronic lung diseases, liver disease, heart disease, stroke, kidney disease, stomach or other digestive disease, emotional, nervous, or psychiatric problems, memory-related disease, arthritis or rheumatism, or asthma. In this study, hypertension was defined as individuals who reported having been diagnosed with hypertension.

Covariates

The demographic information included age, sex, and education level (BD001: "What is the highest level of education you have attained?" described as under primary school, primary school, middle school or above), and the per capita gross domestic products (GDPs) of all cities in 2018 was collected from the statistical yearbook of each province (23) were considered as covariates to be controlled. As health behavior variables mentioned in previous hypertension relationship studies (21, 24, 25), alcohol drinking (DA067: "Did you drink any alcoholic beverages, such as beer, wine, or liquor in the past year? How often?", described as drink more than once a month, drink but less than once a month, never drink), sleep time (DA049: "during the past month, how many hours of actual sleep did you get at night?"), physical activity (DA051: "during a usual week, did you do any physical activity for at least 10 minutes continuously?", yes or no), and social activity (DA056: "have you done any of these activities below in the last month?", yes or no) were included in the analysis. Daily cigarette consumption (DA063: "In one day about how many cigarettes do/did you consume?") as a detailed variable of smoking behavior was also included in the analysis.

We used the CHARLS2018 as the data support that included 19,020 respondents from 125 cities. Due to the need to define the one-year exposure period by the month of interview, 12 cities (Fuzhou City, Putian City, Ningde City, Zhangzhou City, Chengdu City, Guangan City, Kunming City, Baoshan City, Zhaotong City, Lijiang City, Lincang City, and Haidong City) that lacked the records of the month of interviews were not included in the analysis, and a total of 2,325 respondents were excluded. Of the remaining 113 cities, eight were not within the scope of the National Ambient Air Quality Monitoring Network. Hence, 853 respondents in these cities were excluded (Chaohu City, Chuxiong Yi Minority Autonomous Prefecture, Ganzi Tibetan Autonomous Prefecture, Liangshan Yi Autonomous Prefecture, Qiandongnan Miao and Dong Autonomous Prefectures, Qiannan Buyei and Miao Autonomous Prefectures, Xiangfan City, and the Xing 'an League). We also excluded 1,155 respondents with missing or illogical data, such as respondents under 45 because the CHARLS does not systematically sample the population below age 45 (26). Finally, 4,087 respondents were excluded due to lack of hypertension diagnostic information, and our final sample included 10,600 respondents from 105 cities. According to the Chi square test, there was no significant difference in the prevalence of hypertension between the excluded 8,420 respondents and the final 10,600 respondents included in the study ($P = 0.425$). Figure 1 shows the specific screening process of the respondents in this study.

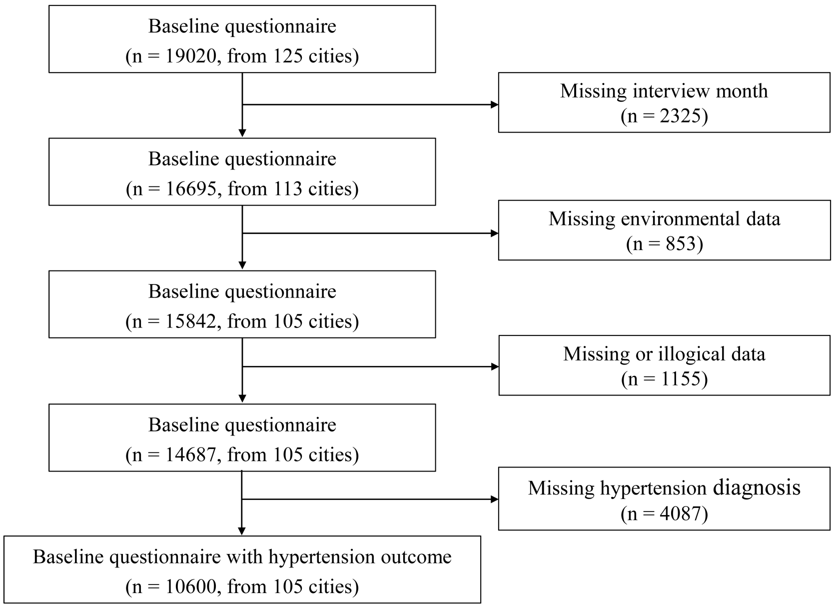

FIGURE 1
Flow chart of selection procedure.

Exposure assessment

Air pollution

The $PM_{2.5}$ data were collected from the National Ambient Air Quality Monitoring Network established by the China National Environmental Monitoring Center. The monitoring network includes a total of 1,436 stations covering 338 cities in China that release daily average concentration data on $PM_{2.5}$ and other air pollutants in each city in hourly terms. The mean daily average of all the fixed monitoring points in each city was considered as the daily $PM_{2.5}$ concentration of the respondents. To explore the long-term exposure effect, we defined the one-year exposure period for each respondent using the last day of the interview month as the end point.

Based on obtaining the daily average concentration, we calculated the annual average concentration to describe the long-term exposure to $PM_{2.5}$. In addition, we introduced O_3 (ozone) and NO_2 (nitrogen dioxide) as covariates in the model control because they have been reported as influencing factors of hypertension (27).

Green space

As a measure of the relative plant health in terrestrial habitats and landscapes, the normalized difference vegetation index (NDVI) is widely used as an index to evaluate the exposure level of green space (28). The NDVI quantifies the density of green vegetation based on the difference between the surface reflectance of near-infrared (NIR) and visible red (VISR) measured by satellite (29).

$$NDVI = \frac{(NIR - VISR)}{NIR + VISR}.$$

NDVI values vary between −1 and 1 where pixels with dense vegetation typically yield high positive numbers, while a negative NDVI value indicates that the ground is covered with clouds, water, or snow that are highly reflective of visible light. An NDVI equal to 0 means that the ground is rock or bare soil, and the NIR and VISR are approximately equal (30). Since this study has not discussed the environmental factors of water, the value of an NDVI <0 is null by default.

The NDVI data of this study were collected from the Moderate Resolution Imaging Spectroradiometer (MODIS). As the primary instrument that monitors the earth's surface onboard the earth observation systems Terra and Aqua (31), MODIS records data to analyze several environmental variables including greenness, and it has been widely used for global research on green spaces and other environmental factors (32). After data screening to determine the cities involved in the study, green space satellite images with spatial resolutions of 1 km * 1 km and time resolutions of one every 30 days (12 images per year) were used to extract the monthly average NDVI of all cities in study. With reference to the long-term exposure assessment of $PM_{2.5}$, the average annual NDVI exposure concentration of each respondent was calculated with the month of the interview as the end point.

Statistical analysis

Multilevel model

Respondent data from CHARLS contains two levels of variables: health and demographic factors at the individual level and environmental exposure factors and socio-economic factors at the regional level. This means that the data in this study followed a hierarchical structure (25). Considering that the traditional binary logistic regression model only describes effects from a single level, multilevel binary logistic mixed effects models were used to examine the relationship between smoking and hypertension under different environmental conditions (33). For all analysis, we constructed an unadjusted model (Model 0), a model adjusted for age, sex, education level, the per capita GDP, alcohol drinking, daily cigarette consumption, sleep time, physical activity, and social activity (Model 1), and a model additionally adjusted for environmental factors included the NDVI, $PM_{2.5}$, O_3, and NO_2 (Model 2). Generalized variance inflation factors (GVIFs) were used to quantify the multicollinearity between the environmental exposures (30).

Stratified analysis

Based on the significant relationship between smoking and hypertension observed in the main model, a stratified analysis of the environmental factors was conducted. By using the median annual average exposure concentration of the NDVI and $PM_{2.5}$ of each respondent as the dividing line, a single environmental factor stratified analysis for two environmental factors was conducted separately. To verify the comparability of the odds ratios under different regressions, we conducted a significant difference test on the regression coefficients of the different concentration groups. Douglas G (34) mentioned that the standard deviation of the difference between the two estimates has the relationship of the flow equation that follows:

$$\boldsymbol{SE}\,(\boldsymbol{d}) = \sqrt{\boldsymbol{SE}(\boldsymbol{E_1})^2 + \boldsymbol{SE}(\boldsymbol{E_2})^2},$$

where $\boldsymbol{E_1}$ and $\boldsymbol{E_2}$ represent the estimated value of smoking for the increased risk of hypertension in the different groups of environmental factor exposure concentrations. After obtaining the standard deviation of the estimated value difference, $\boldsymbol{SE(d)}$, the test of interaction was based on the flow equation:

$$\boldsymbol{Z} = \frac{\boldsymbol{d}}{\boldsymbol{SE}(\boldsymbol{d})}.$$

The ratio $\boldsymbol{Z}$ gives a test of the null hypothesis that in the population the difference d is zero by comparing the Z score to the standard normal distribution. For this study, the *P*-value obtained by referring the Z score to the normal distribution table was used to described whether the difference between the different pollution concentration groups was significant. In addition, this study also conducted a stratified analysis of age under different single environmental factors. Single environmental factor stratified analyses were conducted in the different age groups (45–64/>64) to observe the difference of their effects. Tests for the difference in the regression estimates in the environmental concentration stratification and age stratification were conducted.

Furthermore, we combined the grouping conditions of the single environmental factor stratified analysis and conducted a dual environmental factor stratified analysis. The double environmental factor stratification describes the level of the NDVI and $PM_{2.5}$ exposure of respondents for the entire population during the study period. All respondents were divided into four groups: Low NDVI / Low $PM_{2.5}$ group, Low NDVI / High $PM_{2.5}$ group, High NDVI / Low $PM_{2.5}$ group, and High NDVI / High $PM_{2.5}$ group. For example, if a respondent was in the Low NDVI / Low $PM_{2.5}$ group, this meant that both the respondent 's exposure to $PM_{2.5}$ and green space during the one-year exposure period ending at the interview date were lower than the median annual exposure concentration of the study population. For all groups that observed a significant association between smoking and hypertension, the difference between their estimates and each other group were tested using the Z score and reported in the form of the *P*-value (P for ORs).

Sensitivity analysis

To evaluate the robustness of our results, we conducted a sensitivity analysis by defining two different exposure periods (a half-year and 2 years). A single environmental factor stratification analysis and dual environmental factor stratification analysis were conducted during two different exposure periods. All of the statistical analyses were conducted using R version 4.2.1, and two-sided *p*-values ($p < 0.05$) were considered statistically significant.

Results

Descriptive statistics

The basic characteristics of the study participants are summarized in Table 1. This study included 10,600 middle-aged or older respondents with a mean age of 59.82 years and an approximately equal sex distribution (46.82% males and 53.18% females). A total of 61.12% of the respondents had never smoked, while 26.85% were current smokers, and former smokers accounted for 12.03% of all the respondents. There were 1,584 participants with hypertension, and this indicated that the prevalence of the study population was 14.94%. The daily cigarette consumption of the survey population was 6.78, and the average GDP per capita reached 52,852 yuan. For the NDVI concentration stratification, significant differences were observed for education level and social activity. While for the $PM_{2.5}$ concentration stratification, education level, smoking

TABLE 1 Descriptive statistics of the study population.

Variable	Total (n = 10,600)	Low NDVI (n = 5,258)	High NDVI (n = 5,342)	*P*-value*	Low $PM_{2.5}$ (n = 5,248)	High $PM_{2.5}$ (n = 5,352)	*P*-value*
Prevalence rate	1,584 (14.94%)	780 (14.83%)	804 (15.05%)	0.776	759 (14.46%)	825 (15.41%)	0.178
Age (mean ± SD)	59.82 ± 9.79	59.85 ± 9.79	59.79 ± 9.80	0.151	59.96 ± 9.93	59.68 ± 9.66	0.750
Gender				0.299			0.190
Male	4,963 (46.82%)	2,489 (47.34%)	2,474 (46.31%)		2,423 (46.17%)	2,540 (47.46%)	
Female	5,637 (53.18%)	2,769 (52.66%)	2,868 (53.69%)		2,825 (53.83%)	2,812 (52.54%)	
Education level				0.000			0.000
Under primary school	4,021 (37.93%)	1,829 (34.79%)	2,192 (41.03%)		1,931 (36.79%)	2,090 (39.05%)	
Primary school	2,397 (22.61%)	1,225 (23.3%)	1,172 (21.94%)		1,256 (23.93%)	1,141 (21.32%)	
Middle school or above	4,182 (39.45%)	2,204 (41.92%)	1,978 (37.03%)		2,061 (39.27%)	2,121 (39.63%)	
Smoking status				0.823			0.017
Never Smoking	6,479 (61.12%)	3,228 (61.39%)	3,251 (60.86%)		3,219 (61.34%)	3,260 (60.91%)	
Former smoker	1,275 (12.03%)	632 (12.02%)	643 (12.04%)		586 (11.17%)	689 (12.87%)	
Current smoker	2,846 (26.85%)	1,398 (26.59%)	1,448 (27.11%)		1,443 (27.50%)	1,403 (26.21%)	
Daily cigarette consumption	6.78 ± 11.75	6.935 ± 9.795	6.619 ± 9.795	0.284	6.697 ± 9.932	6.853 ± 9.657	0.698
Drinking status				0.448			0.005
Never drink	6,863 (64.75%)	3,383 (64.34%)	3,480 (65.14%)		3,385 (64.50%)	3,478 (64.99%)	
Light drinking	2,862 (27.00%)	1,424 (27.08%)	1,438 (26.92%)		1,385 (26.39%)	1,477 (27.60%)	
Habitual drinking	875 (8.25%)	451 (8.58%)	424 (7.94%)		478 (9.11%)	397 (7.42%)	
Sleep time (mean ± SD)	6.27 ± 1.89	6.30 ± 1.87	6.24 ± 1.92	0.586	6.28 ± 1.90	6.26 ± 1.89	0.106
Physical activity				0.905			0.011
No	949 (8.95%)	473 (9.00%)	476 (8.91%)		432 (8.23%)	517 (9.66%)	
Yes	9,651 (91.05%)	4,785 (91.00%)	4,866 (91.09%)		4,816 (91.77%)	4,835 (90.34%)	
Social activity				0.000			0.889
No	4,676 (44.11%)	2,150 (40.89%)	2,526 (47.29%)		2,311 (44.04%)	2,365 (44.19%)	
Yes	5,924 (55.89%)	3,108 (59.11%)	2,816 (52.71%)		2,937 (55.96%)	2,987 (55.81%)	
Per capita GDP (yuan, mean ± SD)	55,852.00 ± 0.43	58,130.40 ± 0.52	53,609.42 ± 0.46	0.829	55,915.61 ± 0.55	55,789.62 ± 0.43	0.000

*The P-value between different exposure concentration groups was calculated using the Chi square test for the categorical variables and the two-sample unpaired t test for the continuous variables.

status, drinking status, physical activity, and GDP per capita showed significant distribution differences. The distribution of daily cigarette consumption and the prevalence of hypertension did not show significant differences in both the NDVI and $PM_{2.5}$ concentration stratification ($P > 0.05$).

The summary statistics on the environmental data during July 2016 to September 2018 of all cities included in this study are shown in Table 2. The average $PM_{2.5}$ concentration of 105 cities from July 2016 to September 2018 was 49.09 $\mu g/m^3$, with a median concentration of 44.86 $\mu g/m^3$. Shijiazhuang City had the highest average $PM_{2.5}$ concentration, reaching 90.70 $\mu g/m^3$, while Hulunbeier City showed the lowest long-term average exposure concentration of $PM_{2.5}$. For O_3 and NO_2, the average concentrations reached 95.98 and 29.06 $\mu g/m^3$, respectively, during the study period. The average value of the NDVI reached 0.54, with a median of 0.53. Anyang City and Siping City were the cities with the lowest and highest NDVI exposures among all of the cities, with NDVI values of 0.13 and 0.73, respectively. Figure 2 shows the average concentration distribution of the NDVI in China during study period. It was found that the NDVI of the central and southern region sin China were higher than that of other regions, and most of the cities included in the study were located in these two areas. Some cities were located in the northeast

TABLE 2 Summary statistics of the air pollutants and NDVI during the study period.

Variable	Mean ± SD	Percentiles					IQR
		Min	25th	50th	75th	Max	
$PM_{2.5}$	49.09 ± 13.86	20.18	38.47	44.86	58.50	90.70	20.02
NO_2	33.86 ± 8.70	17.38	26.82	34.18	39.94	54.12	13.12
O_3	97.11 ± 10.17	70.16	90.50	98.48	104.62	114.99	14.12
NDVI	0.54 ± 0.11	0.13	0.44	0.50	0.60	0.73	0.16

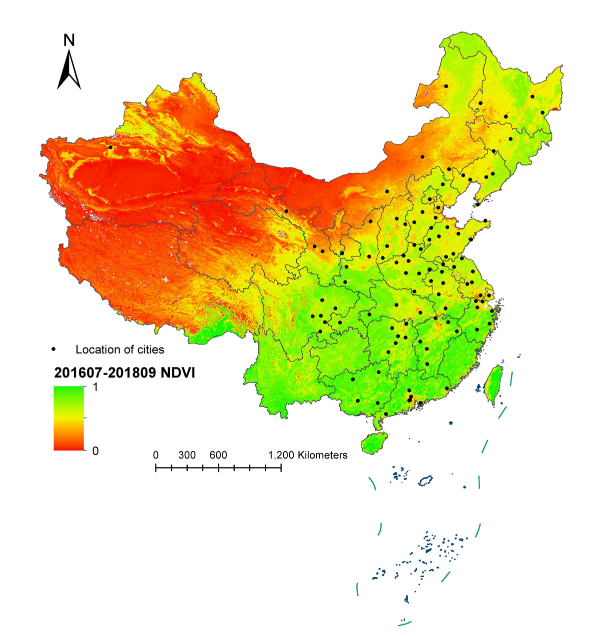

FIGURE 2
Average concentration distribution of the NDVI during July 2016 to September 2018 in China.

region, and the NDVIs of this region were lower than that of the south.

Primary model results

Table 3 shows the primary model results of the relationship between hypertension and smoking. In the unadjusted Model 0, the smoking behavior of the current smokers and former smokers showed a significant relationship with hypertension, and the OR reached 1.064 (95 CI%: 1.012, 1.118) and 1.082 (95 CI%: 1.021, 1.146), respectively. After controlling for demographic factors, such as gender and age, and the health behavior covariates, such as physical activity and social activity, the relationship between the current smokers and hypertension in Model 1 showed a marginal significance ($P = 0.096$), and the OR reached 1.022 (95 CI%: 0.996, 1.048). The smoking behavior of former smokers was still statistically significant for the risk of hypertension ($P = 0.011$), and the risk of hypertension increased by 3.87% (95 CI%: 1.009, 1.070) compared with those who had never smoked. In Model 2 that controls for air pollutants and the NDVI, the correlation strength and significance between smoking behavior and hypertension of former smokers and current smokers increased slightly. The risk of hypertension in former smokers increased by 3.92% (95 CI%: 1.009,1.070) compared with those who had never smoked, and the relationship between former smokers and hypertension was significantly enhanced after controlling for environmental factors ($P = 0.009$). For current smokers, the OR reached 1.024 (95 CI%: 0.998, 1.051) in Model 2, and the relationship between current smokers and hypertension was still marginal significant ($P = 0.071$).

Single environmental factor stratified results

By using the median annual average exposure concentration of the NDVI and $PM_{2.5}$ of the respondents as the dividing line, a single environmental factor stratified analysis was conducted, and the results are presented in Table 4. The smoking behavior of the current smokers and former smokers was significantly related to the risk of hypertension in the different NDVI exposure levels. In the Low-NDVI group, the relationship between smoking behavior and hypertension of the current smokers and former smokers was statistically significant ($P < 0.05$), with the ORs reaching 1.058 (95 CI%: 1.020, 1.097) and 1.071 (95 CI%: 1.026, 1.117), respectively. However, in the High-NDVI group, no significant association with hypertension was observed in both current smokers and former smokers. Table 4 also reports the significance of the OR difference between the current smokers and former smokers in the different NDVI concentration groups. The *P*-value of the OR difference of the current smokers was 0.011, which means that there was a significant difference in the risk of hypertension among current smokers in the different NDVI exposure environments. For former smokers, the OR difference of the different NDVI groups was marginally significant ($P = 0.059$). Multicollinearity of exposures was not an issue in the NDVI stratified analysis (the GVIF values were below 1.808).

TABLE 3 Odds ratios (OR) of hypertension (with 95% confidence intervals, 95%CI) associated with smoking.

Model	Covariates	Smoking status	OR (95%CI)
Crude	Unadjusted	Never smoking	-
		Former smoker	1.082 (1.021,1.146)***
		Current smoker	1.064 (1.012,1.118)**
Basic	Age, sex, education level, the per capita GDP [a], alcohol drinking, daily cigarette consumption, sleep time, physical activity and social activity	Never smoking	-
		Former smoker	1.039 (1.009,1.070)**
		Current smoker	1.022 (0.996,1.048)*
Main	Basic model + NDVI + $PM_{2.5}$ + O_3 + NO_2	Never smoking	-
		Former smoker	1.039 (1.009,1.070)***
		Current smoker	1.024 (0.998,1.051)*

[a]Per capita GDP has been logarithmically converted.
(1) ***p < 0.01; **p < 0.05; *p < 0.10 (2) In all models, the GVIFs were <1.785.

For the stratified analysis of $PM_{2.5}$, we did not observe a significant effect of the current smokers and former smokers on the risk of hypertension in the Low-$PM_{2.5}$ group. For the former smokers with long-term $PM_{2.5}$ exposure above the median of the population, the risk of hypertension caused by smoking behavior was statistically significant, with an OR of 1.052 (95 CI%: 1.008, 1.097). Although the current smokers in the High-$PM_{2.5}$ group showed a trend of an increased risk for hypertension, the association was not statistically significant. It should be emphasized that in the test of the OR difference, the OR difference of the hypertension risk among former smokers in the different $PM_{2.5}$ groups was not significant ($P = 0.406$). After GVIF verification, all models of the $PM_{2.5}$ stratified analysis did not have multicollinearity.

The results of the single environmental factor analysis for the different age groups are shown in Figure 3. For the middle-aged group (45–64), the former smokers (OR = 1.063, 95 CI%: 1.018, 1.110), and current smokers (OR = 1.063, 95 CI%: 1.018, 1.110) in the Low-NDVI group showed a significant risk of hypertension, and the association was significantly different in the different NDVI concentration groups ($P < 0.05$). In the stratified analysis of the $PM_{2.5}$ concentration, the association between the former smokers and hypertension in the High-$PM_{2.5}$ group was statistically significant, with an OR of 1.056 (95 CI%: 1.002, 1.113). However, there was no significant difference between this OR and the effect description of the Low-$PM_{2.5}$ group ($P = 0.760$). The study further tested the difference between the significant effects observed in the low NDVI group in the middle age group and the elderly group. The results showed that the P-values for the difference of the former smokers and current smokers exposed to low green spaces in the different age groups were 0.881 and 0.299, respectively. Therefore, it was considered that there was no statistically significant difference in the effect description of the Low-NDVI groups among the different age groups. In addition, we did not observe any significant association between smoking and hypertension in the elderly group. Supplementary Table 1 shows the specific results of the stratified analysis of the single environmental factors for the different age groups.

Dual environmental factor stratified results

Table 5 shows the results of the hierarchical analysis of the dual environmental factors. In order to facilitate the presentation of the results, the definition of each dual environmental factor subgroup is stated in Supplementary Table 2. In the Low-NDVI/High-$PM_{2.5}$ subgroup, the current smokers and former smokers were significantly associated with hypertension, with an ORs of 1.064 (95 CI%: 1.012, 1.118) and 1.082 (95 CI%: 1.021, 1.146), respectively. No significant association between smoking and hypertension was observed in other subgroups. In order to test whether the significant effects observed in the Low-NDVI/High-$PM_{2.5}$ group were significantly different from other subgroups, the study conducted a difference test for the OR of the Low-NDVI/High-$PM_{2.5}$ group. For the current smokers, there was a significant difference in the risk of hypertension between the Low-NDVI/High-$PM_{2.5}$ subgroup and the High-NDVI/Low-$PM_{2.5}$ subgroup ($P = 0.047$). This means that there was a significant difference in the risk of hypertension between the former smokers who had been long-term exposed to low green spaces and high $PM_{2.5}$ environments and those who had been long-term exposed to high green spaces and low $PM_{2.5}$ particulate matter environments. For the former smokers of the Low-NDVI/High-$PM_{2.5}$ subgroup, although the intensity of hypertension risk effect description was higher than that of the current smokers,

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TABLE 4 ORs of hypertension (with 95% confidence intervals, 95%CI) associated with smoking stratified by a single environmental factor.

Variable	By NDVI [a]					By $PM_{2.5}$ [b]				
	Low-NDVI (n = 5,258)		High-NDVI (n = 5,342)		P for ORs	Low-$PM_{2.5}$ (n = 5,248)		High-$PM_{2.5}$ (n = 5,352)		P for ORs
	n	OR (95%CI)	n	OR (95%CI)		n	OR (95%CI)	n	OR (95%CI)	
Never smoking	3,228	-	3,251	-		3,219	-	3,260	-	
Former smoker	632	1.071 (1.026,1.117)***	643	1.012 (0.972,1.054)*	0.059	586	1.026 (0.985,1.069)	689	1.052 (1.008,1.097)**	0.406
Current smoker	1,398	1.058 (1.020,1.097)***	1,448	0.990 (0.955,1.027)**	0.011	1,443	1.017 (0.981,1.055)	1,403	1.029 (0.992,1.068)	0.645

[a]Gender, education level, alcohol consumption, daily cigarette consumption, social activity, physical activity, sleep time, per capita GDP, NO_2, $PM_{2.5}$, and O_3 were controlled as covariates in the model.
[b]Gender, education level, alcohol consumption, daily cigarette consumption, social activity, physical activity, sleep time, per capita GDP, NDVI, NO_2, and O_3 were controlled as covariates in the model.
(1) ***$p < 0.01$; **$p < 0.05$; *$p < 0.10$ (2) In all models, the GVIFs were <1.808. (3) P for ORs < 0.05 means that there was a significant difference in the ORs of the different exposure concentration groups.

the difference between this effect and the other subgroups was not significant ($P > 0.05$). The results of the model multicollinearity test showed that the GVIFs of the all the models were lower than two, which means that there was no multicollinearity problem in the dual environmental factors analysis.

Sensitivity analysis

The results of the two sensitivity analyses conducted with half a year and 2 years as the exposure periods are presented in Supplementary Tables 3, 4. The sensitivity analysis results were near to the results of the one-year exposure period, and some additional significant relationships were observed. In the stratified analysis of the single environmental factors that utilized 2 years as the exposure period, the risk of hypertension of the former smokers and current smokers in the Low-NDVI group was significant (OR = 1.075, 95 CI%: 1.030, 1.121), and their effect descriptions were both significantly different from that of the High-NDVI group. However, this conclusion was only applicable to the current smokers in the one-year exposure period. In addition, in the stratified analysis of the dual environmental factors with half a year or two as the exposure period, both the former smokers and current smokers in the Low-NDVI/High-$PM_{2.5}$ group were significantly associated with hypertension, and their effect descriptions were significantly different from that of the High-NDVI/Low-$PM_{2.5}$ group (P for ORs < 0.05).

Discussion

To the best of our knowledge, this was the first study to explore the association between smoking and hypertension under different air pollution and green space exposures. Our findings showed that the effects of smoking on hypertension were diverse under different environmental exposure conditions. There was a significant relationship between smoking behavior and hypertension in the Low-NDVI group, and the effect value of this relationship was significantly different from that in the High-NDVI group. Furthermore, for the respondents exposed to low green spaces and high $PM_{2.5}$ environments at the same time (Low-NDVI/High-$PM_{2.5}$ group), their smoking behavior may lead to an increase in the risk of hypertension. Additionally, the description of this effect was significantly different from that of the High-NDVI/Low-$PM_{2.5}$ group. In addition, for middle-aged people (45–64), the risk of hypertension caused by smoking was also more significant under long-term low green space environmental exposure. However, there was

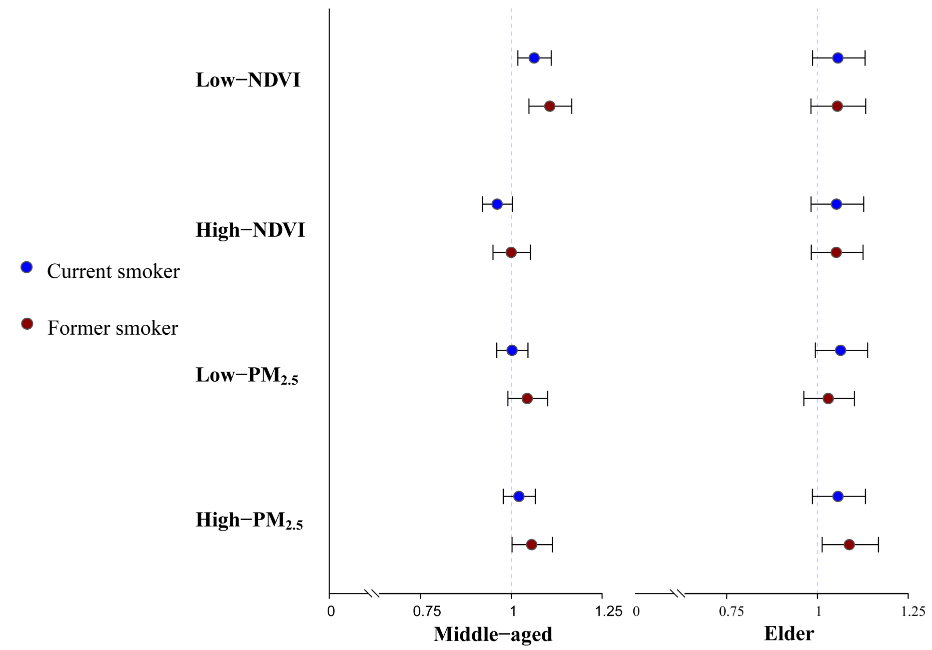

FIGURE 3
Single environmental factor analysis among mid-age and elder group.

no significant difference in the effect among the different age groups.

For the last century, the relationship between smoking and hypertension has been repeatedly emphasized (35, 36), and the results of our study supported this broad consensus as well. However, we further found that under lower green space exposure and higher $PM_{2.5}$ exposure, there was a more significant link between smoking and hypertension. Currently, there are few studies regarding the relationship between smoking and hypertension under different environmental exposure conditions. However, some studies that have investigated the relationship between environmental factors and hypertension have conducted stratified analysis on smoking that support our research results. A cross-sectional study found that the risk of hypertension of current smokers decreased significantly with an increase in the IQR (Inter quartile range) of green space exposure, and the degree of reduction was significantly different from that of people who had never smoked ($P = 0.013$) (37). A prospective cohort study found that with an increase in green space exposure, there was a difference in the effect of hypertension risk changes between smokers and non-smokers (38). Our study also observed a significant relationship between current smokers (OR = 1.058, 95 CI%: 1.020, 1.097) and hypertension in the low green space exposure group, and this effect was significantly different from the high green space exposure group ($P = 0.011$). Liu et al. found that every increase in the concentration of $PM_{2.5}$ by one IQR (41.7 $\mu g/m^3$) increased the risk of hypertension of smokers by 16% (95 CI%: 1.05,1.27), higher than that of never smokers (OR = 1.09,95 CI%: 1.02, 1.16) (21). For our study, Although the effect difference between the concentration levels was not statistically significant, the high PM2.5 group also showed a significant relationship between the former smokers and hypertension (OR = 1.052, 95 CI%: 1.008, 1.097). These similar results suggest that explaining the risk of hypertension from two dimensions of smoking behavior and environmental factors can control more confounding, thus providing a more accurate description of the effects. However, there are still few reports that comprehensively consider health behaviors and environmental factors, and more relevant studies need to be conducted to confirm the relationship between smoking and hypertension under different environmental exposure conditions.

The increased risk of hypertension caused by smoking behavior under adverse environmental exposure may be related to mental health. According to an investigation on some influencing factors of smoking prevalence, mental health and life stress caused by deterioration of the living environment may increase the prevalence of smoking behavior. Yang Chen et al. believed that alleviating life-related stress and insufficient satisfaction with the living environment were important motivations for urban residents to stop or reduce smoking (39). Timmermans et al. also mentioned that excessive smoking was a coping mechanism to reduce stress that was associated with living in an unpleasant environment (40). Interestingly, a study

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TABLE 5 ORs of hypertension (with 95% confidence intervals, 95%CI) associated with smoking stratified by dual environmental factors[a].

Variable	Low-NDVI/Low-$PM_{2.5}$ ($n = 2,328$)			Low-NDVI/High-$PM_{2.5}$ ($n = 2,930$)			High-NDVI/Low-$PM_{2.5}$ ($n = 2,920$)			High-NDVI/High-$PM_{2.5}$ ($n = 2,422$)		
	n	OR (95%CI)	P for ORs	n	OR (95%CI)	P for ORs	n	OR (95%CI)	P for ORs	n	OR (95%CI)	P for ORs
Never smoking	1,447	-		1,781	-		1,772	-		1,479	-	
Current smoker	612	1.046 (0.990,1.104)	0.659	786	1.064 (1.012,1.118)**	-	831	0.991 (0.944,1.041)	0.047	617	0.992 (0.939,1.047)	0.064
Former smoker	269	1.056 (0.992,1.124)*	0.581	363	1.082 (1.021,1.146)***	-	317	1.001 (0.948,1.057)	0.056	326	1.023 (0.963,1.088)	0.196

[a]Gender, age, education level, alcohol consumption, daily cigarette consumption, social activity, physical activity, sleep time, per capita GDP, NO_2, and O_3 were controlled as covariates in the model.
(1) ***p < 0.01; **p < 0.05; *p < 0.10. (2) In all models, the GVIFs were <1.860. (3) P for ORs < 0.05 means that there was a significant OR difference between this group and the Low-NDVI/High-$PM_{2.5}$ group.

conducted in Canada found a 6% lower odds of poor self-rated mental health per increase in the interquartile range (0.12) of the NDVI (500 m buffer) (41), and another prospective cohort study also supported a negative correlation between green space exposure and work-related chronic stress (42). Additionally, a meta-analysis published in 2019 showed that the long-term exposure concentration of $PM_{2.5}$ was significantly associated with depression (pooled OR = 1.102, 95% CI: 1.023, 1.189) (43), while the smoking cessation rate of depressed smokers was always considered to be lower than that of the general population (44). The results of these studies combined with the results of this study indicate that air pollution and green space exposure may induce residents' smoking behavior in the form of stress accumulation or anxiety. This would result in a difference in the hypertension risk among smokers under different environmental exposure conditions. More studies need to be conducted to demonstrate this conclusion.

We observed the most significant relationship between smoking and hypertension in the Low NDVI/High-$PM_{2.5}$ group, and this may have been related to the pathogenesis of hypertension. Many studies have shown that the mechanism of reducing NDVI exposure and increasing $PM_{2.5}$ exposure leading to increased risk of hypertension is similar to that of smoking leading to cardiovascular disease. Exposed in high green space for a long time may improve the immune regulation pathway, thus forming an antagonistic relationship with smoking behavior (45). Similar to the conclusion of our study, Jiang et al. also observed that the risk of hypertension of current smokers decreased significantly in higher green space exposure environments. They claim that long-term exposure to green spaces may expose residents to more microorganisms related to human immune regulation, thus activating the immune regulation system to reduce the risk of chronic inflammation (37), while and the mechanism of smoking affects systemic vascular resistance by inducing an inflammatory response, as has been reported by previous studies (46). In addition, long-term exposure to $PM_{2.5}$ may promote vasoconstriction and weaken the ability of vasodilation (47), while nicotine leads to a rise in low-density lipoprotein and a decrease in high-density lipoprotein that also intensify vasoconstriction and accelerate the progression of blood epithelial cell injury (1). Oxidative stress induced by smoking may trigger cytokine release and systemic vascular inflammation caused by inflammatory cell adhesion and ultimately destroy the integrity of the endothelium as a protective barrier layer (48). Additionally, surface-bound reactive co-pollutants, such as transition metals and endotoxins, may enter the body through the pulmonary circulation with $PM_{2.5}$ as a carrier, and this would also promote endothelial dysfunction in the form of oxidative stress, thus causing hypertension (49). In conclusion, green space exposure may antagonize the risk of hypertension caused by smoking through the immune pathway, while $PM_{2.5}$ exposure and smoking have multiple synergistic effects on the pathogenesis of hypertension.

The mechanism effect superposition of environmental factors and smoking behavior may be one reason why the Low NDVI/high $PM_{2.5}$ group was observed to have the most significant effects, but this still needs to be verified by more relevant experiments.

In addition, our study observed in the age group analysis that middle-aged smokers aged 45–64 years had a higher risk of hypertension under low green space exposure. A survey on smoking influencing factors in 31 provinces in China showed that residents aged 40–59 were the primary group of Chinese smokers, and middle-aged people have a more serious tobacco dependence rate than the elderly (OR = 1.50, 95 CI%: 1.30, 1.70) (20). A 19-year follow-up investigation conducted in Asia showed that compared with the elderly, the attribution rate of CVD death caused by smoking was higher in men younger than 60 years old (50). However, middle-aged people were also reported as a high-risk group in the study of green space exposure and hypertension risk. A study conducted in Alpine valley showed that the diastolic blood pressure of participants aged 46–58 years decreased significantly under high green space exposure (value = −2.98, 95 CI%: −5.33, −0.63), while elderly participants (aged 58–81 years) had no significant relationship between blood pressure and green space exposure environment (51). However, some studies believed that the risk of smoking induced hypertension was not different among different age groups (9). However, a survey conducted in two European cities suggested that the risk of hypertension among people over 65 years old was more likely to decrease with an increase in green space exposure (19). The risk of smoking induced hypertension in the different age groups under the different environmental exposure conditions requires more research and exploration.

This study may have several strengths. First, this is the first study to explore the impact of smoking on the risk of hypertension under different environmental conditions. A description of the relationship between health behavior and the risk of chronic diseases under different environmental exposure conditions has rarely been reported in previous studies. Second, the study established a series of two factor subgroup analyses based on the median exposure concentrations of $PM_{2.5}$ and the NDVI, and this may have reduced the potential confounding by or interaction with other environmental factors compared with the stratification of a single one (52). In addition, our study conducted a difference test for the effects of each environmental subgroup to ensure that the effect description difference of the different environmental conditions was reliable statistically. Third, this study was based on a large nationwide cohort in China (CHARLS), ensuring sufficient statistical power and generalizability of the results (21).

Several limitations of this study should be recognized. The $PM_{2.5}$ exposure data were collected from fixed monitoring stations in cities. The summarizing of health data into a rough temporal and spatial range for the exposure analysis may have increased the uncertainty of environmental exposure and led to the wrong classification of the individual level exposure (53). Combining the address information of the interviewees and simulating the individual exposure assessment level through a land use regression model and other methods will make the description of the environmental variables of the interviewees more accurate (54). Second, as an important risk factor of CVD and hypertension, the BMI was not included in the model control in our study. Considering the association between obesity and CVD, the description of the relationship between smoking and hypertension in this study may have been affected. Third, the description of smoking behavior lacked detail. Due to the insufficient response rate or illogical data of the corresponding questionnaire items, the length of smoking was not included in our study for discussion. Although this study was sufficient to support the conclusion that smoking behavior has an effect on the increase in hypertension risk under different environmental conditions, there might still be a better classification scheme for the different types or degrees of smokers to explore the differences in effects. In addition, CHARLS did not record the frequency of respondents' green space use and the type of green space around the residence. To describe respondents' green space exposure more accurately, future relevant research should consider collecting respondents' subjective measurement information of green space, such as the self-reported quality of the neighborhood green space and the self-reported walking frequency in green spaces (55).

In conclusion, our research showed that smoking had different effects on hypertension under different environmental exposure conditions. Respondents exposed to low green spaces were more likely to suffer from hypertension due to smoking. Furthermore, the risk of hypertension caused by smoking in the Low NDVI/High $PM_{2.5}$ group was significantly higher than that in the High NDVI/High $PM_{2.5}$ group. In addition, for middle-aged people, the risk of hypertension caused by smoking was also more significant under long-term low green space environment exposure. Our results indicate that controlling environmental exposure can reduce the risk of smoking induced hypertension.

Data availability statement

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

Author contributions

LM provided the guidance of environmental epidemiology methods and statistical models for the study. QC completed the data analysis, chart drawing, and article writing. XM was responsible for the format and typesetting of the paper and participated in the analysis of tables and pictures. YG participated in the establishment of the database. JL provided guidance for the English writing of this article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1026648/full#supplementary-material

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Mortality benefits of reduction fine particulate matter in Vietnam, 2019

Nguyen Thi Trang Nhung[1,2]*, Vu Tri Duc[2], Vo Duc Ngoc[2], Tran Minh Dien[2], Le Tu Hoang[1], Tran Thi Thuy Ha[3], Pham Minh Khue[3], Ngo Xuan Truong[4], Nguyen Thi Nhat Thanh[4], Edward Jegasothy[5], Guy B. Marks[5,6] and Geoffrey Morgan[5,6]

[1]Department of Biostatistics, Faculty of Fundamental Sciences, Hanoi University of Public Health, Hanoi, Vietnam, [2]Vietnam National Children's Hospital, The Training and Research Institute for Child Health, Hanoi, Vietnam, [3]Faculty of Public Health, Haiphong University of Medicine and Pharmacy, Haiphong, Vietnam, [4]University of Engineering and Technology, Vietnam National University, Hanoi, Vietnam, [5]Faculty of Medicine and Health, Sydney School of Public Health, University Centre for Rural Health, University of Sydney, Sydney, NSW, Australia, [6]Centre for Air Pollution, Energy and Health Research, University of New South Wales, Sydney, NSW, Australia

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EDITED BY
Ruoyu Wang,
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United Kingdom

REVIEWED BY
Vera Ling Hui Phung,
National Institute for Environmental Studies (NIES), Japan
Shazia Rehman,
Pak-Austria Fachhochschule Institute of Applied Sciences and Technology, Pakistan

*CORRESPONDENCE
Nguyen Thi Trang Nhung
ntn2@huph.edu.vn;
nhungnguyenbio@gmail.com

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Introduction and objectives: Studies assessing the health benefits of air pollution reduction in Vietnam are scarce. This study quantified the annual mortality burden due to $PM_{2.5}$ pollution in Vietnam above the World Health Organization recommendation for community health (AQG: 5 $\mu g/m^3$) and the proposed National Technical Regulation on Ambient Air Quality (*proposed QCVN:* 15 $\mu g/m^3$).

Methodology: This study applied a health impact assessment methodology with the hazard risk function for non-communicable diseases (NCDs) and lower respiratory infections (LRIs) in the Global Exposure Mortality Model (GEMM) to calculate attributable deaths, Years of Life lost, and Loss of Life expectancy at birth due to air pollution in the Vietnamese population above 25 years of age in 11 provinces. We obtained annual average $PM_{2.5}$ concentrations for Vietnam in 2019 at a 3x3 km grid modeled using Mixed Linear regression and multi-data sources. Population and baseline mortality data were obtained from administrative data system in Vietnam. We reported the findings at both the provincial and smaller district levels.

Results: Annual $PM_{2.5}$ concentrations in all studied provinces exceeded both the AQG and the *proposed QCVN*. The maximum annual number of attributable deaths in the studied provinces if they had complied with WHO air quality guidelines was in Ha Noi City, with 5,090 (95%CI: 4,253–5,888) attributable deaths. At the district level, the highest annual rate of attributable deaths if the WHO recommendation for community health had been met was 104.6 (95%CI: 87.0–121.5) attributable deaths per 100,000 population in Ly Nhan (Ha Nam province).

Conclusion: A much larger number of premature deaths in Vietnam could potentially be avoided by lowering the recommended air quality standard. These results highlight the need for effective clean air action plans by local authorities to reduce air pollution and improve community health.

KEYWORDS
air pollution, $PM_{2.5}$, Vietnam, mortality burden, health benefits

Introduction

Fine particulate matter (denoted as $PM_{2.5}$) concentrations have declined globally for the last decade. For example, the annual mean $PM_{2.5}$ in the United States was reduced by approximately 41% from 2000 to 2020 (1). In Europe, the decrease in $PM_{2.5}$ concentrations across countries was 29% from 2005 to 2019 (2). In China, a decline in annual $PM_{2.5}$ concentration was observed, ranging from 22.2 to 56.6% during 2015–2020 (3). These improvements in outdoor air quality throughout the world are the result of affordable clean air action. For example, the "Air Pollution Prevention and Control Action Plan," first implemented in China in 2013, contributed to 15% reduction in $PM_{2.5}$ in the Pearl River Delta (4). In other words, evidence quantifying the health benefits of reducing exposure to $PM_{2.5}$ is urgently needed to support further clean air policy development and implementation, particularly in high-exposure countries such as Vietnam.

Though air quality in Vietnam has improved in recent years, it is still poor by international comparisons. Annual mean $PM_{2.5}$ concentrations in Vietnamese provinces ranged from 9–41 $\mu g/m^3$ in 2019 to 8–36 $\mu g/m^3$ in 2020 (5). However, the annual $PM_{2.5}$ concentration in 10 out of 63 provinces in Vietnam in 2020 exceeded the National Technical Regulation on Ambient Air Quality- QCVN 05:2013 (set at 25 $\mu g/m^3$), and no provinces reached the new World Health Organization's air quality guidelines (AQG, set at 5 $\mu g/m^3$) (5, 6). Provinces in the Red River Delta such as Hung Yen (32.7 $\mu g/m^3$) and Bac Ninh (33.0 $\mu g/m^3$) experienced the poorest air quality, rather than the major cities such as Ha Noi and Ho Chi Minh City (5).

Exposure to the high concentration of $PM_{2.5}$ can cause many diseases including cardiovascular, respiratory diseases, diabetes, lung cancer (7), and contribute to premature deaths (8–10). The evidence also indicates no threshold of air pollutant concentration for community health. The effect of $PM_{2.5}$ remained even where the exposure level is low such as in the European Union region and Australia (7, 11, 12). Therefore, in September 2021, the World Health Organization (WHO) updated its 2015 recommendation in which it set the annual mean concentration of $PM_{2.5}$ at 5 $\mu g/m^3$ (6). Though this guideline is not a regulation, it can drive the air quality policy worldwide.

In recent years, the Vietnamese government has attempted to address poor air quality through a series of actions. In 2016, the Vietnamese Prime Minister issued the National Action Plan on air quality management by 2020 including a vision for 2025 (Decision No 985a/QĐ-TTG) which targeted improved air quality management by controlling emissions and increasing ambient air quality monitoring (13). Directive No 03/CT-TTg on enhancing air quality management was signed by the Prime Minister on 18 January 2021 (14). This latter document also called for the assessment of the adverse health impacts of air pollution on community health (14). Decision No 1973/QĐ-TTg states that Vietnam will take actions to improve air quality management *via* controlling emissions and monitoring ambient air pollutants and also conduct research to provide information *via* early warning systems that predict air quality in each province (15). These documents emphasize the importance of assessing the health impacts of air pollution to evaluate the implemented policy and associated interventions in local areas (13–15). The Official Dispatch No 3051/BTNMT-TCMT on the technical guidelines of building air management plan at the provincial level recommends the use of AirQ+ software (a software developed by the World Health Organization–WHO) to assess the health impacts of air pollution (16). Ha Noi, in particular, issued Directive No 15/CT-UBND on entirely replacing and eliminating the use of the beehive coal fuel to reduce the adverse impacts of air pollution in the city (17). Also, in 2021, the Ministry of Natural Resources and Environment issued a draft of the National Technical Regulation on Ambient Air Quality (called *proposed QCVN* in this study) (18) in order to establish a policy to improve ambient air quality in Vietnam. This study quantifies the mortality impact of air pollution in Vietnam in response to the call for such policies by the Vietnamese government.

Evidence of the health impacts of ambient air pollution in Vietnam is scarce, and mainly in Ha Noi and Ho Chi Minh City. Two studies showed an association between air pollutants, including $PM_{2.5}$, and hospital admissions amongst Hanoi children (19, 20). Another study demonstrated the relationship between ambient air pollutants and hospital admissions for cardiovascular and respiratory diseases in adults in Hanoi, Quang Ninh, and Phu Tho (21) and a study in Ho Chi Minh City showed the association between hospitalization due to acute lower respiratory infection and $PM_{2.5}$ (22). The first Vietnamese health impact assessment study of exposure to $PM_{2.5}$ was conducted in Ha Noi in 2017 (23). The findings from this study showed the life expectancy at birth of the Hanoi population due to exposure to $PM_{2.5}$ had decreased by 1.8 years in 2017 (23). Research in Ho Chi Minh City also found that 1,136 premature deaths were attributed to $PM_{2.5}$ in 2017 (24). Such findings highlight the large burden of diseases due to $PM_{2.5}$ exposure in Vietnam.

This study aimed to quantify the health burden due to ambient $PM_{2.5}$ concentrations above the World Health Organization guideline and the proposed National Technical Regulation on Ambient Air Quality in several provinces of Vietnam, including Bac Ninh, Hung Yen, Hai Duong, Ha Noi, Thai Binh, Hai Phong, Ninh Binh, Ha Nam, Ho Chi Minh, Quang Ninh, and Dien Bien. The burden of mortality is expressed as attributable deaths (AD) (number and rate per 100,000 population), Years of life lost (YLL) (number and rate per 100,000 population), and Loss of Life Expectancy (LLE) (in years) for these provinces in Vietnam. Moreover, we also calculated the attributable deaths (rate per 100,000 population) using the AirQ+ software to compare our results with the estimate according to the technical guidelines of the Official Dispatch No 3051/BTNMT-TCMT of the Ministry of Natural Resources and Environmental (16). This study not only provides scientific data on the health impact of air pollution in Vietnam but also responds to the Vietnamese government's call for evidence to establish air quality control that will improve health.

Materials and methods

Study areas

We conducted a health impact assessment of ambient $PM_{2.5}$ concentrations in 11 Vietnamese provinces, including 10 provinces in the northern region (Ha Noi, Bac Ninh, Hung Yen, Ha Nam, Hai Duong, Thai Binh, Hai Phong, Ninh Binh, Quang Ninh, Dien Bien) and Ho Chi Minh City in the south of Vietnam. The total 2019 population of Vietnam was 96,208,984 people and our study region included an exposed population of 18,342,836 (19%) inhabitants (25) covering the most polluted provinces (5) and also the two megacities of Hanoi (the capital) and Ho Chi Minh City.

$PM_{2.5}$ exposure

We assessed exposure using a previously published study (23). Daily $PM_{2.5}$ maps for Vietnam at 3x3 km resolution were estimated by Mixed Effect Models developed on a 9-year dataset (2012-2020) of $PM_{2.5}$ measured at ground stations, combined with satellite Aerosol Optical Depth (AOD), meteorological conditions (i.e., humidity, planetary boundary layer height) and land use (i.e., normalized difference vegetation index (NDVI), road density) (26). The detailed method, data source, and model validation for estimating daily $PM_{2.5}$ maps is described in our previous study (23). The daily mean $PM_{2.5}$ maps were validated by comparing them with ground-based $PM_{2.5}$ measurements, with a Pearson coefficient (r) of 0.87 and a Root Mean Square Error (RMSE) of 11.76 $\mu g/m^3$. The daily maps were then aggregated into monthly maps and annual maps. The annual average $PM_{2.5}$ map in 2019 had high agreement with ground $PM_{2.5}$ measurements ($r = 0.84$, $RMSE = 5.07$ $\mu g/m^3$). The annual $PM_{2.5}$ mean concentration data in 2019 was calculated for each district of the selected provinces for the health impact assessment process.

Mortality data and exposure population

Death cases including age, address (district and province), gender, and specific causes of death were obtained from the Vietnam A6 registration. A6 document is a death registration at the commune health, the lowest level of the health sector in Vietnam—and data on death cases of permanent inhabitants was collected by community health staff. This document covers approximately 89% of the total deaths in the commune (27). The report also confirmed that data on death due to injury is robust (27) and so we were able to exclude injury-related deaths from our analysis.

The number of inhabitants in each district by age group and gender were extracted from the Population and Household census in 2019 by the General Statistics Office of Vietnam (hereafter called GSO) (25, 28). This census obtained information on the population including fertility, gender, migration, urbanization, and population aging in Vietnam.

Health impact assessment estimation

We applied the Global Exposure Mortality Model (GEMM) risk function to estimate the attributable deaths due to ambient $PM_{2.5}$ pollution (29) for each province. Burnett et al. developed GEMM by pooling hazard ratios from 41 cohorts (29), including the Chinese cohort where the ambient $PM_{2.5}$ concentration and emission sources are more similar to Vietnam compared to European and North American studies.

In each province, we estimated attributable deaths (AD), years of life lost (YLL) and loss of life expectancy (LLE) due to air pollution for populations above 25 years of age in each province separately. The AD for each 5-year age subgroup in a district is estimated from applying the hazard ratio to specific age groups and $PM_{2.5}$ concentration using the GEMM risk function (29), the death rate for each age group in a district, and the population at that age group for the corresponding district. We applied the estimate for non-communicable diseases (NCDs) and lower respiratory infections (LRIs) in GEMM (denoted as GEMM NCD+LRI). We set the counterfactual concentration as defined by 1) the WHO air quality guidelines (AQG: 5 $\mu g/m^3$) and 2) the proposed QCVN (15 $\mu g/m^3$). YLL is calculated by multiplying the attributable deaths in each age group by the life expectancy in the corresponding age group. This life expectancy is calculated by applying the life-table method with the baseline death rate per 5-year age group in 2019. Thirdly, the LLE in days was calculated by subtracting the life expectancy without the contribution of $PM_{2.5}$ to the $PM_{2.5}$ attributed life expectancy. For each province and district, LLE was expressed in years by dividing the LLE in days by 365.25. The rates of deaths and YLL for each district per 100,000 inhabitants were calculated by dividing the number of the corresponding indicators by the population size. We present the findings at the provincial and district levels.

The other analysis was conducted in R version 4.0.3 (R Core Team Vienna, R Foundation for Statistical Computing, Vienna,

TABLE 1 Annual means of the $PM_{2.5}$ concentration (in μg/m^3), population and death rates per 1,000 population above age 25 years in 11 study region provinces, Vietnam, 2019.

Province's name	$PM_{2.5}$ annual mean concentration (μg/m^3)	Population above age 25	Death rates above aged 25+ years (per 1,000 population)
Ha Noi	40.8	4,889,379	4.6
Bac Ninh	37.8	812,711	5.4
Hung Yen	35.2	789,408	4.1
Ha Nam	31.5	543,823	7.9
Hai Duong	31.2	1,222,568	4.3
Thai Binh	27.1	1,237,051	8.3
Hai Phong	25.8	1,311,556	7.4
Ninh Binh	23.5	622,278	7.8
Ho Chi Minh	20.9	5,795,749	4.8
Quang Ninh	18.9	825,247	5.8
Dien Bien	15.8	293,066	6.3

Austria) with the iomlifetR package (30), apart from the AirQ+ comparison calculaltions.

Comparison analysis

For comparison, we also estimated the attributable deaths (rate per 100,000 population) by province using the AirQ+ software and selecting the long-term impact assessment option for total natural causes. By default this option utilized the log-linear model with the relative risks retrieved from the literature and meta-analysis of Hoek et al. (31). Since this model only applies to adults 30 years of age or older, we only calculated attributable deaths for this population *via* AirQ+.

Results

Population and mortality data for people above 25 years old in 11 provinces in 2019 are provided in Table 1. Ha Noi and Ho Chi Minh were the two most populous areas, with the population over 25 years old reaching approximately 5 to 6 million inhabitants. Crude death rates by province ranged from 4.1 deaths per 1,000 population in Hung Yen to 8.3 deaths per 1,000 population in Thai Binh.

The annual $PM_{2.5}$ concentration ranged from 15.8 μg/m^3 in Dien Bien to 40.8 μg/m^3 in Ha Noi (Table 1, Figure 1). All annual mean concentrations in each of the 11 provinces exceeded the WHO air quality guidelines and the proposed QCVN. Notably, Bac Ninh, Hung Yen and Ha Nam, adjacent to Hanoi, experienced highly polluted levels. The annual mean of $PM_{2.5}$ concentration in Ha Noi was 2.72 times higher than the proposed QCVN (Table 1, Figure 1).

At the district level, the highest $PM_{2.5}$ concentration was observed in all districts of Bac Ninh, Hai Duong, Hung Yen, Ha Nam province, and the central districts of the capital Ha Noi (Figure 1).

Compliance with the WHO air pollution guideline could potentially avoid 5,090 (95%CI: 4,253–5,888) annual premature deaths in Hanoi from exposure to $PM_{2.5}$ (Table 2) and 4,076 (95% CI: 3,377–4,754) premature deaths in Ho Chi Minh City. The highest $PM_{2.5}$ attributable death rates were Ha Nam, Thai Binh, and Hai Phong, with 95.1 (95% CI: 79.1–110.4), 93.4 (95% CI: 77.6–108.7), and 81.9 (95% CI: 68.0–95.3) deaths per 100,000 population, respectively.

Our study also observed great variability in attributable deaths at district levels (Supplementary Table S1). The attributable death rates range from 22.3 deaths per 100,000 population in Muong Nhe district (Dien Bien) to 104.6 deaths in Ly Nhan (Ha Nam province). In Ha Noi, the capital of Vietnam, districts with the greatest attributable death rate are located in the central districts (Hoan Kiem, Ba Dinh, Hai Ba Trung, Dong Da, and Tay Ho) of the province.

Figure 2 illustrates the number and the rate (per 100,000 population) of attribute deaths due to $PM_{2.5}$ concentrations above the proposed QCVN. The rate of attributable deaths due to annual ambient $PM_{2.5}$ in the selected provinces above the proposed QCVN was 52.3 deaths per 100,000 population in Ha Noi and 66.6 per 100,000 population in Thai Binh.

Discussion

In this study, we estimated 37.0 to 95.1 deaths per 100,000 population are attributable to $PM_{2.5}$ pollution in 2019 above the WHO air quality guidelines for annual average $PM_{2.5}$ in the selected provinces. These numbers were generally higher

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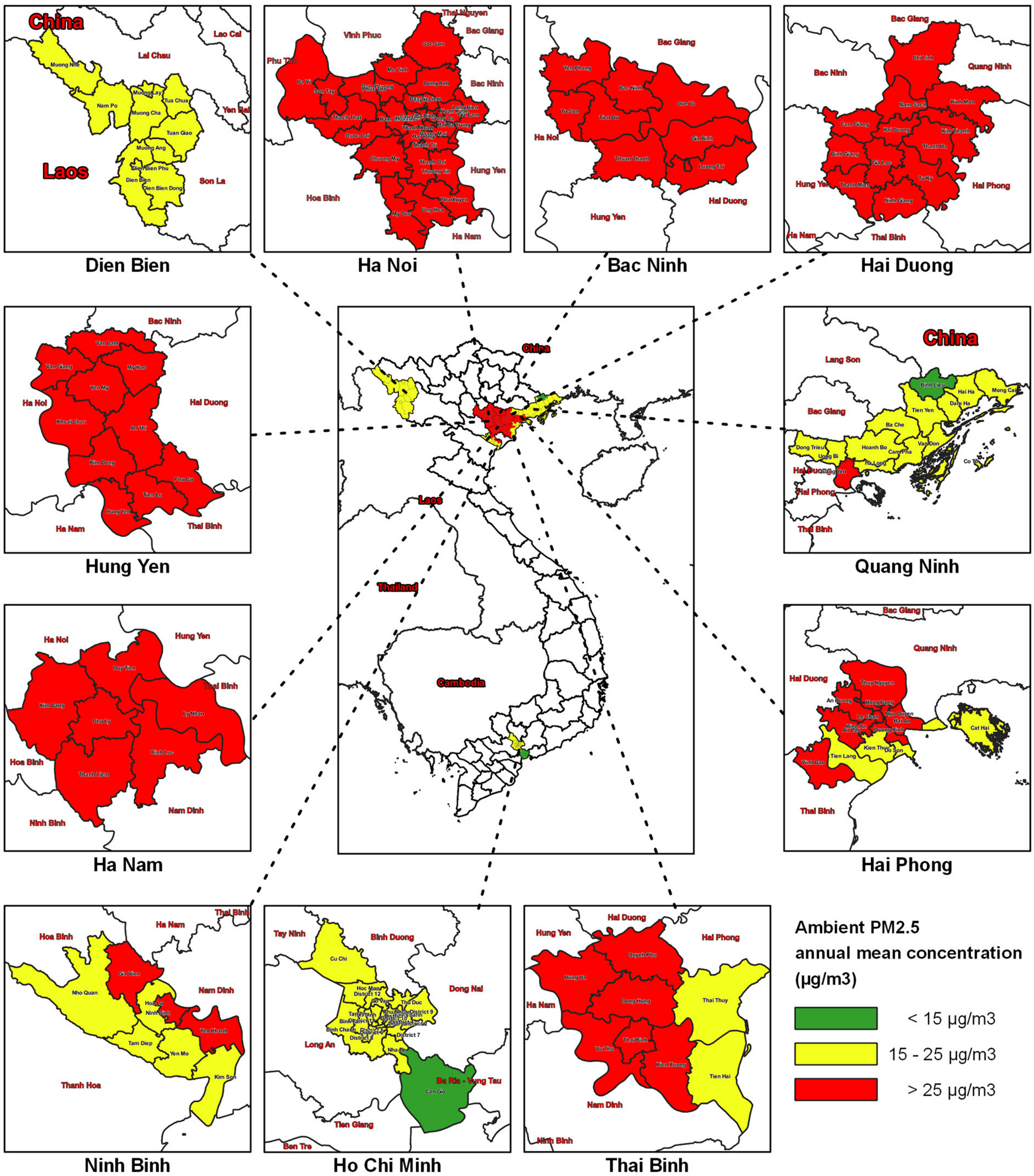

FIGURE 1
$PM_{2.5}$ concentrations by districts in the 11 study region provinces of Vietnam, 2019.

than the $PM_{2.5}$ attributable mortality rate in Vietnam (44.8 per 100,000 population) according to the calculation of the Global Burden of Disease (GBD) study (32). The discrepancy will be influenced by the difference in resolution of the $PM_{2.5}$ concentration maps we used of 3 x 3 km that is smaller (higher spatial resolution) compared to the air pollution maps used in the GBD. Nonetheless, both these analyses present a high rate of attributable mortality due to exposure to $PM_{2.5}$ in Vietnam and highlight the urgency to effectively implement the National Action Plan for air quality management in Vietnam.

TABLE 2 Avoidable deaths, years of life lost and loss of life expectancy (expressed in number and rate per 100,000 population) and confidence interval (95% CI) when compliance with The World Health Organization's Air Quality Guidelines in Vietnam study region provinces, 2019.

Province's name	Avoidable deaths		Years of life lost		Loss of life expectancy (years) (95%CI)
	Number (95%CI)	Rate per 100,000 population (95%CI)	Number (95%CI)	Rate per 100,000 population (95%CI)	
Ha Noi	5,090 (4,253–5,888)	63.2 (52.8–73.1)	152,828.6 (124,123.8–181,963.7)	1,897.6 (1,541.2–2,259.4)	4.9 (3.9–5.9)
Bac Ninh	946 (789–1,096)	69.1 (57.7–80.0)	23,779.8 (19,353.7–28,252.8)	1,737.2 (1,413.9–2,064.0)	3.8 (3.1–4.6)
Hung Yen	658 (548–763)	52.5 (43.7–60.9)	23,940.0 (19,392.6–28,573.7)	1,911.0 (1,548.0–2,280.9)	5.7 (4.6–6.8)
Ha Nam	811 (675–942)	95.1 (79.1–110.4)	19,520.0 (15,881.1–23,196.9)	2,288.9 (1,862.2–2,720.1)	3.4 (2.8–4.1)
Hai Duong	968 (805–1,124)	51.1 (42.5–59.4)	32,989.8 (26,753.7–39,327.5)	1,743.4 (1,413.9–2,078.3)	4.8 (3.9–5.8)
Thai Binh	1,738 (1,443–2,022)	93.4 (77.6–108.7)	39,772.4 (32,368.7–47,244.1)	2,137.8 (1,739.8–2,539.4)	2.9 (2.4–3.5)
Hai Phong	1,661 (1,380–1,933)	81.9 (68.0–95.3)	38,360.9 (31,294.0–45,461.7)	1,891.7 (1,543.2–2,241.8)	2.8 (2.2–3.3)
Ninh Binh	758 (628–883)	77.1 (64.0–89.8)	18,422.6 (15,029.6–21,830.2)	1,875.1 (1,529.8–2,221.9)	2.7 (2.2–3.2)
Ho Chi Minh	4,076 (3,377–4,754)	45.3 (37.5–52.9)	88,710.3 (72,525.0–104,897.0)	986.4 (806.5–1,166.4)	1.9 (1.6–2.3)
Quang Ninh	687 (569–801)	52.0 (43.1–60.7)	18,436.3 (15,042.3–21,844.0)	1,396.3 (1,139.3–1,654.4)	2.5 (2.1–3.0)
Dien Bien	222 (183–259)	37.0 (30.6–43.3)	6,437.5 (5,258.7–7,617.9)	1,075.0 (878.1–1,272.1)	2.2 (1.8–2.6)

To address this issue, the Prime Minister of Vietnam stated 6 objectives in Decision No 1973/QĐ-TTg in 2021, including: 1) Complete the structure, policies, and constitutions regarding air quality management; 2) Prevent and reduce emission; 3) Complete the financial structure and diversify the investment for air quality management; 4) International cooperation and scientific research regarding technology and air quality management; 5) Monitor and evaluate the compliance of air quality management; 6) Communicate, educate, and improve the capacity and acknowledgment regarding air quality management (15). Implementing these objectives is an interdisciplinary task and requires the involvement of the entire Vietnamese administrative structures (the details of the assignments were described in Decision No 1973/QĐ-TTg and the Law 72/2020/QH14 on Environmental Protection) (15, 33). Our study findings demonstrate the health benefits which Vietnam can obtain from effectively implementing air pollution control measures. Parallel with the above strategies, the Vietnam government has planned to reduce QCVN from 25 $\mu g/m^3$ to 15 $\mu g/m^3$. However, the proposed QCVN and a time frame for achieving this standard have not yet been officially issued.

The Official Dispatch No. 3051/BTNMT-TCMT suggests using the AirQ+ software developed by the WHO (16). In this study, the death rates for provinces estimated by AirQ+ were higher than the findings using GEMM, though the exposure population is marginally smaller (Table 3). The likely reason for these differences is that the population attributable fraction estimated by GEMM compared to that estimated using the Hoek et al. (31) risk function at lower $PM_{2.5}$ concentrations, but the opposite situation occurs when the $PM_{2.5}$ concentration is high (34). Therefore, using the log-linear model in AiQ+ for Vietnam might overestimate the actual burden of mortality due to the high ambient $PM_{2.5}$ concentrations.

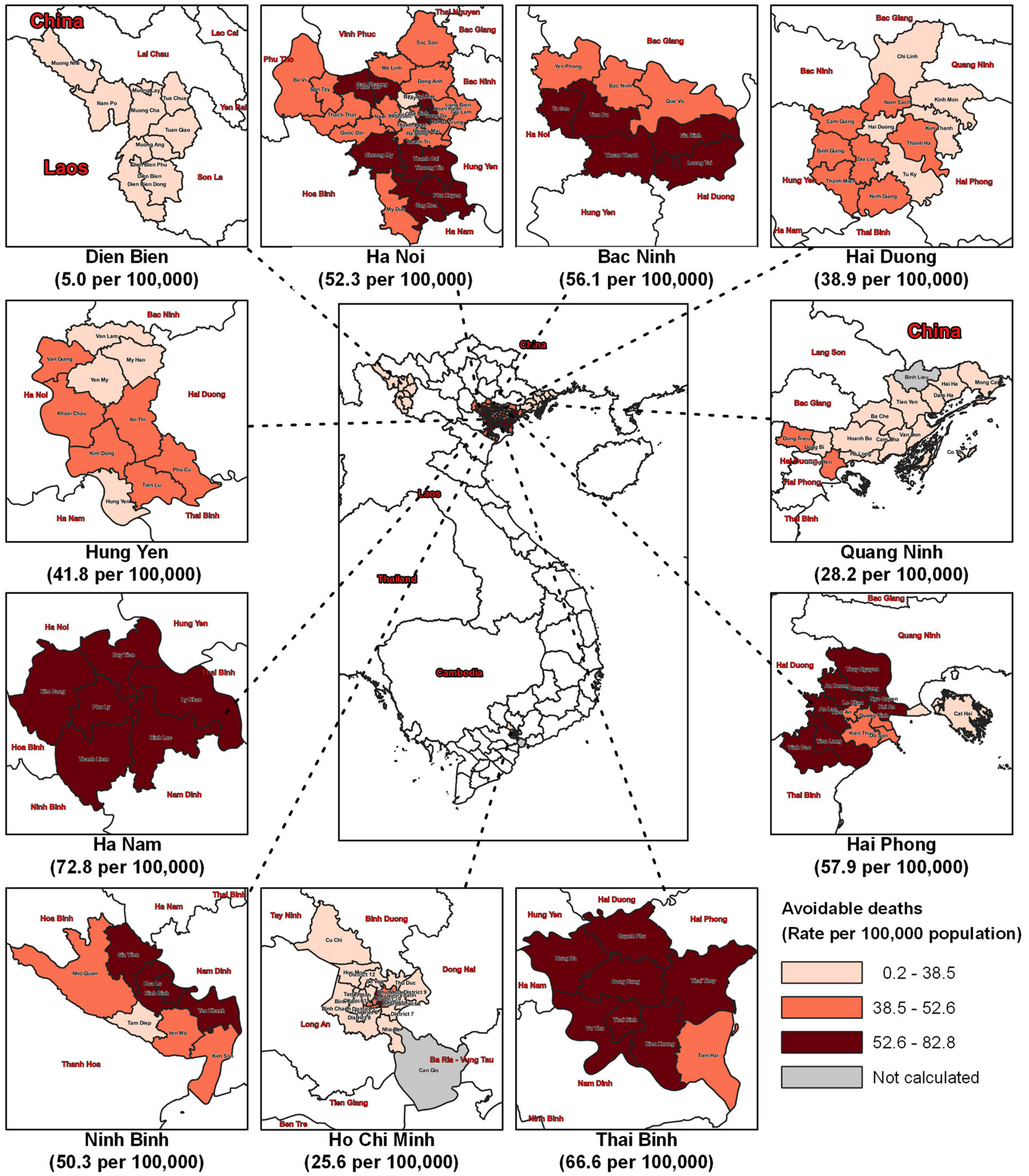

FIGURE 2
Attributable deaths (expressed in rate per 100,000 population) by districts in 11 provinces in Vietnam due to $PM_{2.5}$ concentrations above the proposed QCVN (15 $\mu g/m^3$) 2019. The "Not calculated" areas had the $PM_{2.5}$ concentration lower than the proposed QCVN (15 $\mu g/m^3$).

The attributable mortality rates in the central northern provinces (such as Thai Binh or Ha Nam and Hai Duong) were high and this is likely due to the industrial areas located in these provinces (35). A greater number of thermal power stations, cement manufacturer factories, and factories with older technology are located in the northern region, especially in Hai Duong and Thai Binh (35). Moreover, Bac Ninh includes many villages with traditional industries that lack pollution control systems (35). Our study indicates that the substantial health burden due to air pollution in the Bac Ninh province could be reduced by implementing effective interventions to manage the air quality in these polluted areas.

The National Action Plan on air quality management for 2021–2025 in Vietnam is in its initial stages and authorities should be aware of the range of air pollutants that need to be reduced to decrease the health burden (15). In this study, we primarily focus on the mortality burden due to a reduction in $PM_{2.5}$. A study in China found an inverse association between $PM_{2.5}$ and ground-level Ozone (O_3) concentration (36). According to the authors reducing the Nitrogen Oxide (NO_x) and Volatile Organic Compounds (VOCs) components in $PM_{2.5}$ could potentially increase the photochemical formation of O_3, thus resulting in the higher concentration of O_3. Ground-level ozone has been found to have an impact on hospital admissions in Vietnam (37). Therefore, future interventions should consider the proportion of air pollutants in the mixture and their interrelation before implementing interventions to reduce any specific pollutant.

In this study, we applied the GEMM risk function to estimate the attributable deaths due to ambient $PM_{2.5}$. This risk function has been used in numerous studies to assess not only the health impact of air pollution, but also the economic health benefits of an intervention. For example, Haikun Wang (2020) used GEMM to estimate the health benefits of control programs relating to on-road transportation in China during the period of 1998 to 2015 (38). Another study used GEMM to assess the health and economic impact of China's air pollution shift from 2013 to 2018, as well as to suggest implications for air pollution control policies during this time period (36). This approach is more suitable for countries and regions with severe pollution. The estimation is similar to the GBD approach. In addition, the Environmental Benefits Mapping and Analysis Program—Community Edition (BenMAP-CE) by the United States Environmental Protection Agency integrated this approach into the software; therefore so it can be easily applied (39). We recommend that Vietnam use this approach to estimate both the health and economic benefits of interventions to reduce air pollution.

Our study has several limitations. While we were unable to collect data from all the areas in Vietnam we obtained data for the most polluted provinces, including both the north and south of Vietnam. The mortality data used in our analysis is estimated to include around 89% of all deaths based on a study in Quang Ninh and Thai Nguyen provinces (27). Although we performed the quality assurance process on the mortality data (details of the procedure were described elsewhere (27)) the attributable mortality due to air pollution we estimated is likely to be an underestimate due to the $<$ 100% covered of the mortality data we used. The air quality data we used was modeled using data from a limited number of fixed site air pollution monitoring stations in Vietnam and this could introduce error in our estimated $PM_{2.5}$ exposures. Our study applied a hazard ratio obtained from the analysis of 41 cohorts, including China (29). While this hazard ratio is estimated from a number of large cohort studies there may be some differences when generalizing to different populations.

TABLE 3 Attributable deaths (rate per 100,000) between the calculation by Log−linear model in AirQ+ and the calculation by GEMM for each province.

Province's name	Attributable deaths (Rate per 100,000 population) by Log−linear model in AirQ + (95%CI)	Attributable deaths (Rate per 100,000 population) by GEMM(95%CI)
Ha Noi	103.7	63.2
Bac Ninh	118.8	69.1
Hung Yen	79.3	52.5
Ha Nam	132.8	95.1
Hai Duong	70.5	51.1
Thai Binh	115.2	93.4
Hai Phong	103.7	81.9
Ninh Binh	95.4	77.1
Ho Chi Minh	53	45.3
Quang Ninh	59.7	52.5
Dien Bien	46.6	37.0

Conclusion

Our study found that there is a substantial burden of mortality due to air pollution in Vietnam above the air quality guidelines by the WHO and the proposed Vietnam QCVN. These findings highlight the health benefits of reducing air pollution in Vietnam including actions by local provincial and district authorities to implement policies to improve air quality.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Hanoi University of Public Health (Ref. No. 020-265/DD-YTCC). Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional Requirements.

Author contributions

NTTN, GBM, and GM conceived, designed the study, and acquired data. NTNT and NXT conducted statistical analysis for $PM_{2.5}$ concentration. NTTN, VTD, VDN, and LTH conducted statistical analyses for health impact assessment. NTTN and VTD drafted the manuscript. All authors provide statistical support, interpretation, professional support, and made several critical revisions to the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

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

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Supplementary material

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EDITED BY
Zhiming Yang,
University of Science and Technology Beijing, China

REVIEWED BY
Dorina Cadar,
Brighton and Sussex Medical School, United Kingdom
Robert Bradley,
Arizona State University, United States

*CORRESPONDENCE
Shi Qiu
qiushi@scu.edu.cn
Birong Dong
birongdong123@outlook.com

†These authors have contributed equally to this work and share first authorship

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Association between the domestic use of solid cooking fuel and increased prevalence of depression and cognitive impairment in a big developing country: A large-scale population-based study

Yuming Jin[1†], Xianghong Zhou[1†], Linghui Deng[2†], Xingyu Xiong[1], Yifan Li[1], Qiang Wei[1], Birong Dong[2]* and Shi Qiu[1,3]*

[1]Department of Urology, National Clinical Research Center for Geriatrics, Institute of Urology, West China Hospital, Sichuan University, Chengdu, China, [2]National Clinical Research Center of Geriatrics, The Center of Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, China, [3]Institute of Oncology Research (IOR) and Oncology Institute of Southern Switzerland (IOSI), Bellinzona, Switzerland

Background: Previous studies have suggested that air pollution affects physiological and psychological health. Using solid fuel at home is a significant source of indoor air pollution. The associations between solid fuel use and depressive symptoms and cognitive health were unclear among older adults from low- and middle-income countries (LMICs).

Methods: To evaluate the association of solid fuel use with depressive symptoms and cognitive health among older adults, we obtained data from the Longitudinal Aging Study in India (LASI) and excluded subjects younger than 60 years and without critical data (solid fuel use, depressive symptoms, and cognitive health). The 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10) was used to assess depressive symptoms, with more than ten indicative of depression. Cognitive health was assessed using measures from the Health and Retirement Study (HRS), and subjects with the lowest 10th percentile were considered to have cognitive impairment. The participants' responses defined solid fuel use. Multivariable logistic regression, linear regression, subgroup analysis, and interaction tests were performed to appraise the relationship between solid fuel use and depression and cognitive impairment.

Results: A total of 29,789 participants over 60 years old were involved in this study. Almost half of the participants (47.5%) reported using solid fuel for home cooking. Compared with clean fuel use, solid fuel use was related to an increased prevalence of depression [odds ratio (OR) 1.09, 95% CI 1.03–1.16] and higher CES-D-10 scores (β 0.23, 95% CI 0.12–0.35) after fully adjusted covariables. Using solid fuel was also related to a higher risk of cognitive impairment (OR 1.21, 95% CI 1.11–1.32) and a lower cognitive score (β −0.63, 95% CI −0.79 to −0.47) compared with those who used clean fuel. In the subgroup analysis, the prevalence of depression increased in females and non-smokers. The association of solid fuel use with depression and cognitive impairment exists in subgroups of BMI, economic status, caste, living area, education, and drinking.

Conclusions: The use of solid fuel at home was associated with an increased prevalence of depression and cognitive impairment among older adults in India.

KEYWORDS

indoor air pollution, solid fuel, depression, older adults, cognitive impairment

Introduction

Older adults have received extensive attention for the decline in physical function and lifestyle changes in recent decades. Older adults suffer a higher risk of chronic diseases due to the influence of long-term unhealthy lifestyles and dysfunction (1, 2). As people get older, they are more likely to suffer from cognitive impairment owing to cerebral atrophy, which harms their quality of life (3–5). Loneliness, functional disabilities, and chronic diseases are commonly significant risk factors for depression in older adults (6–8). Depression is the most common mental disorder in older adults, and the prevalence is higher in older adults than in young and middle-aged adults (8–10). The economic costs of depression and cognitive decline in the elderly are substantial, and they will rise as the severity of their symptoms worsens due to the higher costs associated with treating their illness (11, 12). Therefore, it is vital to prevent depression and cognitive impairment. Social and environmental factors and lifestyle are also positive indicators of depression (13, 14). As reported previously, air pollution is associated with depression and cognitive impairment with dose response (15, 16).

Over the years, air pollution has been recognized as a significant threat to public health, especially in low- and middle-income countries (LMICs) (17). Previous studies have shed light on the associations between air pollution and chronic disease, as well as the fact that air pollution increases the risk of unsatisfactory healthy status (18–20). Similarly, there is more evidence that air pollution is related to the prevalence of mental disorders and is correlated with the aggravation of depressive symptoms and cognitive impairment (21, 22). Household solid fuel produces particulate matter (PM), polycyclic aromatic hydrocarbons (PAHs), nitrogen dioxide (NO_2), and carbon monoxide (CO), which are primary sources of indoor pollution and can have detrimental ramifications (23–26). Evidence from previous studies has suggested that oxide nanoparticles enter the central nervous system through the alveolar epithelium; PMs reduce the cognitive learning abilities of rats (27, 28). It is worth noting that indoor air pollution was linked to depressive symptoms and cognitive impairment among elderly adults (29, 30). It is unclear whether indoor pollution is simultaneously related to depression and cognitive impairment.

In India, with the largest elderly population in the world, there will be 316 million people aged 60 years and above in 2050 (31). Approximately 9 and 13.5% of older adults live with depression and cognitive impairment in India (32, 33). More homes continue to use solid fuels because of their low cost and the lack of predictability in their revenue; only 22.5% of homes use clean fuels, and only 10% of rural homes use clean fuels (34, 35). Hence, it is essential to determine how indoor solid fuel use affects human health. Due to the widespread use of solid fuel in India, it makes sense to focus on the health outcomes of solid fuel use based on its population. A study from India suggested that solid fuel use for cooking was a risk factor for depression among premenopausal females (36). However, solid fuels have an opaque association with depression and cognitive impairment in older Indian adults. Using data from the Longitudinal Aging Study in India (LASI), the present study aimed to evaluate the association between the use of solid fuels with depression and cognitive impairment.

Methods

Participants and design of the study

We performed a cross-sectional study to evaluate the association between solid fuel use with depression and cognitive impairment. Data for the present study came from the Longitudinal Aging Study in India (LASI). Health, economic, and social data from 72,250 adults aged 45 and up across all Indian states and union territories, with the exception of Sikkim, were collected over the course of 2 years (2017 and 2018) (37). LASI aimed to provide data regarding demography, financial status, self-reported health information, family, etc. In this study, we used the data from the first wave of the LASI. Variables of household fuel information and score of the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10) and the cognitive score of method from the Health and Retirement Study (HRS) were analyzed in the present study. We excluded those under 60 years old, those who lost data on household fuel details and CES-D-10 scores, and those without information on their cognition. Finally, 29,789 participants were included in this study. The inclusion and exclusion criteria of the study population are shown in Figure 1.

Definition of solid fuel use

In the LASI study, subjects were required to answer the type of cooking fuel. Participants who reported using clean fuels such as liquefied petroleum gas, biogas, or electricity were classified as such, whereas those who reported using other fuels were classified as solid fuel users.

Assessment of depression

The LASI study used the 10-item Center for Epidemiologic Studies Depression Scale (CES-D-10) to evaluate depressive symptoms, a short version of the CES-D-20, which is widely used for screening depression. It assesses the depressive symptoms of subjects with ten items about depressive feelings and behaviors in the past week, including three items, five items, and two items about the depressive, somatic, and positive effects, respectively (38). The score range of each item is 0–3 points, corresponding to "<1 day," "1–2 days," "3–4 days," and "5–7 days." They were measured on a Likert scale. The scores of each item are summed, and the total score of the CES-D-10 ranges from 0 to 30. The CES-D-10 has good reliability and validity in older adults (39). According to a previous study, a CES-D-10 score of more than 10 was defined as a symptom of depression (40).

Evaluation of cognition

The methods of evaluating cognition from the HRS were used in the present study, which includes several aspects of cognition, such as orientation, function, arithmetic, object naming, and word recall. In the LASI study, subjects were asked to perform word repetition, the orientation of time and place, backward counting, serial computation, implementation of paper folding and pentagon drawing, and object naming to measure their memory ability. During a session on word repetition, subjects immediately recited a list of words that had been shown to them before, and the procedure was to assess their memory function (score from 0 to 10). The test of the orientation of time and place made subjects identify the place, day, month, and year to measure the orientation score (from 0 to 4). The arithmetic test consisted of backward counting, serial seven, and computation, and the scores were 0–2, 0–5, and 0–2, respectively. In the implementation test, subjects were asked to fold a paper and draw scores from 0 to 3 and from 0 to 1. In addition, subjects were required to name and identify a specific object (score from 0 to 2). The scores of all domains were calculated into cognitive scores from 0 to 43 to assess older adults' cognition, and higher cognition scores indicated better cognitive health in older adults. Subjects with lower than 10% cognitive scores were identified as having cognitive impairment.

Measurement of covariates

We included the following factors as covariates: The sociodemographic information included age (continuous), gender (male, female), education (never, middle school or under, secondary or above), marital status (married or in a relationship, widowed, or other), living area (urban or rural), whether to work (yes, no), economic status (tertile group-low/middle/high), caste (scheduled caste, scheduled tribe, other backward class, no or other castes), religion (Christian, Muslim, Hindu, or other); biological behavior information included moderate physical activity (more than once a week or hardly ever), body mass index (BMI) (<18.5, ≥ 18.5 and <25, ≥ 25 and <30, ≥ 30), drinking (never, current, ever), smoking (never, current, ever), combined chronic diseases (CCDs) (0, 1, 2, 3, or more), sleep disorder (no, yes); house environment information included other indoor pollution (no, yes), and indicators of poor housing quality (0, 1, 2, 3, 4, 5).

Several variables need to be explained in this study. Economic status was defined by annual per capita consumption expenditure. BMI (kg/m^2) is defined as the weight (kg)/square of height (m). CCDs include hypertension, diabetes, tumors, lung disease, chronic heart disease, stroke, arthritis, mental disease, Alzheimer's disease, hypercholesterolemia, asthma, congestive heart failure, heart attack, abnormal heart rate, osteoporosis, abnormal thyroid function, digestive disease, skin disease, kidney stones, presbyopia, cataracts, glaucoma, myopia, hyperopia, tooth decay, and periodontal disease. Sleep disorder was identified as any of the following five situations that subjects reported: difficulty sleeping, waking up at night, waking up early, feeling sleepy during the day, and taking medicine to help sleep. Other indoor pollution included incense sticks (agarbatti), mosquito coils, liquid vaporizers/mosquito repellents/mats, fast cards/sticks/cakes, or if the housing respondent reports that a usual member of their household smokes inside their home. The subjects' answers (no, yes) to the above substances were analyzed. Indicators of poor housing quality were used to assess the quality of houses, which consisted of five indicators: house material, sanitary facilities, electric power, water source, and crowding (41). One score was recorded for each missing

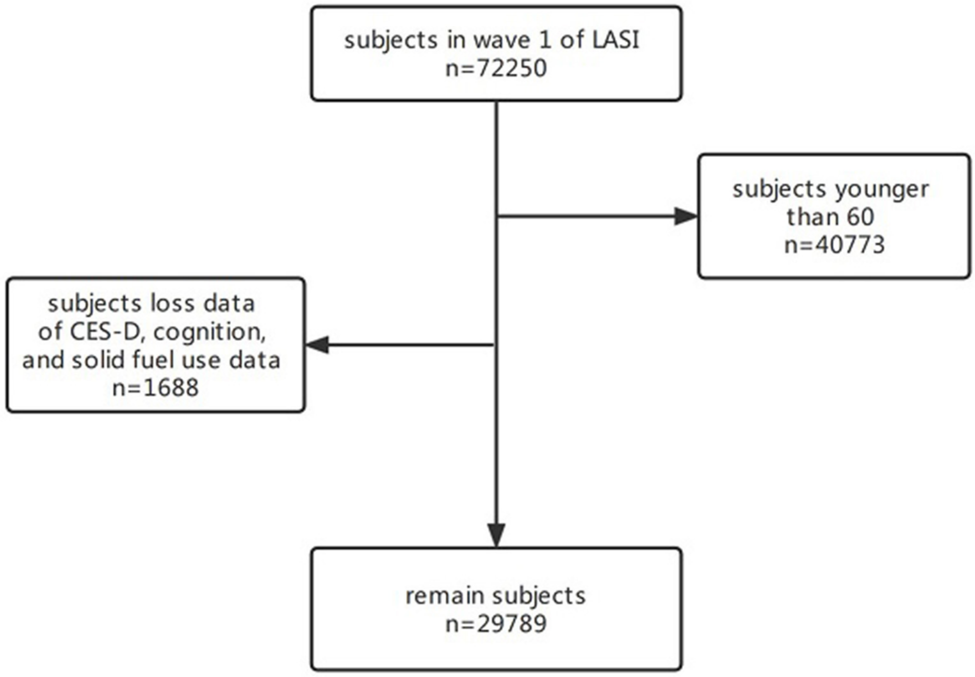

FIGURE 1
Inclusion and exclusion of the study population.

indicator of the subject's house, and the total score range was 0–5. The higher the score indicates, the worse the house quality.

Statistical analysis

In the present study, we classified participants into two groups based on solid fuel use, and we presented categorical and continuous variables as percentages and means ± standard deviations. Multivariable logistic regression models evaluated the associations of solid fuel use with depressive symptoms and cognitive impairment. Multivariable linear regression models assessed the associations of solid fuel use with the CES-D-10 score and cognitive score. We used five models in each analysis: the unadjusted model, model I (adjusted for age, gender, and BMI), model II (adjusted for age, gender, and BMI, education, marriage, living area, whether someone works, caste, religion, and economic status), model III (adding indicators of drinking, smoking, sleep disorders, CCDs, and vigorous physical activity into model II), model IV (adding other indoor pollution and indicators of poor housing quality). Subgroup and interaction analyses were performed and stratified by gender, caste, living area, education, economic status, smoking, drinking, and BMI to explore potential effect modification. The sample size for each analysis is shown in the Supplementary material. The results with $p <$ 0.05 and 95% confidence intervals (95% CI) were considered statistically significant. All analyses were performed by the statistical software package R 4.1.2 (http://www.R-project.org, The R Foundation).

Result

Characteristics of the study population

A total of 29,789 participants over 60 years old were included in this study. Of whom, there were 15,507 females and 14,282 males, and the total mean age was 68.7 years. For solid fuel, 14,203 participants reported using solid fuel at home, and 15,586 participants reported using clean fuel. Compared with those using clean fuel, solid fuel users showed a higher mean CES-D-10 score (solid fuel users: 10.2; clean fuel users: 9.5) and a higher rate of depression (solid fuel users: 49.8%; clean fuel users: 42.6%). The cognitive score of solid fuel users was 21.6, which was lower than that of clean fuel users (25.4). The incidence of cognitive impairment was 23.9% in solid fuel users, which was higher than that in clean fuel users (11.5%). Solid fuel users were more likely to have a low education level, live in the village, be unemployed, have low economic status, have a low BMI, drink alcohol, smoke, and live with other indoor pollution. However, there was no significant difference in age, gender, marriage status, or indoor pollution between clean and solid fuel users. Table 1 shows the characteristics of the study participants classified by using solid fuel.

Association of solid fuel use at home with depression and cognitive impairment

We found a positive and significant association between solid fuel use and depression in logistic regression analysis. In the unadjusted model, using solid fuel was associated with a higher risk of depression, with an OR of 1.37. In model I, adjusted for age, gender, and BMI, the relationship between solid fuel use and depression remained unchanged (OR 1.27, 95% CI 1.21–1.33). In model II, the OR of depression from solid fuel use decreased after adjusting for sociodemographic information, which still met statistical significance (OR 1.15, 95% CI 1.08–1.22). After adding covariates of biological information, solid fuel use was significantly correlated with depression (OR 1.18, 95% CI 1.11–1.25) in model III. In the fully adjusted model (model IV), the significance of the relation between solid fuel use and depression decreased, with an OR of 1.09 (95% CI 1.03–1.16). There was a trend for the OR of depression from solid fuel consumption to decrease when additional covariates were included in the analysis.

With the similarity of trend, there was a significant association between solid fuel use and cognitive impairment in all models based on the logistic regression analysis that domestic solid cooking fuel use was associated with a higher prevalence of cognitive impairment (unadjusted model, OR 2.42, 95% CI 2.27–2.57; mode l I, OR 2.14, 95% CI 1.99–2.30; model II, OR 1.29, 95% CI 1.18–1.40; model III, OR 1.27,95% CI 1.16–1.38; model IV, OR 1.21, 95% CI 1.11–1.32).

We considered the CES-D-10 score a continuous variable in linear regression analysis, and the results were similar to those from logistic regression analysis. In the unadjusted model, solid fuel users had a higher CES-D-10 score than clean fuel users (β 0.77, 95% CI 0.67–0.86). In mode I, those using solid fuel were associated with a 0.60 higher CES-D-10 score than clean fuel users. The result stating solid fuel use was related to a higher CES-D-10 score remained unchanged in model II (β 0.38, 95% CI 0.27–0.49). After adjusting for biological information, the CES-D-10 score of solid fuel users was 0.39 points higher than that of clean fuel users (95% CI, 0.27–0.50). In the fully adjusted model, the difference between solid and clean fuel users decreased but met significance (β 0.23, 95% CI 0.12–0.35). Solid fuel use was negatively related to cognitive scores. Compared with those who used clean fuel, the cognitive score decreased by 3.89 in those who used solid fuel in the unadjusted model (95% CI, −3.96 to −3.65). With more covariates included in analyses, the OR-value of the cognitive score between solid fuel users and clean fuel users decreased. In the fully adjusted model, the relation between solid fuel use and the cognitive score remained unchanged (model I, β −2.91, 95% CI −3.07 to −2.76; mode lII, β −0.78,95% CI −0.93 to −0.62; model III, β −0.75, 95% CI −0.91 to −0.60; model IV, β −0.63, 95% CI −0.79 to −0.47). Table 2 presented the association between solid fuel use and depression and cognitive impairment by logistic regression and linear regression analysis.

Subgroup analyses and interaction analyses

In this present study, subgroup analyses were stratified by gender (female, male), education (never, middle school or under, and secondary or above), living area (urban, rural), caste (scheduled caste, scheduled tribe, other backward class, no or other castes), and economic status (tertile group), BMI ($<$18.5, $\geq$18.5 and $<$25, $\geq$25 and $<$30, $\geq$30), smoking (never, current, ever), and drinking (never, current, ever). We observed significant interactions in the association between solid fuel use and depression on the relation of solid fuel with depression, in different gender and smoking (p for interaction: gender 0.009, smoking 0.002). After classifying participants by gender, the association between solid fuel use and depression still existed among females (OR 1.18, 95% CI 1.08–1.28), while the relationship between the two did not have statistical differences in males (OR 1.01, 95% CI 0.92–1.10). Those who never smoked were more likely to suffer from depression due to solid fuel use (OR 1.14, 95% CI 1.07–1.23). The correlation of solid fuel use with depression disappeared among those who ever smoked or currently smoked. We did not observe a significant interaction of BMI, economic status, caste, living area, education, or drinking on the association between solid fuel use and depression.

After adjusting for all confounders, no significant interaction of gender, education, living area, caste, BMI, smoking, or drinking on the correlation between solid fuel use and cognitive impairment was observed. We did not obtain any evidence to prove the existence of differences in the relation of solid fuel use with cognitive impairment in different subgroups. Subgroup analysis is presented in Figure 2.

Discussion

This cross-sectional study assessed the associations of solid fuel use with depression and cognitive impairment. Solid fuel use was associated with a 37% higher prevalence of depression and a 142% higher prevalence of cognitive impairment than clean fuel use in the unadjusted model. After adjusting biological

TABLE 1 Characteristics of participants using solid fuel or using clean fuel.

Characteristics	Total	Using clean fuel	Using solid fuel	*P*-Value
Numbers	29,789	15,586	14,203	
Age, year	68.7 ± 7.4	68.8 ± 4.2	68.6 ± 7.3	0.141
Gender, *n* (%)				0.397
Female	15,507 (52.1%)	8,050 (51.6%)	7,457 (52.5%)	
Male	14,282 (47.9%)	7,536 (48.4%)	6,746 (47.5%)	
CES-D-10 scores	9.83 ± 4.10	9.46 ± 4.17	10.23 ± 4.00	<0.001
Depression using a cutoff of 10				<0.001
<10	16,074 (54.0%)	8,951 (57.4%)	7,123 (50.2%)	
≥10	13,715 (46.0%)	6,635 (42.6%)	7,080 (49.8%)	
Cognitive score	23.5 ± 7.1	25.4 ± 7.0	21.6 ± 6.7	<0.001
Cognitive impairment				<0.001
No	24,604 (82.6%)	13,794 (88.5%)	10,810 (76.1%)	
Yes	5,185 (17.4%)	1,792 (11.5%)	3,393 (23.9%)	
Education, *n* (%)	<0.001	15,956 (53.6%)	6,379 (40.9%)	9,577
	Never			(67.4%)
Middle school or under	9,303 (31.2%)	5,379 (34.5%)	3,924 (27.6%)	
Secondary or above	4,530(15.2%)	3,828 (24.6%)	702 (4.9%)	
Marriage status, *n* (%)				0.061
Married or partnered	19,195 (64.4%)	10,138 (65.0%)	9,057 (63.8%)	
Widowed	9,988 (33.5%)	5,143 (33.0%)	4,845 (34.1%)	
Others	606 (2.0%)	305 (2.0%)	301 (2.1%)	
Living area, *n* (%)				<0.001
Urban	10,029 (33.7%)	8,493 (54.5%)	1,536 (10.8%)	
Rural	19,760 (66.3%)	7,093 (45.5%)	12,667 (89.2%)	
Whether work				<0.001
No	19,472 (65.4%)	11,097 (71.2%)	8,375 (59.0%)	
Yes	10,317 (34.6%)	4,489 (28.8%)	5,828 (41.0%)	
Caste, *n* (%)				<0.001
Scheduled caste	4,884 (16.5%)	2,118 (13.7%)	2,766 (19.6%)	
Scheduled trible	4,925 (16.6%)	1,431 (9.3%)	3,494 (24.7%)	
Other backward class	11,291 (38.1%)	6,130 (39.7%)	5,161 (36.5%)	
No or other caste	8,484 (28.7%)	5,774 (37.4%)	2,710 (19.2%)	
Religion, *n* (%)				<0.001
Others	1,467 (4.9%)	906 (5.8%)	561 (4.0%)	
Hindu	21,846 (73.3%),	11,525 (73.9%)	10,321 (72.7%)	
Muslim	3,490 (11.7%)	1,819 (11.7%)	1,671 (11.8%)	
Christian	2,985 (10.0%)	1,336 (8.6%)	1,649 (11.6%)	
Economic status, *n* (%)				<0.001
Low	10,560 (35.5%)	3,548 (22.8%)	7,012 (49.4%)	
Middle	10,039 (33.7%)	5,418 (34.8%)	4,621 (32.5%)	
High	9,188 (30.8%)	6,620 (42.5%)	2,568 (18.1%)	
BMI, *n* (%)				<0.001
<18.5	6,372 (23.3%)	1,961 (13.8%)	4,411 (33.5%)	
≥18.5, <25	14,379 (52.6%)	7,325 (51.6%)	7,054 (53.6%)	
≥25, <30	5,044 (18.4%)	3,644 (25.7%)	1,400 (10.6%)	
≥30	1,564 (5.7%)	1,264 (8.9%)	300 (2.3%)	

(Continued)

TABLE 1 (Continued)

Characteristics	Total	Using clean fuel	Using solid fuel	*P*-Value
Drinking, *n* (%)				<0.001
Never	24,647 (82.8%)	13,313 (85.5%)	11,334 (79.8%)	
Current	2,661 (9.0%)	1,133 (7.3%)	1,528 (10.8%)	
Ever	2,469 (8.3%)	1,131 (7.3%)	1,338 (9.4%)	
Smoking, *n* (%)				<0.001
Never	23,734 (79.7%)	12,930 (83.0%)	10,804 (76.1%)	
Current	4,205 (14.1%)	1,714 (11.0%)	2,491 (17.5%)	
Ever	1,832 (6.2%)	928 (6.0%)	904 (6.4%)	
Vigorous physical activity, *n* (%)				<0.001
More than or equal to once a week	7,979 (26.8%)	3,508 (22.5%)	4,471 (31.5%)	
Hardly ever	21,791 (73.2%)	12,070 (77.5%)	9,721 (68.5%)	
CCDs				<0.001
0	4,987 (16.9%)	1,665 (10.8%)	3,322 (23.6%)	<0.001
1	6,312 (21.4%)	2,795 (18.1%)	3,517 (25.0%)	
2	6,073 (20.6%)	3,221 (20.8%)	2,852 (20.3%)	
3, or more than 3	12,169 (41.2%)	7,785 (50.3%)	4,384 (31.1%)	
Sleep disorder	25,153 (84.5%)	13,231 (84.9%)	11,922 (83.9%)	<0.001
Without sleep disorder				
With sleep disorder	4,627 (15.5%)	2,347 (15.1%)	2,280 (16.1%)	
Other indoor pollution, *n* (%)				<0.001
No	3,755 (12.6%)	1,616 (10.4%)	2,139 (15.1%)	
Yes	26,031 (87.4%)	13,967 (89.6%)	12,064 (84.9%)	
Indicators of poor housing quality, *n* (%)				<0.001
0	11,265 (37.8%)	8,525 (54.7%)	2,740 (19.3%)	
1	9,620 (32.3%)	4,601 (29.5%)	5,019 (35.3%)	
2	5,489 (18.4%)	1,789 (11.5%)	3,700 (26.1%)	
3	2,712 (9.1%)	608 (3.9%)	2,104 (14.8%)	
4	696 (2.3%)	63 (0.4%)	633 (4.5%)	
5	7 (<0.1%)	0 (0.0%)	7 (<0.1%)	

SD, standard deviation; BMI, body mass index.
Mean ± SD for continuous variables: The P-value was calculated by the weighted linear regression model.
Number (%) for Categorical variables: The P-value was calculated by weighted chi-square test.

and social demographic covariates, the association of solid fuel use with depression and cognitive impairment remained unchanged. After adding house quality and indoor pollution as covariates into the analysis, the value of solid fuel use on depression and cognitive impairment decreased. However, the results still showed a significant difference. In the subgroup analysis, we found that females and non-smokers suffered a higher prevalence of depression related to solid fuel use. The relationship between solid fuel and cognitive impairment was stable in different subgroups.

We analyzed the association of solid fuel use with depression and cognitive impairment among older adults based on a population sample from representable LMICs. At the same time, the current study included the largest and latest sample size among similar studies (29,789). The prevalence of depression and cognitive impairment in LMICs is increasing, especially in the elderly population, but the relevant research has been insufficient in recent years. For the extensive research on the adverse health effects of air pollution, reducing the use of solid fuels has been considered a way to improve indoor pollution (42, 43). Previous studies have also demonstrated the enormous economic burden of indoor solid fuel use (44). Our research shows that the adverse effects on health caused by solid fuels still exist based on the latest data from LASI Wave 1, even though such negative consequences had been reported beforehand. As noted previously, in the different subgroups of gender, education, BMI, smoking, or drinking, there are different susceptibilities to depression, so it is necessary to determine the association of solid fuel use with depression and cognitive impairment in those subgroups (45–54). In India,

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TABLE 2 Association of using solid fuel with symptoms of depression, CES-D-10 score, cognitive impairment, and cognitive scores.

	OR/β (95% CI)				
Score of CES-D-10	Unadjusted model	mode I	model II	model III	model IV
Categorical variable (depression)*					
Using clean fuel	Reference	Reference	Reference	Reference	Reference
Using solid fuel	1.37 (1.28, 1.40)	1.27 (1.21, 1.33)	1.15 (1.08, 1.22)	1.18 (1.11, 1.25)	1.09 (1.03, 1.16)
Continuous variable					
Using clean fuel	Reference	Reference	Reference	Reference	Reference
Using solid fuel	0.77 (0.67, 0.86)	0.60 (0.50, 0.70)	0.38 (0.27, 0.49)	0.39 (0.27, 0.50)	0.23 (0.12, 0.35)
				<0.0001	
Cognitive score	Unadjusted model	mode I	model II	model III	model IV
Categorical variable (cognitive impairment)**					
Using clean fuel	Reference	Reference	Reference	Reference	Reference
Using solid fuel	2.42 (2.27, 2.57)	2.14 (1.99, 2.30)	1.29 (1.18, 1.40)	1.27 (1.16, 1.38)	1.21 (1.11, 1.32)
Continuous variable					
Using clean fuel	Reference	Reference	Reference	Reference	Reference
Using solid fuel	−3.80 (−3.96, −3.65)	−2.91 (−3.07, −2.76)	−0.78 (−0.93, −0.62)	−0.75 (−0.91, −0.60)	−0.63 (−0.79, −0.47)

CES-D-10, the Center for epidemiologic studies depression scale; OR, odds ratio; β, effect sizes; 95% CI, 95% confidence interval.

*Depression was defined as CES-D-10 score over 10; **Cognitive impairment was identified as a cognitive score lower than 10 %; Model I: adjusted for age, gender, and BMI; Model II: adjusted for age, gender, BMI, education, marriage, live area, whether works, caste, religion, and economic status; Model III: adjusted for age, gender, BMI, education, marriage, live area, whether works, caste, religion, economic status, drinking, smoking, sleep disorder, CCDs, and vigorous physical activity; Model IV: adjusted for age, gender, BMI, education, marriage, live area, whether works, caste; religion, economic status, drinking, smoking, sleep disorder, CCDs, vigorous physical activity, other indoor pollution, and indicators of poor housing quality.

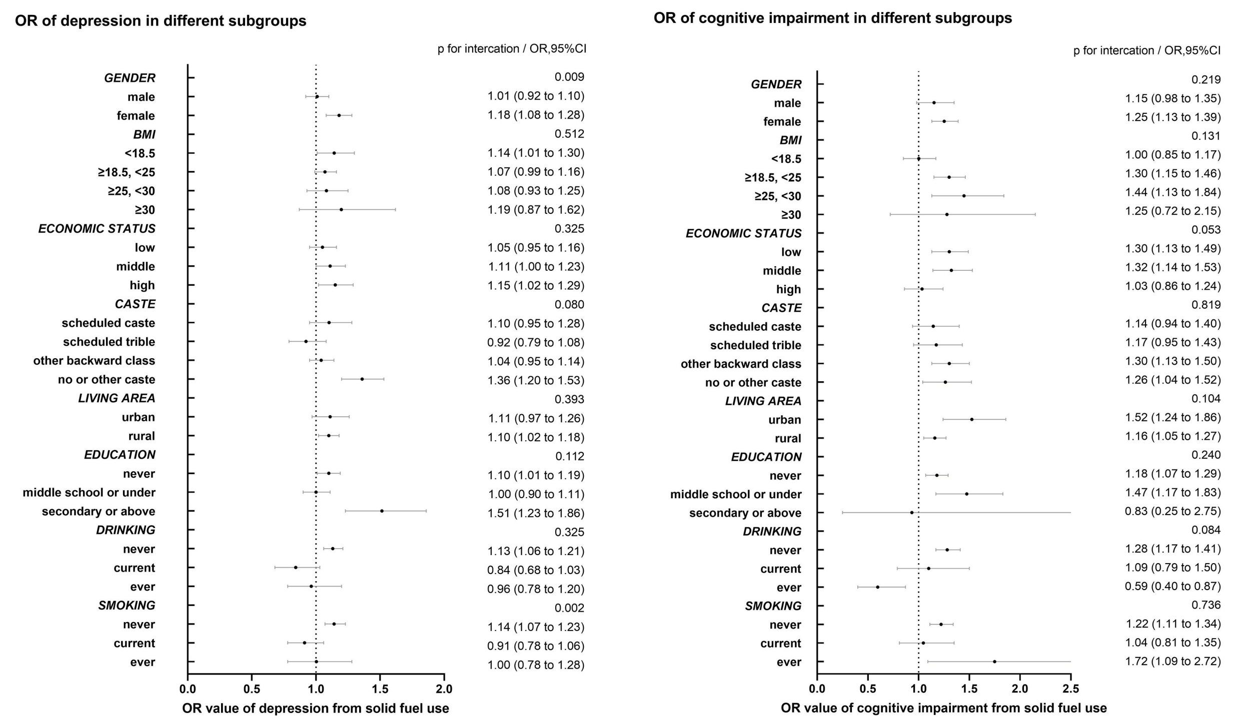

FIGURE 2
Subgroup analysis in the association of solid fuel use with depression and cognitive impairment. Subgroup analysis were adjusted by age, gender, BMI, education, marriage, live age, whether works, caste, religion, economic status, drinking, smoking, sleep disorder, CCDs, vigorous physical activity, other indoor pollution, indicators of poor housing quality.

populations with different economic statuses, living areas, and castes used different ratios of solid fuel. According to our findings, subgroup analyses based on economic status, living area, and castes used different ratios of solid fuel, according to our findings of subgroup analyses.

The associations between the use of solid fuel and depression and cognitive impairment have been provided by previous studies, but the underlying molecular mechanism for the effects of air pollution on depression and cognitive impairment is not clear (30, 36, 55–60). Several explanations show possible links. First, solid fuel increases oxidative stress (OS) in the human body through a high concentration of PM and chemical substances, which promotes the progression of depression and cognitive impairment. OS plays a major role in neurodegeneration, which involves depressive pathogenesis (61, 62). Animal experiments have shown that $PM_{2.5}$ promotes oxidative stress through the Nrf2/NF-κB pathway and increases the level of inflammatory cytokines (63). PM was also related to the activation of the nuclear transcription factors Nrf-2 and NF-κB in male rats, and PM may lead to physiological changes in the central nervous system (64). A study on females with solid fuel use suggested that solid fuel users had 32% more leukocytes in circulation, and reactive oxygen species (ROS) were generated at higher levels in neutrophils, lymphocytes, eosinophils, and alveolar macrophages (65). Second, metabolic alterations resulting from PM and chemical substances may lead to depression. After short- and long-term exposure to PM, triglyceride levels increased; after long-term exposure to PM, free fatty acid levels also increased (66). PM also hurts glucose metabolism: exposure to $PM_{2.5}$ increases insulin resistance (67). PAHs, NO_2, and CO are related to biological toxicity (68–70). Similarly, higher levels of triglycerides and free fatty acids were observed among those living with depression, and it was reported that higher glucose concentrations of the pregenual anterior cingulate were associated with major depressive disorder (71–73). In a study from China, hyperlipidemia and hyperglycemia were related to cognitive impairment (53). Finally, solid fuel use was related to depression and cognitive impairment, which may be linked to chronic disease. Solid fuel users suffer a higher risk of chronic disease. A meta-analysis suggested that multimorbidity was related to depression and cognitive impairment, which means that chronic diseases resulting from solid fuel led to the emergence of depression and cognitive impairment (26, 53, 74, 75).

As reported by previous studies, using solid fuel was related to depression, which is consistent with the results of our study (36, 55–59). The adjusted OR and 95% CI of solid fuel use for depression were OR 1.09 and 95% CI 1.03–1.16 in our study, respectively. The value differed from previous studies due to the difference in study populations and definitions of solid fuel use and depression. In the subgroup analysis, we found that females and non-smokers suffer a higher OR from solid fuel use for depression, and there was no interaction on economic status, which was different from the findings in previous studies. Contrary to our findings, research from China found no connection between gender and smoking solid fuel and depression (59). The India Human Development Survey study found that in 98% of households, females cooked, which seems to explain why females have a higher OR of solid fuel use for depression than males in the Indian population due to the higher exposure to pollutants from solid fuel (34). Secondhand smoke exposure is related to depressive symptoms among those who never smoke (76). People who are not exposed to tobacco appear to be more sensitive to air pollution, and nonsmokers who suffer a higher OR from solid fuel use for depression need further study. In a previous study, associations between using solid fuel and depression were generally higher in females and those with low household economic levels among older Chinese adults (55). In our study, low household economic levels were not related to a higher risk of depression, which may be associated with the broader use of solid fuel in India. In the subgroup of caste, different relations of solid fuel to depression were observed for the differences in health and lifestyle (77).

The association between solid fuel use and cognitive impairment has been frequently determined in China, while the evidence from other areas is limited (30, 60, 78). A study from Mexico suggested that solid cooking fuels may represent a risk factor for cognitive decline (79). Additionally, the association between solid fuel and depressive symptoms for ten years depended on the WHO Study on Global AGEing and Adult Health (SAGE) (80). A meta-analysis suggested that a 24% higher risk of depression was related to solid fuel use, while the OR of solid fuel use for depression was 1.08, according to our findings (81). Compared with another study based on the LASI study, we excluded those younger than 60 and involved indicators of poor housing quality as covariants to accurately evaluate the relationship between solid fuel use and cognitive impairment among older adults (82). Evidence from a study from northern China suggested that domestic solid fuel consumption was a dose-dependent risk factor for cognitive impairment (83). Although we did not find a significant p for interaction in subgroups between solid fuel use and cognitive impairment, there were still subgroups suffering from the different effects of solid fuel on cognitive impairment. Among males, we found a negative relationship between solid fuel and cognitive impairment compared with females because of their lower exposure to pollutants (34). There was no significant association between solid fuel use and cognitive impairment in subgroups of high economic status and high educational status, which indicates the protective effect of the two (51, 84). In our study, the correlations between solid fuel use and cognitive impairment were stable and consistent with the findings from a previous study (82).

There were several limitations to this study. First, the present study is cross-sectional, making it difficult to identify the causal relationship between solid fuel use and depression or cognitive impairment. Second, our study's definitions of depression and cognitive impairment were based on screening tools (the CES-D-10 and HRS) but not diagnostic criteria. The CES-D-10 was primarily used for assessing depression symptom severity (40). Although the HRS cognitive assessment method is widely used in various studies as a face-to-face interview-based test, there are still some limitations (85). Third, the patient's answer determined whether the subjects used solid fuel, which may not have been objectively observed and have certain recall biases. Fourth, due to the lack of relevant data, we did not evaluate the impact of the total time of solid fuel use every day and the total time of solid fuel use on the association between solid fuel use and depressive symptoms. Fifth, because of the lack of kitchen ventilation, we used indicators of poor housing quality to assess the quality of the house. Indicators of poor housing quality helped us reduce the statistical bias caused by the lack of kitchen ventilation information in a previous study (41). Sixth, due to the low concentration of air pollution to which the subjects were exposed, we did not analyze the dose relationship of air pollutant concentrations with depression and cognitive impairment. Seventh, the population we studied was comprised of elderly individuals over the age of 60 and did not include people under 60. The relationship of solid fuel use with depression and cognitive impairment in these populations needs further verification.

Although evidence from a 10-year study suggested a link between solid fuel use and depression, solid fuel use was also related to depression in our research, indicating that solid fuel's effect still existed. Therefore, more government measures to improve indoor pollution are needed (59, 80). Older adults should use clean fuel at home for cooking, which is beneficial for their mental health and cognition. Our study first provided the association of solid fuel use with depression and depression at the same time among older adults, and more policies on reducing the use of solid fuels, promoting clean fuels, and improving air quality are needed.

Conclusion

Domestic solid cooking fuel use was associated with the increased prevalence of depression and cognitive impairment among older adults in India.

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://doi.org/10.25549/h-lasi.

Ethics statement

The studies involving human participants were reviewed and approved by the Indian Council of Medical Research. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SQ, XZ, and QW were involved in the conception and design of the work. YJ, LD, and XX contributed to the acquisition, analysis, and interpretation of the data. YJ and YL finished the first draft. SQ and BD revised the manuscript for important intellectual content. All authors reviewed and approved the final version.

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Conflict of interest

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

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Supplementary material

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Zhiming Yang,
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REVIEWED BY
Sasho Stoleski,
Saints Cyril and Methodius University of Skopje, North Macedonia
Vladimir Koblizek,
University Hospital Hradec Kralove, Czechia

*CORRESPONDENCE
Pixin Ran
pxran@gzhmu.edu.cn
Yumin Zhou
zhouyumin410@126.com

†These authors have contributed equally to this work

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Traffic-related air pollution is a risk factor in the development of chronic obstructive pulmonary disease

Jinzhen Zheng[1,2†], Sha Liu[1,3†], Jieqi Peng[1,4†], Huanhuan Peng[1,5], Zihui Wang[1], Zhishan Deng[1], Chenglong Li[1], Naijian Li[1], Longhui Tang[1,6], Jianwu Xu[1], Jingwen Li[1], Bing Li[1,7], Yumin Zhou[1,4]* and Pixin Ran[1,4]*

[1]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Diseases, The Guangzhou Institute of Respiratory Health, and The First Affiliated Hospital of Guangzhou Medical University, Guangdong, China, [2]Department of Pulmonary and Critical Care Medicine, Shantou Central Hospital, Shantou, Guangdong, China, [3]The Second Affiliated Hospital, Hengyang Medical School, University of South China, Hengyang, Hunan, China, [4]Guangzhou Laboratory, Bio Island, Guangzhou, Guangdong, China, [5]Department of Pulmonary and Critical Care Medicine, The Fourth People's Hospital of Chenzhou, Chenzhou, Hunan, China, [6]Department of Pulmonary and Critical Care Medicine, Chenzhou Third People's Hospital, Chenzhou, Hunan, China, [7]College of Life Sciences, Guangzhou Medical University, Guangzhou, Guangdong, China

Background: Outdoor traffic-related air pollution has negative effects on respiratory health. In this study, we aimed to explore the effect of outdoor traffic-related air pollution on chronic obstructive pulmonary disease (COPD) in Guangzhou.

Methods: We enrolled 1,460 residents aged 40 years or older between 21 January 2014 and 31 January 2018. We administered questionnaires and spirometry tests. The distance of participants' residences or locations of outdoor activities from busy roads (as indicators of outdoor traffic-related air pollution), indoor air pollution, and smoking history were queried in the questionnaires.

Results: Of the 1,460 residents with valid survey and test results, 292 were diagnosed with COPD, with a detection rate of 20%. Participants who lived and did their outdoor activities near busy roads had a higher detection rate of COPD. Among residents living at distances of <50 meters, 50–199 meters, and more than 200 meters from busy roads, the detection rates were 20.6, 21.2, and 14.8%, respectively; the rates for outdoor activities at these distances were 23.8, 24.5, and 13.7%, respectively ($p < 0.05$). After adjusting for sex, age, smoking status, family history, and smoking index, the distance of outdoor activities from busy roads was an independent risk factor for COPD. Participants whose outdoor activities were conducted <50 meters and 50–199 meters of main roads had odds ratios of 1.54 (95% confidence interval 1.01–2.36) and 1.84 (95% interval 1.23–2.76) for the risk of COPD in comparison with a distance of more than 200 meters from busy roads.

Conclusions: Residents of Guangzhou whose outdoor activities were close to busy roads had a high risk of COPD. Traffic-related air pollution presents a risk to human health and a risk of COPD.

KEYWORDS

chronic obstructive pulmonary disease (COPD), air pollution, traffic pollution, risk factors, health

Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, characterized by persistent respiratory symptoms and irreversible airflow (1). COPD usually involves airway or alveolar abnormalities caused by noxious particles or exposure to gases (2). Exposure to noxious particles or gases (e.g., *via* smoking, household wood burners, fires, or environmental pollutants) is the main risk factor for COPD (3). The European Study of Cohorts for Air Pollution Effects project showed that greater exposure to ambient nitrogen dioxide and exposure to particulate matter (PM) with a 50% cutoff aerodynamic diameter of 10 μm (PM_{10}) were related to lower levels of forced expiratory volume in 1 sec (FEV1) and forced vital capacity (FVC) (4). Traffic-related air pollution is an important source of atmospheric pollution, especially PM, sulfur dioxide, nitrogen oxides, and carbon monoxide (5). It has been reported that outdoor traffic-related air pollution negatively affects respiratory health in Europe and the United States, where pollution is mild (6). It is, therefore, crucial to reducing the emission of air pollution.

Air pollution could increase the risk of respiratory mortality, with a negative association between lung function and obstructive lung diseases. It has been reported that incomplete combustion of biomass fuel could result in COPD (7). Each 10-$\mu g/m^3$ increase in fine PM is linked to a 3.1% increased risk of hospitalization and a 2.5% increase in mortality (8). In China, studies on the association of traffic-related air pollution with risk factors for COPD remain scarce, especially in community districts. We aimed to explore whether traffic-related air pollution (assessed according to the distance from the main road) affects lung function and whether it is a risk factor for developing COPD in a population of community residents of Guangzhou.

Materials and methods

Study design and participants

This was a cross-sectional observational analysis of a prospective study. We requested that doctors working in community hospitals ask local residents to participate in our project. Between 21 January 21 2014 and 31 January 31 2018, we recruited permanent residents in three communities in Guangzhou's central areas (Figure 1), including the Nanyuan community in Liwan District, the Hongqiao community in Yuexiu District, and the Xingang community in Haizhu District. We included participants aged 40–80 years who could complete the questionnaires and lung function tests. We excluded participants who had undergone thoracic, abdominal, or eye surgery or experienced myocardial infarction in the past 3 months; those who had been hospitalized for COPD exacerbation in the past 4 weeks; those who had received antibacterial treatment or chemotherapy for active tuberculosis or a newly discovered tumor; and those with other respiratory diseases, except for asthma, such as lung cancer, pneumoconiosis, and extensive bronchiectasis.

Questionnaire

The questionnaire related to air pollution was revised from the National German Health Survey (9) and the Air Pollution on Lung, Inflammation, and Aging (SALIA) study (10) based on a standardized questionnaire from the international BOLD (Burden of Obstructive Lung Diseases) study. The study questionnaire included demographic characteristics (age, sex, and body mass index [BMI]), tobacco smoking history, family history of respiratory disease, the distance of residence or location of outdoor activities from busy roads, medical history, history of medical therapy, chronic respiratory symptoms, and frequency of acute COPD exacerbations during the preceding year. The smoking index was calculated as smoking years multiplied by the number of packs of cigarettes smoked (pack-years). A family history of respiratory diseases was defined as one or more immediate family members having a respiratory disease such as asthma, COPD, lung cancer, interstitial lung disease, or obstructive sleep apnea-hypopnea syndrome. The frequency of acute COPD exacerbations during the preceding year was defined as the new or worsening of at least two of the following respiratory symptoms: cough, phlegm, purulent sputum, wheezing, and dyspnea lasting over 48 h, (11) excluding left and right cardiac dysfunction, pulmonary embolism, pneumothorax, pleural effusion, and arrhythmia. Our team used self-reported distance to measure the distance from participants' homes and the location of outdoor activities to the nearest road.

We asked participants to report the distance from their homes or where they performed outdoor activities to the main road with heavy traffic every day. The response options were <50 meters, 50–199 meters, and more than 200 meters (12, 13). Questionnaires were administered by trained investigators.

Exposure assessment

Subjects were merged into a Geographical Information System (GIS). Geocoding (longitude and latitude) was done using home addresses. For the subject geocoding, we used cartographic data provided by the GIS Service of Guangzhou City: buildings, streets, and home addresses. We applied address geocoding techniques provided by Arcgis Pro3.0.2: a file extracted from the epidemiological questionnaire containing participants' addresses (street names and house numbers) was matched with vector data. Distances of houses from the main road were used to assess traffic-related pollution exposure. In Nanyuan Community, the main roads included Nanan Road and Zengcuo Road. In Hongqiao Community, the main roads included Xiaobei Road and Dongfengxi Road. In Xingang Community, the main roads included Xinjiaozhong Road and Dongxiaonan Road. Using GIS buffering and overlaying functionalities, we classified the population sample into three groups: <50 meters, 50–199 meters, and more than 200 meters, respectively (Figure 1).

Spirometry

Spirometry testing was performed using a portable MasterScreen Pneumo Spirometer (CareFusion, CA, USA). The instrument calibration was checked before each assessment, following the methods and criteria recommended in the American Thoracic Society and European Respiratory Society guidelines (14). Spirometry tests were performed according to American Thoracic Society/European Respiratory Society standards (14) and were conducted by skilled physicians. Participants were excluded if they had allergies to medication or uncontrolled hypertension under the premise of albuterol sulfate (salbutamol) aerosol use. Prebronchodilator spirometry testing was done before the inhalation of 400 μg salbutamol, and postbronchodilator spirometry was conducted after 20 min following the same process. If the participant was using inhaled or oral respiratory medication to relieve airway obstruction or symptoms, we suggested they stop short-acting bronchodilator medications for 12 h or long-acting bronchodilator medications for 24 h before testing. We asked participants whether they used bronchodilator medications before performing spirometry; if they used medication, spirometry was performed the following day. We chose at least three acceptable curves and two repeatable measurement curves (maximum and submaximum values of FVC and FEV_1 within 150 mL or 5%) when performing lung function tests.

The Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University approved the study protocol (2013-37). All participants signed informed consent forms.

Statistical analysis

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). We used analysis of variance for continuous variables and the chi-squared test for categorical variables. Analysis of potential risk factors for COPD was

FIGURE 1
(A–C) Classification of subjects based on distance of each home from the main road in Nanyuan, Hongqiao and Xingang Community. The three maps represented classification of subjects according to distance of each home from the main road (<50 m, 50–199 m, and ≥200 m groups) in Nanyuan, Hongqiao and Xingang Community.

performed using a logistic regression model in a stepwise estimation process, with risk factors as the dependent variable and age, sex, BMI, smoking status, family history of respiratory disease, and community district as a fixed covariate. Multivariate analysis of variance was used to evaluate lung function, with sex, smoking status, family history of respiratory disease, distance from residence, and location of outdoor activities to the nearest busy road as independent indices, age, and height as covariates, and lung function values as dependent variables. All p-values were double-sided, with a p-value of < 0.05 indicating statistical significance.

Results

Analysis of detection rate and risk factors in patients with COPD

Of the 1,490 participants in this study, 1,460 completed the questionnaire and spirometry, and 292 individuals were diagnosed with COPD, with a prevalence of 20% (Figure 2). Of the 1,460 participants, 638 were men, among whom 38.1% had COPD; the adjusted odds ratio (OR) for the male sex was 3.47 (95% confidence interval [CI]: 2.10–5.74, $p < 0.001$), with the female sex as reference. With increasing age, the prevalence of COPD increased in the age groups 40–49 (1.4%), 40–59 (7.1%), 60–69 (21.7%), and ≥70 (33.3%) years, with the age group of 40–49 years as a reference; the adjusted ORs showed the same tendency (OR 2.83, 95% CI: 0.35–22.85, $p = 0.329$; OR 8.60, 95% CI: 1.11–66.69, $p = 0.039$; OR 20.14, 95% CI: 2.59–156.85, $p = 0.004$) in the age groups 40–59, 60–69, and ≥70 years, respectively (Table 1).

The detection rates of COPD among never, former, and current smokers were 7.6, 44.4, and 28.2%, respectively. Compared with never smokers, the adjusted ORs of former and current smokers were 2.84 (95% CI: 1.55–5.21, $p = 0.001$) and 1.54 (95% CI: 0.54–4.08, $p = 0.388$), respectively. We also analyzed the smoking index, divided into four groups, as shown in Table 1. The detection rate of COPD increased with a higher smoking index, with rates of 10.3, 39.3, 50.0, and 58.0% in the groups 0–15, 15–29.9, 30–44.9, and more than 45 pack-years, respectively. With 0–15 pack-years as a reference, the adjusted OR ratios of the other three groups were 1.36 (95% CI: 0.72–2.57, $p = 0.336$), 2.34 (95% CI: 1.24–4.42, $p = 0.009$), and 2.42 (95% CI: 1.27–4.63, $p = 0.007$), respectively.

BMI has an important role in COPD, and we found that the lower the BMI, the higher the incidence of COPD, with 28.1, 22.7, 16.9, and 12.4% in participants with BMIs 0–18.5, 18.5–24.9, 25–30, and >30 kg/m^2, respectively. With BMI >30 kg/m^2 as a reference, the adjusted ORs for BMI 0–18.5, 18.5–24.9, and 25–30 kg/m^2 were 2.73 (95% CI: 1.08–6.93, $p = 0.034$), 2.69 (95% CI: 1.46–4.97 $p = 0.002$), and 1.52 (95% CI: 0.80–2.92, $p = 0.203$), respectively.

Family history of respiratory disease is a risk factor for COPD. Participants with a family member with a respiratory disease, such as asthma or chronic bronchitis, had a higher prevalence of COPD than their counterparts with such a family history (27.6 vs. 17.1%, $p < 0.001$). The adjusted OR for individuals with a family history of respiratory diseases was 2.93 (95% CI: 2.03–4.23, $p < 0.001$).

We divided the distance from the participant's residence to the nearest busy road into three groups. The incidence rates of COPD by distance were 20.6, 21.2, and 14.8% among participants who lived <50 meters, 50–199 meters, and ≥200 meters from a busy road, respectively. Adjusted ORs were 1.06 (95% CI: 0.70–1.61, $p = 0.787$) and 1.33 (95% CI: 0.88–1.99, $p = 0.175$) in the groups <50 meters and 50–199 meters, respectively, with ≥200 meters as the reference. Similarly,

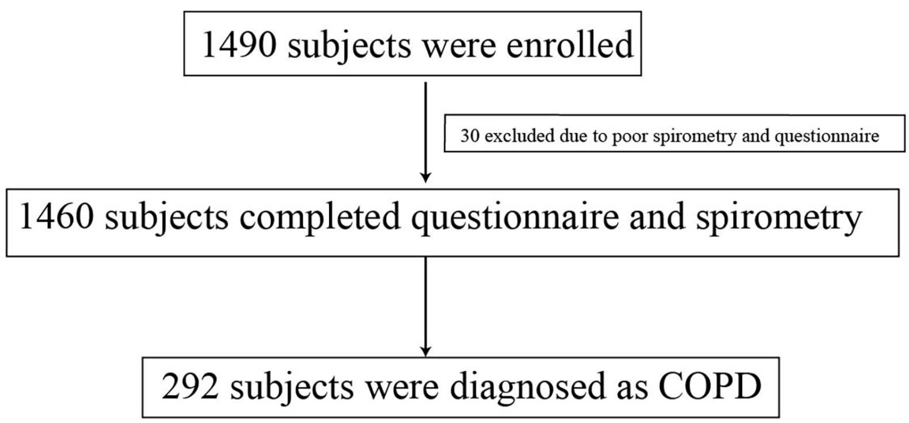

FIGURE 2
Flow chart. COPD, chronic obstructive pulmonary disease.

TABLE 1 Clinical characteristics and risk factors in patients with COPD.

	N	COPD		OR (95% *CI*)	*P*-values	Adjusted OR (95% *CI*)	Adjusted *P* values
		n	%				
Gender					<0.001		<0.001
Male	638	243	38.1%	9.71 (6.98–13.50)		3.47 (2.10–5.74)	
Female	822	49	6.0%	1.00 (reference)		1.00 (reference)	
Age, yrs					<0.001		<0.001
40–49	72	1	1.4%	1.00 (reference)		1.00 (reference)	
40–59	396	28	7.1%	5.40 (0.72–40.35)	0.100	2.83 (0.35–22.85)	0.329
60–69	577	125	21.7%	19.64 (2.70–142.73)	0.003	8.60 (1.11–66.69)	0.039
≥70	415	138	33.3%	35.37 (4.86–257.28)	<0.001	20.14 (2.59–156.85)	0.004
Smoking status					<0.001		0.002
Never smokers	955	73	7.6%	1.00 (reference)		1.00 (reference)	
Former smokers	441	196	44.4%	9.67 (7.13-13.10)	<0.001	2.84 (1.55-5.21)	0.001
current smokers	39	11	28.2%	4.75 (2.27-9.92)	<0.001	1.54 (0.58-4.08)	0.388
Smoking index, pack-years					<0.001		0.015
<15	1,070	110	10.3%	1.00 (reference)		1.00 (reference)	
15–29.9	117	46	39.3%	5.65 (3.72–8.61)	<0.001	1.36 (0.72–2.57)	0.336
30–44.9	112	56	50.0%	8.73 (5.74–13.28)	<0.001	2.34 (1.24–4.42)	0.009
≥45	100	58	58.0%	12.05 (7.74–18.78)	<0.001	2.42 (1.27–4.63)	0.007
BMI, kg/m^2					0.002		0.001
<18.5	64	18	28.1%	2.76 (1.35–5.66)	0.006	2.73 (1.08–6.93)	0.034
18.5–24.9	752	171	22.7%	2.08 (1.26–3.42)	0.004	2.69 (1.46–4.97)	0.002
25–30	479	81	16.9%	1.44 (0.85–2.43)	0.178	1.52 (0.80–2.92)	0.203
≥30	161	20	12.4%	1.00 (reference)		1.00 (reference)	
Whether the family has respiratory diseases					<0.001		<0.001
No	1,045	179	17.1%	1.00 (reference)		1.00 (reference)	
Yes	406	112	27.6%	1.84 (1.41–2.42)		2.93 (2.03–4.23)	
Distance from living place to closest busy roads					0.016		0.367
<50 m	383	79	20.6%	1.49 (1.07–2.09)	0.020	1.06 (0.70–1.61)	0.787
50–199 m	425	90	21.2%	1.54 (1.11–2.14)	0.009	1.33 (0.88–1.99)	0.175
≥200 m	580	86	14.8%	1.00 (reference)		1.00 (reference)	
Outdoor activities away from the busy roads					<0.001		0.008
<50 m	282	67	23.8%	1.96 (1.39–2.77)	<0.001	1.54 (1.01–2.36)	0.047
50–199 m	355	87	24.5%	2.04 (1.48–2.82)	<0.001	1.84 (1.23–2.76)	0.003
≥200 m	737	101	13.7%	1.00 (reference)		1.00 (reference)	

ORs were adjusted by confounding factors including age, sex, BMI, smoking status, family history of respiratory disease and community district. BMI, body mass index; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

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TABLE 2 Multivariate analysis of variance in pulmonary function.

	Pre-FVC¶ ($n = 1,457$, L)	Pre-FEV1¶ ($n = 1,457$, L)	Pre-FEV1/FVC¶ ($n = 1,457$, %)	Post-FVC♮ ($n = 1,420$, L)	Post-FEV1♮ ($n = 1,420$, L)	Post-FEV1/FVC♮ ($n = 1,420$, %)
Dwelling away from busy roads						
<50 m	2.81 ± 0.68	2.09 ± 0.55	74.3 ± 10.0	2.82 ± 0.68	2.15 ± 0.3	76.82 ± 10.47
50–199 m	2.74 ± 0.70	1.99 ± 0.56	73.17 ± 11.93	2.76 ± 0.70	2.07 ± 0.54	75.76 ± 12.14
≥200 m	2.65 ± 0.66	2.00 ± 0.52	75.43 ± 9.69	2.65 ± 0.63	2.06 ± 0.57	78.41 ± 9.65
P value	0.002	0.014	0.003	<0.001	0.030	0.001
Outdoor activities away from the busy roads						
<50 m	2.84 ± 0.73	2.06 ± 0.57	73.16 ± 11.03	2.85 ± 0.72	2.13 ± 0.55	75.58 ± 11.27
50–199 m	2.73 ± 0.69	1.98 ± 0.56	72.92 ± 11.67	2.77 ± 0.69	2.05 ± 0.54	75.34 ± 12.10
≥200 m	2.67 ± 0.65	2.02 ± 0.52	75.60 ± 9.67	2.67 ± 0.64	2.08 ± 0.52	78.52 ± 9.66
P value	0.007	0.018♮	<0.001	0.001	0.022♮	<0.001
Gender						
Male	3.10 ± 0.70	2.14 ± 0.65	68.7 ± 12.8	3.15 ± 0.67	2.22 ± 0.63	70.9 ± 12.9
Female	2.43 ± 0.51	1.9 ± 0.42	78.1 ± 7.0	2.41 ± 0.47	1.95 ± 0.41	81.2 ± 6.8
P value	<0.001	<0.001	<0.001	<0.00	<0.001	<0.001
Smoke						
No	3.17 ± 0.73	2.17 ± 0.62	68.1 ± 11.4	3.23 ± 0.70	2.25 ± 0.61	70.0 ± 11.6
Yes	2.62 ± 0.63	1.97 ± 0.52	75.4 ± 10.5	2.62 ± 0.61	2.03 ± 0.51	78.3 ± 10.5
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Family members have respiratory diseases						
No	2.72 ± 0.69	2.02 ± 0.55	74.6 ± 10.5	2.73 ± 0.68	2.09 ± 0.53	77.2 ± 10.6
Yes	2.72 ± 0.66	1.96 ± 0.55	72.4 ± 12.2	2.74 ± 0.67	2.03 ± 0.53	75.2 ± 12.6
P value	0.923	0.079	0.001	0.762	0.09	0.003

¶, ♮ Best value before and after bronchodilator, respectively. [#] Multivariate analysis of variance was evaluated using sex, smoking status, family history of respiratory disease, and distance from residence or outdoor activities to closest busy roads as independent indexes and with age and height as covariates. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

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in the analysis regarding the distance of outdoor activities from busy roads, the incidence rates of COPD were 23.8, 24.5, and 13.7%, with adjusted ORs of 1.54 (95% CI: 1.01–2.36, $p = 0.047$) and 1.84 (95% CI: 1.23–2.76, $p = 0.003$) for <50 meters and 50–199 meters, respectively, with ≥200 meters as reference. All OR values were statistically significant ($p < 0.05$).

To sum up, the closer the participants' residence or the location of outdoor activities is to a busy road, the higher the detection rate of COPD. Male sex, age 40–80 years, a lower BMI, smoking, and a family history of respiratory disease were risk factors for COPD.

Differences in pulmonary function according to high-risk factors

After adjusting for high-risk factors, pulmonary function values were significantly different among groups before and after bronchodilation tests. Although lung function tests are affected by various factors (sex, age, smoking status, and BMI), risk factors were used statistically as independent indexes, with age and height as covariates and lung function indicators as dependent variables, such that multivariate analysis of variance was used.

The study findings showed that the distance from participants' residence and outdoor activities to a busy road, male sex, smoking history, and family history of respiratory disease were important factors that resulted in changes in the values of FEV_1 and FVC (Table 2). The post-FEV_1 values (2.15 ± 0.3 L vs. 2.07 ± 0.54 L vs. 2.06 ± 0.57 L, $p = 0.030$) and post-FVC values (2.82 ± 0.68 L vs. 2.76 ± 0.70 L vs. 2.65 ± 0.63 L, $p < 0.001$) were higher for residence <50 meters, compared to 50–199 meters, and ≥200 meters from a busy road. Pre-FEV_1/FVC values were 74.3 ± 10.0% vs. 73.17 ± 11.93% vs. 75.43 ± 9.69%, $p = 0.003$ and post-FEV_1/FVC values were 76.82 ± 10.47% vs. 75.76 ± 12.14% vs. 78.41 ± 9.65%, $p = 0.001$ for residence <50 meters, 50–199 meters, and ≥200 meters from a busy road. The further participants engaged in outdoor activities from a busy road, the lower the values of post-FVC (2.85 ± 0.72 L vs. 2.77 ± 0.69 L vs. 2.67 ± 0.64 L, $p = 0.001$) for <50 meters, 50–199 meters, and ≥200 meters. Pre-FEV_1/FVC and post-FEV_1/FVC values were higher with a further distance of outdoor activities from the main road. As shown in Table 2, female participants had higher pre-FEV_1/FVC values (78.1 ± 7.0% vs. 68.7 ± 12.8%, $p < 0.001$) and post-FEV_1/FVC values (81.2 ± 6.8% vs. 70.9 ± 12.9%, p <0.001) than their male counterparts. Individuals with a family history of respiratory disease had lower pre-FEV_1/FVC (72.4 ± 12.2% vs. 74.6 ± 10.5%, $p = 0.001$) and post-FEV_1/FVC (75.2 ± 12.6% vs. 77.2 ± 10.6%, $p = 0.003$) values than their counterparts without such a family history.

Discussion

Our study findings indicated that respiratory health risks exist for people living and engaging in outdoor activities close to the main road. Our study used participants' residences and outdoor activities as a proxy for traffic-related air pollution exposure. Thus, participants living or participating in outdoor activities at the same distance from a busy road were estimated to have the same exposure levels. Owing to various factors related to the development of COPD, a logistic regression model was fitted, adjusting for age, sex, BMI, smoking status, smoking index, family history of respiratory disease, and distance from the home and outdoor activities to the closest busy road. We found that the distance of outdoor activities from the main road was an independent risk factor for developing COPD, with an adverse influence on lung function.

In our study, we recruited community residents who lived in central Guangzhou and were aged 40–80 years. The detection rate of COPD was 20%, higher than that in a study by Wang et al. (15), who estimated that the prevalence of COPD was 13.7% in the same age group during 2012–2015. The difference in the findings may be due to different regions and insufficient samples. We found that male sex, older individuals with a lower BMI, a smoking history, and a family history of respiratory diseases (chronic bronchitis, emphysema, asthma, and COPD among immediate family members) were more likely to have COPD. Our research showed a higher risk of COPD among ex-smokers than current smokers, which is similar to a large population-based survey that also found a higher prevalence and ORs for COPD among ex-smokers than current smokers (16). This could be related to lifetime exposure to smoking and the longer lifespan of ex-smokers. Smokers frequently lack information about smoking cessation and the health risks associated with smoking, and as a result, they do not quit smoking unless they develop severe diseases (16).

After adjusting for sex, age, BMI, smoking status, and family history of respiratory disease, the distance of outdoor activities from busy roads was an independent risk factor for COPD. The distance from the participant's residence to a busy road was not a significant risk factor for COPD development after adjusting the factors above. However, we found that the closer the residence and outdoor activities were to busy roads, the higher the COPD detection rates and ORs. Living near dense traffic could increase exposure to traffic-related air pollution, including combustion products, nitrogen dioxide, and ultrafine PM (17, 18). In the Canadian Census Health and Environment Cohort (CanCHEC) study during 1991–2001, increased exposure to local roads and living near a major highway were linked to increased mortality owing to respiratory diseases, even after adjusting for air pollution concentrations (19). However, the odds ratio of developing COPD for living <50 meters from a busy road was lower than that for living at a 50–199-meter distance in our research. This may be because residents in the <50 meters group used more ways to decrease the influence of air pollution, such as by closing windows. People living further from the main road might not implement such protective measures, resulting in greater exposure to air pollution. Other possible causes for our findings must be further explored. Nuvolone et al. found that the highest values of lung function were observed in the intermediate group (100–250 meters) than in the 100-meter and 250–800-meter groups, which suggests that respiratory health impairment owing to traffic-related air pollution occurs at a distance over 100 meters (20) vs. other studies showing negative effects of living near a busy road up to a distance of 500 meters (9).

The World Health Organization estimates that 22% of global mortality and disability can be attributed to environmental causes. Air pollution contributes to approximately 9% of COPD cases (21). Traffic-related air pollution mainly comes from motor vehicle exhaust and road dust (22). As a megacity in China, Guangzhou currently has more than 2 million cars. With the increasing number of vehicles, the traffic volume on main roads in urban areas is large, and congestion during peak hours is serious. As vehicle emissions increase, the concentration of incomplete combustion materials also increases (23). Research on the mechanism of air pollutants such as PM, nitrogen dioxide, and ozone in the development and exacerbation of asthma showed that air pollutants are associated with the induction of both eosinophilic and neutrophilic inflammation driven by stimulation of the airway epithelium and increased pro-inflammatory cytokine production, oxidative stress, and DNA methylation changes (24). Higher ambient air pollution and exposure to nitrogen oxides and PM can result in respiratory mortality and a decline in lung function (25), which can lead to the development of COPD. In the 1970s, Fletcher found that the decline of lung function, especially FEV_1, could be sustained over a lifetime. In vulnerable people, smoking leads to a risk of irreversible obstructive changes because tobacco smoke may cause exposure to PM (26). Schikwski et al. found that chronic exposure to air pollution and living close to a major road increased the risk of developing COPD and had a harmful effect on lung function in women (27). Téllez-Rojo et al. found that an increase of 10 $\mu g/m^3$ in PM_{10} was related to a 4.1% increase in COPD deaths (28). A review found that every 5-$\mu g/m^3$ increment in $PM_{2.5}$ was associated with a decrease of 1.18% for FVC, 1.46% for FEV_1, 1.65% for maximum mid-expiratory flow (MMEF), and 0.21% for FEV_1/FVC; the interpretation of the findings was that long-term exposure to $PM_{2.5}$ would result in faster lung function decline, similar to the findings of a longitudinal cohort study conducted in Taiwan (29). Kwon et al. reported that long-term exposure to PM_{10} was related to both spirometry values and imaging phenotypes in COPD. With an annual 4.4-μg/m3 exposure to PM_{10}, there was an interquartile range difference of 0.13 L lower FVC (30). It is difficult to calculate the amount of traffic-related air pollution exposure during exercise owing to the lack of a complex model to assess multiple and variable exposures to air pollutants and pollutant concentrations (31). We found that the closer to busy road participants engaged in outdoor activities, the poorer their lung function. For example, lung function values of FEV_1/FVC were lower, and the incidence rate of COPD was higher with outdoor activities carried out closer to the main road, suggesting that lung function decline may be related to air pollution from traffic. In a large cohort study in the United Kingdom, the effect of declining lung function was significant even at very low levels of ambient PM2.5. Air pollution had a larger impact on lung function decline in male individuals, those from low-income households, those with occupations in which they were exposed to air pollution, and individuals with obesity (25); these findings were similar to our study's findings. However, unlike other research (20), we did not adjust for occupational exposure as a confounding factor because there was no significant difference in occupational exposure before adjusting for confounders (data not shown).

There are several strengths in our study. This observational study enrolled a large sample in the Guangdong district. This was the first study to use distance from a busy road as an indicator of traffic-related air pollution as an important risk factor for COPD in communities in Guangzhou. In this study, the extent of individual air pollution exposure was measured using the distance of participants' residences and the location of outdoor activities from busy roads. We described the relationship between traffic-related air pollution and COPD in some urban areas of Guangdong Province. Additionally, the findings of this study were consistent with those of other studies in that we identified male sex, smoking, older age, low BMI, and a family history of respiratory disease as risk factors for developing COPD (32).

Despite the strengths, this study also has some limitations. First, some questionnaires had missing responses, which could introduce bias. Second, only urban residents participated in this study; more participants who lived in rural areas were finally enrolled. Third, we only queried the distance from participants' residences and the location of outdoor activities to a busy road; we did not measure the precise distance. Additionally, we did not calculate or evaluate the composition or concentration of air pollutants because we could not obtain real-time air pollution data. Finally, we only used cross-sectional data in this study. Further follow-up studies are expected to analyze the change in lung function among different groups based on the distance of their residence or outdoor activities from main roads.

Conclusion

The distance of outdoor activities from main roads was a risk factor in the development of COPD and had a negative effect on lung function, suggesting that traffic-related environmental pollution is associated with respiratory health. It is important to take steps to reduce vehicle exhaust emissions and traffic-related air pollution to enhance people's health.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University approved this study protocol (2013-37). All subjects signed informed consent. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PR, YZ, BL, JZ, SL, HP, and JP designed the project and planned the statistical analysis. JZ, SL, JP, and ZW drafted and revised the paper. JZ, SL, HP, ZD, CL, NL, LT, JX, and JL collected and monitored data collection. All authors approved the final draft of the manuscript for publication.

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Conflict of interest

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

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EDITED BY
Zhiming Yang,
University of Science and Technology Beijing, China

REVIEWED BY
Zhiwei Gao,
Memorial University of Newfoundland, Canada
Jitian Zhang,
Shandong Provincial Hospital Affiliated to Shandong First Medical University, China

*CORRESPONDENCE
Yuxiang Zhi
✉ yuxiang_zhi@126.com

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Association between exposure to greenness and atopic march in children and adults—A systematic review and meta-analysis

Xue Wang, Nan Zhou and Yuxiang Zhi*

Department of Allergy and Clinical Immunology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, National Clinical Research Center for Immunologic Diseases, Beijing, China

Introduction: Allergic diseases are a global public health problem. Food allergy, atopic dermatitis (AD), allergic rhinoconjunctivitis, allergic rhinitis (AR) and asthma represent the natural course of allergic diseases, also known as the "atopic march". In recent years, a large number of studies have been published on the association between greenness exposure and allergic diseases. However, systematic reviews on the association between greenness exposure and multiple allergic diseases or atopic march are lacking.

Methods: In this study, PubMed, EMBASE, ISI Web of Science, and Scopus were systematically searched. Meta-analyses were performed if at least three studies reported risk estimates for the same outcome and exposure measures.

Results: Of 2355 records, 48 studies were included for qualitative review. Five birth cohort studies, five cross-sectional studies, and one case-control study were included for asthma meta-analysis, respectively. Four birth cohort studies were included for AR meta-analysis. Our results support that exposure to a greener environment at birth reduces the risk of asthma and AR in childhood. In addition, higher greenness exposure was associated with decreased odds of current asthma in children.

Discussion: There was a large heterogeneity among the included studies and most of them did not specify the vegetation type and causative allergens. Therefore the study results need to be further validated. In addition, a small number of studies evaluated the association between greenness and food allergy, AD and allergic rhinoconjunctivitis. More research is needed to strengthen our understanding of the association between greenness and allergic diseases.

KEYWORDS
allergic disease, atopic march, greenness exposure, NDVI, asthma

Introduction

Allergic diseases have become a global public health problem (1). Asthma, allergic rhinitis (AR), atopic dermatitis (AD), and food allergy have been reported to affect 30% of the population and nearly 80% of households (1). Allergic diseases have very complex pathophysiological mechanisms and a strong genetic component (2), but genetic changes alone cannot explain the rapid increase in prevalence over the last 50 years (3, 4). A large number of epidemiological studies have demonstrated complex gene-environment interactions, highlighting environmental exposure as an important factor influencing the phenotype of allergic diseases (3, 5). Increased exposure to greenness is one such factor.

Greenness is a combination of plant species and the ground cover they provide. It can be either scheduled (e.g., gardens and parks) or unscheduled (e.g., existing wooded areas and prairies) (6). In recent years, greenness has been shown to improve physical activity (7), mental health (8), birth outcomes (9), cardiovascular disease (10), obesity (11), diabetes (12), and cancer (13). Although not all studies show consistent findings, overall, the available studies support the benefits of greenness for human health. It is generally accepted that greenness may affect health by providing a greater number and diversity of beneficial microorganisms (14), which contribute to relieving mental and physiologic stress, promoting exercise and socialization, as well as reducing exposures to heat, noise, and air pollution (15).

In recent years, a number of studies on the effects of greenness on several allergic diseases have been published, indicating a growing interest in greenness and allergies. However, research findings are highly inconsistent, even within the same study. Fuertes et al. reported that greenness within the 500 m buffer around the home address (accessible within a short walking time) was a risk factor for AR at age 6–8 years in Swedish (BAMSE) and German (GINI/LISA South), but was a protective factor in German (GINI/ LISA North) and Dutch (PIAMA) (16). Rufo et al. (17) reported that living closer to a green environment at birth had a protective effect on allergic diseases and asthma at age 7 years, while this effect was not significant at age 4 years. Sbihi et al. (18) reported that perinatal exposure to greenness within a 100 m buffer around the home address (the most accessible greenness) was associated with a reduced incidence of asthma. However, Andrusaityte et al. (19) reported that increased greenness within a 100 m buffer around the home address significantly increased the risk of asthma.

A meta-analysis conducted by Lambert et al. (20) reviewed the association between greenness and allergic respiratory diseases in children and adolescents. They reported no significant overall association between residential greenness and asthma or AR. Since this review, a large number of relevant studies have been published, which have enriched the understanding of the relationship between greenness, asthma, and AR. In addition, recent studies have begun to focus on the effects of greenness exposure on AD, food allergy, and allergic rhinoconjunctivitis. These allergic diseases may occur in a chronological order: from AD and food allergy in infancy to asthma and AR in childhood. This phenomenon is known as "atopic march." To our knowledge, there is no meta-analysis of the most recent evidence on the association between greenness, various allergic outcomes, and atopic march. Therefore, the aim of this study was to provide a systematic review of the available evidence to elucidate the association between greenness exposure and allergic diseases based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement (Supplementary Table S1). This may help urban planners and policy makers to better plan urban layouts and thus reduce the risk of allergic diseases.

Methods

Literature search strategy

The PubMed (https://pubmed.ncbi.nlm.nih.gov/), ISI Web of Science (http://www.webofknowledge.com), EMBASE (https://www.embase.com), and Scopus (https://www.scopus.com/) databases were systematically searched for English language, peer-reviewed studies published up to 30 November 2022. Unpublished and ongoing studies were not considered in this review. We used a combination of terms concerning greenness exposure ("greenspace," "green space," "greenness," "greenery," "grassland," "grass land," "green land," "grass cover," "natural area," and "vegetation") and allergic outcomes ("allergy," "allergic disease," "asthma," "hay fever," "allergic rhinitis," "allergic respiratory diseases," "eczema," "atopic dermatitis," "food allergy," and "atopic march") for the search (Supplementary Table S2). No filters were applied to the study designs. The reference lists of the included studies were manually searched to identify any remaining studies.

Inclusion and exclusion criteria

Original studies assessing the relationship between greenness and allergic disease were included. For eligible studies, the definition of allergic outcomes should be clearly stated (medical records, structured interviews, or self-reported physician-diagnosed allergic outcomes). The assessment of greenness exposure should be objective. Assessment methods of greenness include, but are not limited to, the normalized difference vegetation index (NDVI), light detection and ranging (LiDAR) imagery, and distance to the nearest greenness. Eligible articles are also required to report the association of greenness with allergic disease. Odds ratios (OR), relative risks (RR), or hazard ratios (HR), and their 95% confidence intervals (CI) should be provided. Studies with only allergic symptoms (e.g., wheezing, dry cough, and symptom scores), lung function, and sensitization (e.g., immunoglobulin E antibody levels and skin prick tests) as outcomes were not considered in this review.

Study selection

All potentially relevant articles were exported to EndNote 20.2 (Clarivate Analytics, Philadelphia, PA, USA). Duplicate articles were removed. Titles and abstracts were screened to eliminate articles that were obviously irrelevant. The full text of relevant articles was downloaded and read in depth. All processes were performed independently by two authors (XW and NZ). Disagreements were resolved through discussion with the third author (YZ).

Data extraction

For each eligible study, the required information was extracted independently by two authors (XW and NZ). Discrepancies were resolved by discussion with the third author (YZ). The following information was extracted: authors, publication year, study period, study location, study design, participant demographics, sample size, assessment of greenness exposure, definition of allergic outcomes, covariates adjusted for in the statistical model, and effect estimates (OR, RR, or HR, and their 95% CI). Effect estimates were extracted in the "main model" or "fully variable adjusted model" (21). If the results in the original study were presented as figures, Engauge Digitizer 12.1 was used to extract the data.

Quality assessment of included studies

The quality of each eligible study was assessed independently by two authors (XW and NZ). Discrepancies were resolved by discussion with the third author (YZ). The Newcastle-Ottawa scale (NOS) was employed to assess the quality of cohort and case-control studies (22). The NOS contains eight items grouped into three dimensions. Each item is scored with 0 or 1 star, except for one item (comparability of cohorts on the basis of the design or analysis) that is scored with 0 to 2 stars, resulting in a maximum score of 9 stars. We classified studies with scores >7 stars as "high quality"; otherwise, the study was classified as "low quality." The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to evaluate the quality of cross-sectional studies (23). This tool consists of 14 questions, but only seven questions applicable to cross-sectional studies were used (24). Studies were rated as poor, fair, or good; if the study did not adjust for any variables, it was rated as poor.

Meta-analysis methods

Given that multiple allergic diseases were included as outcomes in this review, three studies measuring the same outcome with the same exposure was selected as thresholds in order to decide whether to perform a meta-analysis on a particular outcome. That is, meta-analysis was performed when the number of studies meeting the following conditions was greater than or equal to three: (1) same assessment of greenness exposure, including measurement methods, measurement locations (residential, school), and time windows (for birth cohort: at birth/perinatal or lifetime); (2) same outcome definitions, including ever asthma, current asthma, AR, allergic rhinoconjunctivitis, AD, and food allergy; and (3) similar age of participants, including minors [preschoolers (<5 years old) and post-schoolers (5–18 years old) if a sufficient number of studies were available], and adults (>18 years old). To ensure consistency in the interpretation of the original study results, only studies that used NDVI as a measure of greenness were included in the meta-analysis, as NDVI was used in the majority of the included studies.

Based on the results of the included studies, two independent types of meta-analyses were carried out. In the dose-response meta-analysis, we used adjusted OR (95% CI) per 0.1 unit increase in greenness exposure measured by NDVI. In the categorical meta-analysis, we compared the highest tertile or quartile (Q3 or Q4) with the lowest (Q1). All studies included in the meta-analysis reported OR. Therefore, OR was used as the measure of association across all studies.

Fixed-effect and random-effect models were used to synthesize the associations between greenness exposures and allergic diseases. The between-study heterogeneity and between-study variance were assessed using I^2 and τ^2, respectively. Egger's test and Begg's test were used to assess the publication bias. In addition, since different buffers represent different accessibility to greenness, a 100 m buffer represents the most accessible range of greenness, while a 500 m buffer represents the availability of greenness within a relatively short walking time (i.e., <15 mins). Therefore, subgroup analyses were performed based on the buffer zones. The results of 100 m, more than 100 m and <500 m, 500 m, and more than 500 m buffers were combined, respectively. To test the robustness of the result, sensitivity analyses were performed by excluding studies one by one. All analyses were performed with R software (R Foundation for Statistical Computing), version 3.5.0. A two-sided test was used, and $p < 0.05$ was considered as statistically significant.

Results

The electronic search strategy generated 2,355 records, which were screened for eligibility based on title/abstract after de-duplication. 80 potentially eligible articles were selected for full-text review. Of these, 32 articles were excluded because they did not assess the relationship between greenness exposure and allergic disease. Finally, 48 articles fulfilled the inclusion criteria and were included in the qualitative synthesis (Figure 1).

Study characteristics

Table 1 summarizes the characteristics of the 48 studies included in the review. More than half of the studies ($n = 25$) were published within the past 3 years and almost all ($n = 47$)

were published within the past 10 years, highlighting the growing interest in the association between greenness and allergic diseases. Of the 48 studies, 47 were conducted in more than 20 countries and one study was conducted globally, reflecting the association of greenness with allergic disease in a global context. There were 19 cohort or longitudinal studies, 18 cross-sectional studies, 7 ecological studies, and 4 case-control studies. Supplementary Table S3 shows more detailed information for each study, including exposure definitions, outcome definitions, statistical models, estimates, and adjusted confounders.

Study quality

In general, most cohort and cross-sectional studies were "high quality" or "good" (Supplementary Tables S4, S5). However, of the case-control studies, only one was rated as "high quality." The other three case-control studies were rated 5 or 6 due to self-reported case definitions, hospital controls, and lack of comparability (Supplementary Table S6). A birth cohort study in Chinese toddlers identified allergic diseases based on medical records at age 2 years (54). However, AR usually requires several years of allergen exposure to develop. Accordingly, it is uncommon in children under 2 years of age. We therefore consider that the follow-up period of this study was not long enough for outcomes to occur (Supplementary Table S4).

Bias due to outcome assessment

The definition of outcomes was based primarily on self/parent-reported questionnaires, hospital records, and medication prescriptions. Asthma was the most frequently measured clinical outcomes and were reported by 38 studies. Four studies simultaneously assessed the association between greenness, ever asthma, and current asthma (35, 48, 58, 67). One study used eosinophilic asthma as the outcome, defined as participants reporting asthma-related medication use and elevated eosinophil counts to at least 150 cells per µl (66).

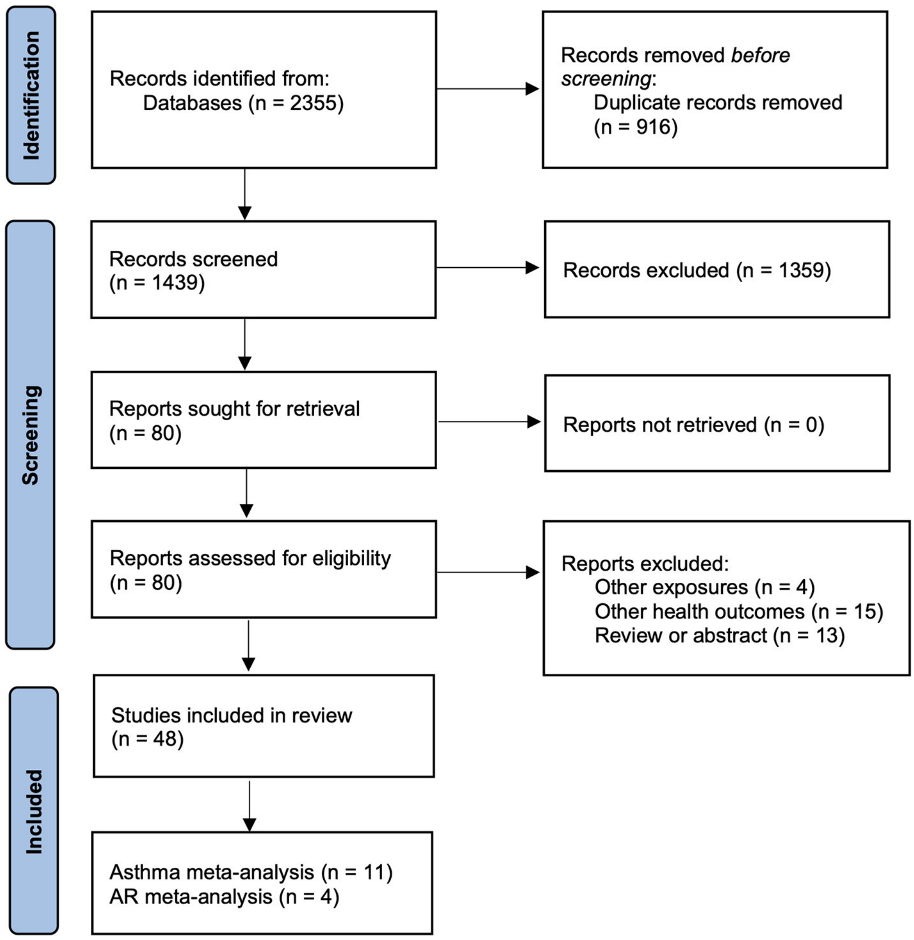

FIGURE 1
PRISMA flowchart for search strategy.

TABLE 1 Characteristics of the included studies.

References	Years of study	Location	Study design	Age of participants	Sample size (n)	Exposure measure	Allergic diseases assessed				
							Asthma	AR	Allergic rhino conjunctivitis	AD	Food allergy
Alcock et al. (25)	1997–2012	England	Cross-sectional	No age limit	26,455	Generalized land use database; ArcGIS	✓				
Andrusaityte et al. (19)	2012–2013	Lithuania	Nested case-control	4–6	1,489	NDVI and distance to the nearest city park	✓				
Brokamp et al. (26)	Ongoing	The United States	Birth cohort	Children born in 2001–2003	762	NDVI	✓				
Cilluffo et al. (27)	2015–2018	Italy	Longitudinal study	5–16	179	NDVI	✓				
Dadvand et al. (28)	2006	Spain	Cross-sectional	9–12	3,178	NDVI and residential proximity to green spaces	✓		✓		
De Roos et al. (29)	2011–2016	The United States	Case-control	<18	23,382	NDVI, LiDAR	✓				
DePriest et al. (30)	–	The United States	Cross-sectional	<18	196	NDVI	✓				
Dong et al. (31)	–	Canada	Cross-sectional	All ages		LiDAR	✓				
Donovan et al. (32)	1998–2016	New Zealand	Birth cohort	Children born in 1998 and followed up until 2016	49,956	NDVI; the total number of natural land-cover types	✓				
Donovan et al. (33)	–	The United States	Ecological	>18	498 cities, 26,367 tracts	NDVI; plant diversity	✓				
Douglas et al. (34)	–	The United States	Ecological	No age limit	2,347 census tracts	Public parks and open space (PPOS)	✓				
Dzhambov et al. (35)	2004–2005	Austria and Italy	Cross-sectional	8–12	1,251	NDVI, tree canopy cover, and agricultural cover	✓	✓		✓	
Eldeirawi et al. (36)	2004–2005	The United States	Cross-sectional	8–18	1,915	NDVI	✓				
Fuertes et al. (37)	GINIplus: 1995; LISAplus: 1997	Germany	Birth cohort	–	5,803	NDVI		✓			
Fuertes et al. (38)	2000–2003	Global	Global ecologic analysis	6–7; 13–14	1,002,617	NDVI		✓			

(Continued)

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TABLE 1 (Continued)

References	Years of study	Location	Study design	Age of participants	Sample size (n)	Exposure measure	Allergic diseases assessed				
							Asthma	AR	Allergic rhino conjunctivitis	AD	Food allergy
Fuertes et al. (16)	Recruited in 1990–1997	Sweden, Australia, Netherlands, Canada, Germany	Birth cohort	6–8; 10–12	13,016	NDVI		✓			
Gernes et al. (39)	2001–2003	The United States	Birth cohort	–	478	NDVI and LiDAR		✓			
Hartley et al. (40)	2001–2003	The United States	Birth cohort	–	617	NDVI	✓				
Hsieh et al. (41)	2001–2013	Taiwan, China	Case-control	Younger than 18 years	7,040	NDVI	✓				
Hu et al. (42)	2019	China	Cross-sectional	3–12	16,605	NDVI and EVI	✓				
Idani et al. (43)	2017–2018	Iran	Cross-sectional	20–65	5,672	Questionnaire	✓				
Ihlebæk et al. (44)	2000–2001	Norway	Cross-sectional	29, 30, 39 40, 44, 45, 58, 59 60	8,638	Vegetation cover greenness (VCG) and land use greenness (LUG)	✓				
Kim et al. (45)	2009	Korea	Cross-sectional	49.37 ± 16.24	219,298	Green areas		✓		✓	
Kim and Ahn (46)	2011–2013	The United States	Ecological			LiDAR	✓				
Kuiper et al. (47)	2013–2015	Northern Europe, Spain, Australia	Generation study	Parents: mean age 35; offspring: mean age 6	1,106 parents with 1,949 offspring	NDVI	✓	✓			
Kuiper et al. (48)	2013–2015	Norway, Sweden	Case-control	Mean age 28	3,428	NDVI	✓	✓			

(Continued)

TABLE 1 (Continued)

References	Years of study	Location	Study design	Age of participants	Sample size (n)	Exposure measure	Allergic diseases assessed				
							Asthma	AR	Allergic rhino conjunctivitis	AD	Food allergy
Kwon et al. (49)	2014	Korea	Cross-sectional	>20	10.5 million	NDVI		✓			
Lee et al. (50)	2006–2010	Korea	Birth cohort	Outcomes were evaluated at 6 months	659	Land cover classification maps				✓	
Lee et al. (51)	2003–2011	Taiwan, China	Cohort study	Children diagnosed with AR at age 4 were followed up to age 12	11,281	NDVI		✓			
Lee et al. (52)	2010–2014	The United States	Ecological	Aged 19 years old or below	763 census tracts	Land cover database	✓				
Li et al. (53)	2014–2015	China	Cross-sectional	Mostly between the ages of 12 and 15	5,643	NDVI and distance to the nearest park	✓	✓		✓	
Lin et al. (54)	Baseline (2017–2018)	China	Birth cohort	2	522 mother–child pairs	NDVI, enhanced vegetation index (EVI)		✓		✓	✓
Lovasi et al. (55)	–	The United States	Cross-sectional	<15	Unknown	Street tree density	✓				
Lovasi et al. (56)	–	The United States	Birth cohort	Children born in 1998–2006	549	LiDAR	✓	✓			
Markevych et al. (57)	Neonates were recruited between 1997 and 1999	Germany	Birth cohort	2–15	631	NDVI	✓	✓			✓
Parmes et al. (58)	1991–2010	Italy, France, Slovenia and Poland	Ecological	3–14	8,063	Land cover classification maps	✓	✓		✓	

(Continued)

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TABLE 1 (Continued)

References	Years of study	Location	Study design	Age of participants	Sample size (n)	Exposure measure	Allergic diseases assessed				
							Asthma	AR	Allergic rhino conjunctivitis	AD	Food allergy
Peters et al. (59)	2007–2011	Australia	Wave 1 of the population-based HealthNuts study	12-month-old	5,276	NDVI					✓
Pilat et al. (60)	2005–2006	The United States	Ecological	<17	–	NDVI	✓				
Putra et al. (61)	Recruited in 2004 and then followed-up biennially	Australia	Longitudinal study	2–15	9,589	Perceptions of green space quality	✓				
Cavaleiro Rufo et al. (17)	2005–2012	Portugal	Birth cohort	7	1,050	NDVI and SRI	✓	✓		✓	
Sbihi et al. (18)	1999–2009	Canada	Birth cohort	0–5; 6–10	51,857	NDVI	✓				
Sbihi et al. (62)	1999–2009	Canada	Birth cohort	0–10	65,254	NDVI	✓				
Squillacioti et al. (63)	2002–2010	Italy	Cross-sectional	10–13	126	NDVI	✓				
Tischer et al. (64)	Ongoing	Spain	Birth cohort	4	2,472	NDVI	✓	✓			
Winnicki et al. (65)	–	Denmark	Cohort study	Individuals born 1995–2015	40,249	Percentage greenspace	✓				
Wu et al. (66)	2006–2010	UK	Cross-sectional	37–73	351,717	NDVI	✓				
Yu et al. (67)	2009–2013	China	Cross-sectional	2–17	59,754	Green view index (GVI) and NDVI	✓				
Zeng et al. (68)	2012–2013	China	Cross-sectional	10.3 ± 3.6	59,754	NDVI, SAVI	✓				

Five studies reported the association between greenness and asthma emergency department visits or hospitalization rates (25, 34, 46, 52, 55). AR was reported by 17 studies. One study classified AR as intermittent and persistent rhinitis (38). Two studies used the number of clinic visits for AR as the outcome (49, 51). AD, allergic rhinoconjunctivitis, and food allergy were reported in 7, 1 and 2 studies, respectively.

Bias due to exposure assessment

The reviewed studies all used different methods to assess participants' exposure to greenness, including normalized difference vegetation index (NDVI), soil-adjusted vegetation index (SAVI) (68), green view index (GVI) (67), light detection and ranging (LiDAR) imagery (29, 31, 39, 46, 56), land cover classification maps (50, 58), and questionnaire (43), with varying buffer levels. The most common method is NDVI, which was used in 33 studies. NDVI is a satellite image-based vegetation index provided by the National Aeronautics and Space Administration (NASA) to measure greenness at the regional level (51), and has been validated for use in epidemiological studies (69). NDVI is calculated from the visible (red) and near-infrared light reflected by vegetation. NDVI values range between −1 and 1, with higher values corresponding to a higher density of healthy vegetation and lower values corresponding to barren rocky, sandy or snowy areas. Most studies used NDVI to assess greenness exposures at the individual-level, including residential greenness (16–19, 26–28, 35–37, 39–42, 47, 48, 51, 53, 54, 57, 59, 62–64, 66) and school greenness exposure (35, 67, 68). Studies have also evaluated NDVI values at the district-level and country-level (38, 49, 60). For birth cohorts, different exposure time windows (e.g., at birth, a certain age range, and lifetime) also contributed to the heterogeneity of studies. In addition, seasonal differences may have a significant influence on NDVI (20). Most studies used images taken during the most vegetated season of the year (spring/summer) to calculate NDVI, which was able to maximize the spatial contrast of greenness (16, 17, 19, 26, 28, 35–37, 39, 40, 47, 48, 57, 63, 67, 68). Two studies used images from spring, summer, fall and winter to calculate NDVI (51, 53). Some studies also used annual or seasonal median NDVI values to represent greenness (29, 42, 59). Overall, the diversity of exposure measurement makes it difficult to compare the effect estimates reported in these studies.

Association between greenness exposure and asthma

Results of five cross-sectional studies and one case-control study reporting on the association between per IQR increase in NDVI and asthma were considered for quantitative synthesis. Two studies included both ever asthma and current asthma as outcomes (35, 53), two studies used ever asthma as an outcome (19, 36), and two study used current asthma as an outcome (28, 42). Quantitative analysis was performed separately for both outcomes. Figure 2 shows that an IQR increase in NDVI was associated with decreased odds of current asthma, with a pooled OR of 0.94 (95% CI: 0.88–1.00). However, no significant association was found between residential greenness exposure and ever asthma, regardless of buffer distance. The pooled OR of ever asthma per IQR increase in NDVI were 1.00 (95% CI: 0.93–1.08, Supplementary Figure S1). Sensitivity analyses yielded consistent results (Supplementary Figures S2, S3).

Five birth cohort studies exploring the association between residential greenness exposure at birth and subsequent childhood asthma risk were considered for quantitative synthesis (17, 18, 26, 32, 40). The pooled results from these five studies showed a significant association (OR: 0.96, 95% CI: 0.94–0.98 per 0.1-unit change in NDVI, Figure 3), suggesting that living close to a greener environment at birth has a protective effect on the development of childhood asthma. Specifically, increased greenness within a buffer distance of 100–500 m around the residential address at birth might reduce the risk of asthma at 6–18 years of age (OR: 0.95, 95% CI: 0.91–1.00 per 0.1-unit change in NDVI, Supplementary Figure S3). To test the robustness of this result, sensitivity analyses were performed by one-by-one exclusion of studies with buffers of 100–500 m. The results of sensitivity analyses were consistent with the main results (Supplementary Figure S4). In addition, no significant publication bias was found for asthma outcomes (Supplementary Figures S5–S7).

Three studies investigated the association between greenness surrounding schools and the prevalence of asthma in children. Dzhambov et al. (35) reported that naturalness within 100 m of schools had no significant effect on asthma. However, Yu et al. (67) and Zeng et al. (68) reported that increased greenness within 100, 300, 500 and 1,000 m around schools was associated with a reduced risk of asthma.

In addition, several studies have evaluated the effects of greenness on adult asthma. Their findings are also contradictory. Using data from the Centers for Disease Control and Prevention 500 Cities Project, Donovan et al. (33) found that each 1 SD increase in NDVI was associated with a 3.8% increase in adult asthma rates. A study conducted in Norway and Sweden showed that lifelong exposure to greenness was not associated with asthma, but was a risk factor for poor lung function in adulthood (48). However, another study conducted among adults in southwestern Iran demonstrated that green space and home gardening were important protective factors against asthma (43).

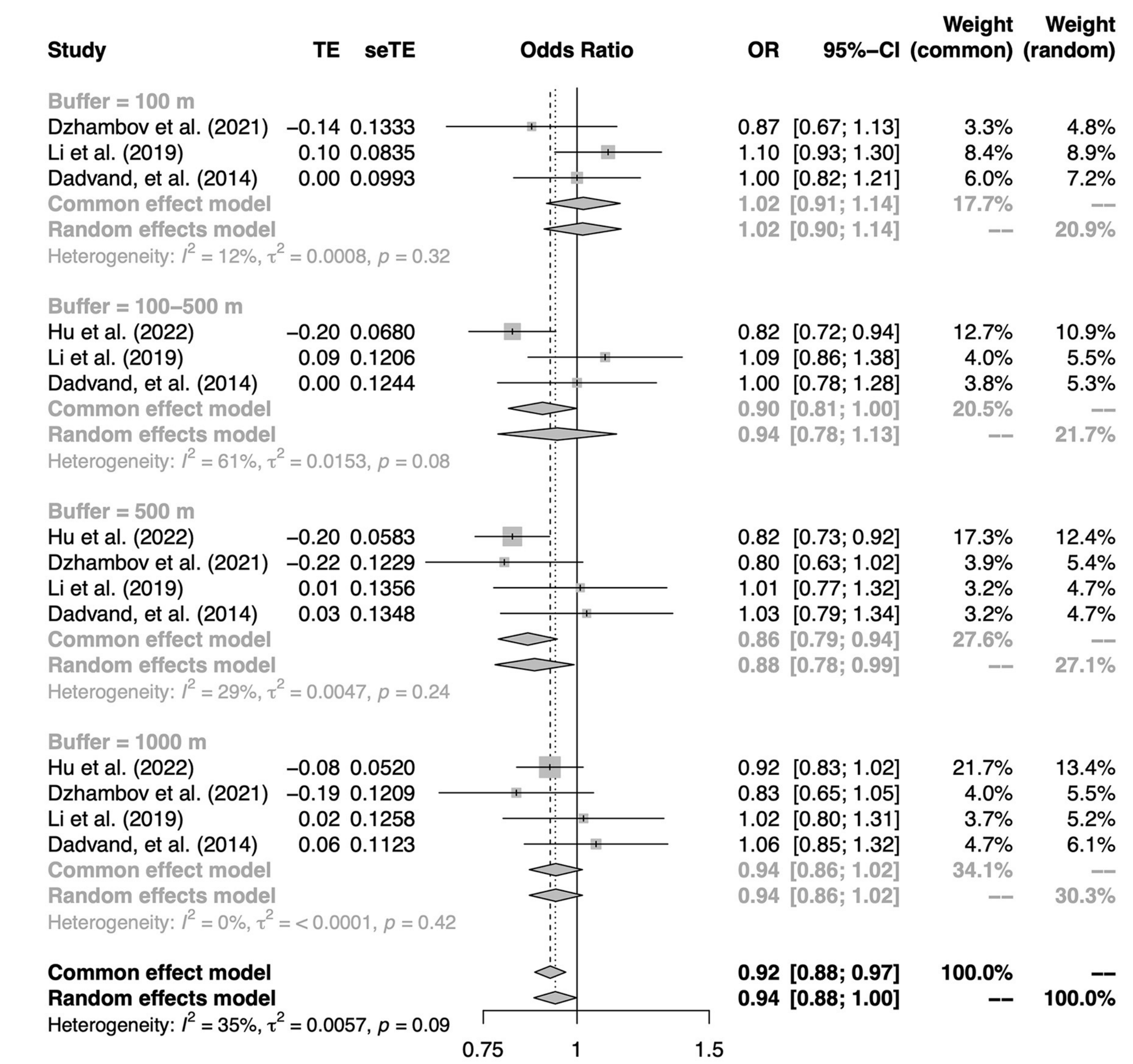

FIGURE 2
The association between residential greenness and current asthma. Subgroups were defined according to the buffers of the exposure measure.

Association between greenness exposure and AR

Four birth cohort studies reporting the association between residential NDVI at birth and the incidence of AR were considered for quantitative analysis (17, 54, 57, 64). As shown in Figure 4, the pooled OR for AR was 0.83 (95% CI: 0.72–0.96). Higher NDVI (3rd tertile vs. 1st tertile) was statistically significantly associated with a lower risk of AR within a buffer distance of 100–500 m (OR: 0.75, 95% CI: 0.59–0.95). No significant publication bias was found (Supplementary Figure S8).

Birth cohort studies by Fuertes et al. (16) and Gernes et al. (39) reported the effect of each 0.1 unit increase in NDVI on the incidence of AR. Fuertes et al. (16) reported that the direction of the association between NDVI and AR varied by region. Gernes et al. (39) reported that the association between NDVI or land cover-derived urban greenspace and AR was not statistically significant. In addition, although the number of studies is insufficient to be quantified, several cross-sectional studies have reported associations between greenness and AR. Dzhambov et al. (35) reported that among children aged 8–12 years, a higher distance from nature was associated with a higher prevalence of AR (OR: 1.32, 95% CI: 1.09–1.60), and conversely, the higher levels of NDVI and tree

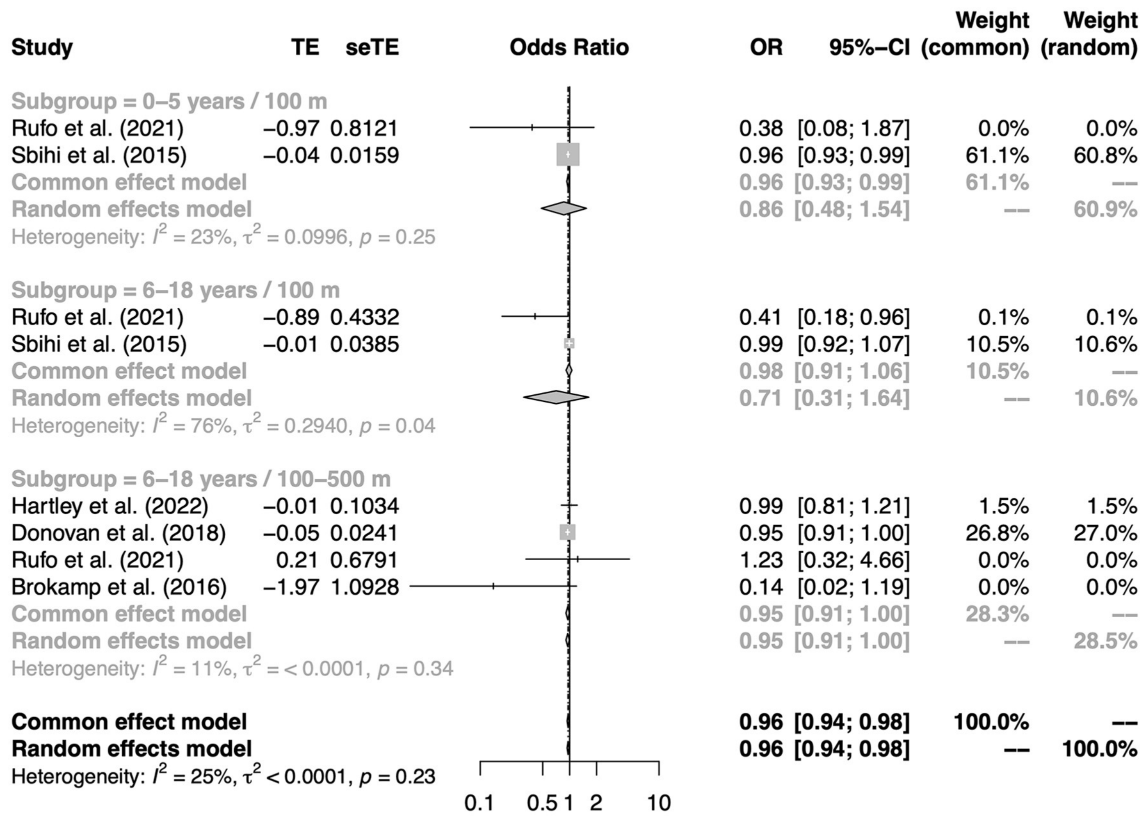

FIGURE 3
The association between residential greenness at birth and asthma in childhood. Subgroups were defined according to the age of the outcome measure and the buffers of the exposure measure.

cover were slightly associated with a lower prevalence of AR. However, Li et al. (53) reported that no statistically significant associations were observed between residential NDVI values or distance to parks and AR among Chinese middle school students.

Studies conducted among Korean adults showed consistent results. Kim et al. (45) reported inverse associations between green areas (m^2) and AR in Korean adults. Kwon et al. (49) reported that NDVI values were negatively correlated with the prevalence of AR.

Association between greenness exposure and AD

There are not many studies examining the relationship between greenness and AD, and only qualitative analysis can be performed. Overall, studies have yielded inconsistent results. At present, it is difficult to clarify the effect of greenness exposure on atopic dermatitis.

Lin et al. reported that NDVI within 500 m of residence during pregnancy, 0–2 years of age, and the first 1,000 days of life was associated with a higher odd of having AD (54), whereas this association was not significant within a radius of 250 m (54). However, Lee et al. (50) reported the opposite finding. They reported that an increase in green space area within a buffer of 200 and 300 m around the home address was associated with a statistically significant decrease in AD risk (50). Another birth cohort study by Rufo et al. showed that high NDVI and species richness index (SRI) within 100 m at birth were not significantly associated with eczema at 4 or 7 years of age (17). Two cross-sectional studies conducted in school-aged children did not find a significant association between greenness and AD (35, 53). A cross-sectional study in Korean adults observed an inverse association between greenness and AD (45).

Association between greenness exposure and food allergy

In general, studies exploring the effects of greenness exposure on food allergy have drawn inconsistent conclusions. Peters et al. reported that in Melbourne, Australia, increased

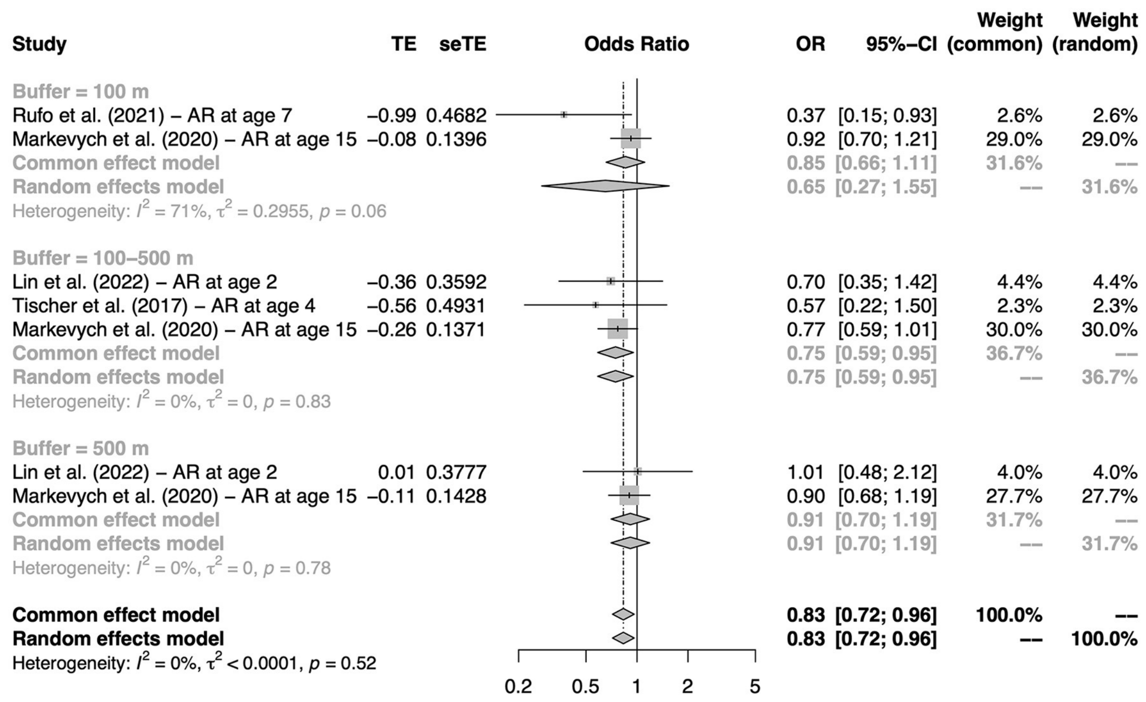

FIGURE 4
The association between residential greenness at birth and AR in childhood. Subgroups were defined according to the buffers of the exposure measure.

residential greenness exposure in most buffer zones was associated with an increased risk of food allergy in 12-month-old infants, especially associated with peanut allergy and egg allergy (59). However, another birth cohort study conducted in Guangzhou, China, did not observe a significant association between greenness exposure and food allergy in children up to 2 years of age (54). A study of German birth cohort did not observe a significant association between residential greenness and food sensitization, but a positive relationship was found between allergenic trees and food sensitization (57).

Association between greenness exposure and allergic rhinoconjunctivitis

Only a cross-sectional study conducted among 3,178 schoolchildren in Spain investigated the association between greenness exposure and allergic rhinoconjunctivitis, and no significant association was reported (28). In addition, a birth cohort study in young Chinese children collected data on allergic rhinoconjunctivitis, but no separate regression analysis was performed due to limited numbers in the preliminary analysis (54).

Discussion

In this study, we systematically reviewed the association between greenness and various allergic diseases in adults and children. There was substantial heterogeneity among the available studies, including study populations, study designs, greenness measurement methods, spatial buffers, exposure time windows, definitions of allergic outcomes, adjustment for confounders, and scaling of effect estimates. These differences make it difficult to make comparisons across studies. Therefore, although 48 articles met our inclusion criteria, only five birth cohort studies, five cross-sectional studies, and one case-control study were included in the meta-analysis for asthma, and four birth cohort studies were included in the meta-analysis for AR. Our meta-analysis showed that exposure to more greenness at birth was associated with a reduced risk of asthma and AR during childhood. In addition, higher individual-level greenness exposure was associated with reduced odds of current asthma in children. Greenness in the 100–500 m buffer around residences appears to play an important protective role.

The atopic march begins with AD and food allergy in infancy and subsequently progresses to AR and asthma in childhood. Although the atopic march does not exactly follow a temporal pattern of genes and environment, it is interesting to assess the impact of environmental factors on allergic disease from a progression perspective. The available evidence is not yet sufficient to support an effect of greenness on AD, food allergy, and allergic rhinoconjunctivitis. Furthermore, although the present study showed a protective effect of greenness on AR and asthma, it is uncertain whether this result was obtained by chance or reflects a true pattern. Because there is substantial heterogeneity among existing studies and, more importantly, most studies did not specify greenness structure and allergens. We consider that it is important to identify vegetation types and allergens causing allergic diseases, because some vegetation can produce pollen allergens that directly affect allergic diseases, or there is cross-reactivity between some pollen and food allergens.

The results of our study are inconsistent with the meta-analysis of Lambert et al. (20). Lambert et al. reported a non-significant association between greenness and asthma and AR, with pooled ORs of 1.01 (95% CI: 0.93, 1.09) and 0.99 (95% CI: 0.87, 1.12), respectively (20). However, only three studies were included in the meta-analysis of asthma and two studies were included in the meta-analysis of AR. The limited number of studies may have masked the statistical significance. In addition, a meta-analysis conducted by Wu et al. (70) also reported that the effects of greenness exposure on asthma and AR were not significant. However, this study did not separately assess cross-sectional studies as well as birth cohorts in the meta-analysis, which may have masked the temporal relationship between exposure and outcome, leading to non-significant results. In this study, we found that greenness exposure at birth was a protective factor for asthma and AR in childhood. The differences between our study and others suggest that the effect of greenness exposure on allergic outcomes may be a long process, and that early life exposure may be a critical stage in influencing the development of allergic disease. Future studies should use study designs with higher levels of evidence to explore the effects of greenness exposure on allergic disease, as well as the atopic march.

Another important issue in existing studies is the method of exposure measurement. Most studies use NDVI to represent greenness exposure. NDVI can capture small-scale greenness in a standardized manner at multiple time points, with global availability and comparability. However, this approach may not be sufficiently detailed when assessing impacts on allergic diseases, because it does not allow for differentiation of specific vegetation types. Five studies have used LiDAR and obtained inconsistent conclusions (29, 31, 39, 46, 56). Compared to NDVI, LiDAR can provide higher resolution images and distinguish between different types of greenness, such as tree canopy, shrub, and grass cover (31). When evaluating the impact of greenness, it is important to consider the type and proportion of vegetation, especially in the field of allergic diseases. This is because different greenness structures can not only produce different types and concentrations of allergens, but also have different effects on air pollution and microbiota (31). However, LiDAR is not freely available to the public, which may be the reason why many studies do not use it. In this review, we did not perform a meta-analysis of studies using LiDAR due to the limited number of eligible studies. Future studies should explore the suitability of LiDAR for assessing the effects of greenness on allergic diseases. In addition, we recommend that future studies describe in detail the mean or median of each exposure level, as well as the number of participants and patients at each exposure level. This will help to further explore the linear or non-linear relationship between greenness and allergic diseases.

Conclusions

Overall, our analysis supports that exposure to greener environments early in life may be a protective factor for AR and asthma in childhood. However, given the great heterogeneity among the included studies and the fact that most studies did not clarify the greenness structure and causative allergens, this result may only be applicable in some regions and populations. More high-quality studies are awaited to validate our results. In addition, most studies have focused on the terminal manifestations of the atopic march (AR and asthma), while only a few studies have explored the early manifestations of the atopic march (AD and food allergy). Future studies should continue to explore the effects of greenness on AD and food allergies.

Data availability statement

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

Author contributions

XW: conceptualization, methodology, software, data curation, visualization, investigation, and writing—original draft preparation. NZ: data curation. YZ: conceptualization, methodology, and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1097486/full#supplementary-material

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EDITED BY
Ang Li,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

REVIEWED BY
Jie Song,
Xinxiang Medical University, China
Renjie Chen,
Fudan University, China
Wei Wei Xing,
Academy of Military Medical Sciences, China

*CORRESPONDENCE
Dongqun Xu
✉ xudq@chinacdc.cn

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Cardiovascular benefits of air purifier in patients with stable coronary artery disease: A randomized single-blind crossover study

Zhe Liu[1], Qin Wang[1], Na Li[1], Chunyu Xu[1], Yunpu Li[1], Jun Zhou[1], Liu Liu[1,2], Haijing Zhang[1], Yang Mo[1], Feng Han[1,3] and Dongqun Xu[1]*

[1]China CDC Key Laboratory of Environment and Population Health, National Institute of Environmental Health, Chinese Center for Disease Control and Prevention, Beijing, China, [2]Chaoyang District Center for Disease Control and Prevention, Beijing, China, [3]National Institute for Occupational Health and Poison Control, Chinese Center for Disease Control and Prevention, Beijing, China

Background: Exposure to $PM_{2.5}$ will accelerate the progression of cardiovascular diseases. Air purifier can reduce the $PM_{2.5}$ exposure and theoretically alleviate the influence of $PM_{2.5}$ on patients with stable coronary artery disease (SCAD). However, few studies of the protective effect showed significant results because the interferent effects of routine medication had not been taken into account. In order to explore the actual effect on patients with SCAD, we conducted a randomized single-blind crossover air purifier intervention trial.

Method: Levels of $PM_{2.5}$ exposure during intervention and cardiovascular indicators (inflammation, coagulation, plaque stability, and blood lipids) after intervention were detected, meanwhile the information of drug use was obtained by questionnaire. The kinds of drug used by more than 20% of the subjects were sorted out. And the influence of these drugs on cardiovascular indicators was summarized through literature review. Based on that, the drug use was included as a variable in linear mixed effects models that used to analyze the associations between $PM_{2.5}$ exposure reduction by air purifier and cardiovascular indicators.

Results: The result revealed that the interpretation contribution rate of drug use was more than that of $PM_{2.5}$ exposure. The level of C-reactive protein significantly decreased by 20.93% (95%CI: 6.56%, 33.10%), 23.44% (95%CI: 2.77%, 39.39%) and 24.11% (95%CI: 4.21%, 39.69%) on lag1, lag01 and lag02 respectively, while the level of high-density lipoprotein cholesterol significantly increased by 5.10% (95%CI: 0.69%, 9.05%), 3.71% (95%CI: 0.92%, 6.60%) and 6.48% (95%CI: 2.58%, 10.24%) respectively on lag0, lag1 and lag01 associated with an interquartile range decrease of 22.51 $\mu g/m^3$ in $PM_{2.5}$ exposure.

Conclusion: The study shows positive effects of air purifier on SCAD, and also provides methodological reference for future related research.

KEYWORDS

air purifier, intervention trial, $PM_{2.5}$, SCAD, drug use, health protection

1. Introduction

$PM_{2.5}$ exposure has been confirmed to cause changes of cardiovascular indicators, thus promoting the occurrence and development of cardiovascular diseases (1). Air purifier with high efficiency particulate air filter (HEPA) can significantly reduce the indoor $PM_{2.5}$ concentration (2, 3) then the personal exposure (4). Therefore, there is theoretical basis for using air purifier to reduce health hazards, in areas and seasons with high incidence of $PM_{2.5}$ pollution.

The results of a series of intervention studies demonstrated that the use of air purifiers has different effects on the cardiovascular indicators of different groups. For healthy adults, the use of air purifiers has significant effects on the levels of monocyte chemokines, interleukin-1beta, soluble cluster of differentiation 40 ligand (sCD40L) and endothelin-1 (ET-1) in their circulatory system (5, 6), while the effects on C-reactive protein (CRP) (5, 7–9) and fibrinogen (FIB) (5, 10) are still controversial, and no significant effects on tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and cluster of differentiation 62 platelet (CD62P) have been found (5, 7, 8, 11). For the elderly, most studies showed no significant impacts on circulatory CRP, TNF-α, IL-6 and FIB levels by using air purifier, except on a physiological index microvascular function (2, 4, 12). But stratification analysis in one correlational study (2) found that the protective effect of air purifiers on microvascular function was not statistically significant in the elderly taking cardiovascular disease medicine. Thus, it can be seen that the conventional cardiovascular disease medicine may interfere the cardiovascular benefits of air purifiers for the elderly.

Patients with stable coronary artery disease (SCAD) usually receive comprehensive drug treatment, including mutiple drugs, to control the development of disease by regulating various functions of the circulatory system. For example, statins are mainly used to regulate the blood lipid balance; β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers (ARB) and calcium-channel blockers (Ca-channel blockers) are used to regulate the cardiac load and vasoconstriction; and aspirin is used to inhibit the platelet aggregation. These drugs may independently or synthetically change some cardiovascular indicators, involving inflammation, coagulation, plaque stability and blood lipids, which can also be affected by $PM_{2.5}$ exposure (1, 13, 14). Therefore, it is essential to comprehensively control the interference effects of these drugs, when intervention studies on the protective effect of air purifiers on the cardiovascular system are carried out.

To explore the actual protective effect of $PM_{2.5}$ exposure reduction by air purifiers, a randomized crossover intervention design was adopted to the enrolled patients with SCAD. Air purifiers were used in their residences to reduce the indoor $PM_{2.5}$ concentration. At the same time of $PM_{2.5}$ exposure monitoring, the drug use of the subjects during the intervention was investigated. And levels of the cardiovascular indicators of inflammation, coagulation, plaque stability and blood lipids after the intervention were detected. Interference effects of drug use were controlled in liner mixed effect models, which used to analyze the associations between $PM_{2.5}$ exposure and cardiovascular indicators.

Abbreviations: SCAD, stable coronary artery disease; HEPA, high efficiency particle air filter; sCD40L, soluble CD40 ligand; ET-1, endothelin-1; CRP, C-reactive protein; FIB, fibrinogen; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; CD62P, cluster of differentiation 62 platelet; MMP-2, matrix metalloprotein-2; MMP-9, matrix metalloprotein-9; CHO, cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; Ca-channel blockers, calcium-channel blockers; BMI, body mass index; ICAM-1, intercellular cell adhesion molecule-1; NO, nitric oxide; RH, relative humidity; AIP, atherogenic index of plasma; SD, standard deviation; IQR, interquartile range; NOS, Newcastle-Ottawa Scale; AIC, Akaike's Information Criterion; hsCRP, high-sensitivity C-reactive protein.

2. Materials and methods

2.1. Study design and subject recruitment

In this study, the randomized single-blind crossover intervention design was adopted. 24 SCAD patients were recruited, and the intervention trial was conducted in their residences, with air purifiers placed in their main activity space. Air purifiers equipped with HEPA filter were "real-intervention," with a clean air delivery rate of 500 m^3/h for $PM_{2.5}$, while those without HEPA were "sham-intervention." The experiment was completed in 4 batches with 6 subjects in each batch. Every intervention period was 3 days and the washout period was more than 14 days. The arrangement of the intervention is shown in Figure 1.

The subjects were recruited from 3 community-level (or above) general hospitals in Beijing, who were clinically diagnosed with SCAD according to the diagnostic requirements of *2013 European Society Cardiology Guidelines on the Management of Stable Coronary Artery Disease* (15) published by the European College of Cardiology and *2010 Chinese Consensus on the Management of Chronic Stable Coronary Artery Disease* (16) issued by China. In addition, the inclusion criteria include: (a) the age was between 55 and 80 years old; and (b) they lived near the hospital for a long time and the house was not decorated within 1 year. The exclusion criteria are as follows: (a) someone in their house smoked or themselves had just quitted smoking for <1 year; (b) patients were diagnosed with acute myocardial infarction within 3 months, or receive percutaneous coronary intervention and bypass transplantation within 6 months; (c) patients wore a

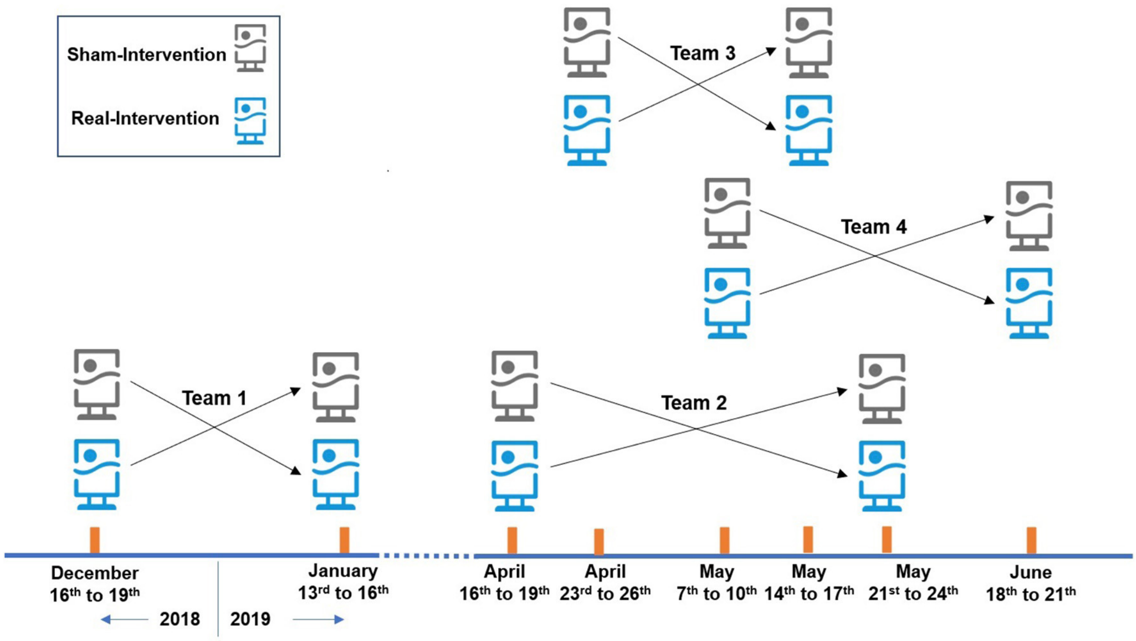

FIGURE 1
Arrangement of the intervention.

pacemaker; and (d) patients suffered from liver injury, cancer and other serious diseases.

During the intervention, the individual exposure to $PM_{2.5}$ and the concentration of $PM_{2.5}$ indoor and outdoor the residence was monitored continuously. The age and body mass index (BMI) of the subjects was investigated, and their travel behaviors, window opening time and medication were recorded. The subjects stayed at home for more than 20 h/d, and the window opened for no more than 2 h/d during the intervention. Drug use records focused on conventional medicine for CAD treatment. Blood samples were collected at the end of each intervention, and the following indicators were detected: (a) inflammation indicators such as IL-6, TNF-α, CRP and FIB; (b) coagulation indicators such as CD62P, CD40L, intercellular adhesion molecule-1 (ICAM-1), nitric oxide (NO) and ET-1; (c) plaque stability indicators such as matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-2 (MMP-9); (d) blood lipid indicators such as total cholesterol (CHO), triglyceride (TG), high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C).

2.2. $PM_{2.5}$ exposure

Particulate matter sampling pumps MicroPEM^{TM} (RTI Company, USA) based on the principle of light scattering were used to monitor $PM_{2.5}$ concentration with sampling flow of 500 mL/min. It can monitor the environmental temperature and relative humidity (RH) simultaneously. Daily average concentration of $PM_{2.5}$ was calculated from 8 a.m. to 8 a.m. Lag and moving average levels of $PM_{2.5}$ exposure are represented by "lag."

Sampling pumps for monitoring the indoor $PM_{2.5}$ concentration were placed in the open area of the house to avoid air conditioner vent, kitchen, doors and windows, about 1.5 m above the ground, more than 1 m far from the wall, and at least 2 m far from the air purifier. Sampling pumps for monitoring the outdoor $PM_{2.5}$ concentration were placed outside the residential window and avoid air conditioner unit and kitchen and its air outlet. Sampling pumps for monitoring individual exposure to $PM_{2.5}$ were taken along by the subjects.

2.3. Blood collection and indicator measurements

Fasting blood samples (5 mL anticoagulant and 5 mL non-anticoagulant) were collected from 8:00 to 9: 00 on the day at the end of each intervention. IL-6, TNF-α, CRP, FIB, CD62P, CD40L, ICAM-1, NO, ET-1, MMP-2 and MMP-9 levels were tested by a professional testing institution. CHO, TG, HDL-C and LDL-C levels were tested by the laboratory of the hospital. IL-6, TNF-α, CD62P, CD40L and ICAM-1 was detected by a bead-based multiple flow cytometry on Luminex 200 system (Luminex Corporation, Austin, TX, USA) with chips (IL-6 and TNF-α: Merck Millipore, Germany; CD62P, CD40L and ICAM-1: R&D, USA). CRP, NO, MMP-2, MMP-9, FIB and ET-1 was separately detected by ELISA kit (CRP, NO, MMP-2, MMP-9: R&D, USA; FIB: NOVUS, USA; ET-1: Elabscience Biotechnology Co. Ltd, Wuhan, China).

In addition, a compound index-atherogenic index of plasma (AIP) was calculated by the results of TG and HDL-C levels and the formula: **AIP**$= \log\left(\frac{\textbf{TG}}{\textbf{HDL-C}}\right)$.

2.4. Statistical analyses

Descriptive statistics were conducted for general characteristics of the environmental exposure and effects. Data with normal distribution were described by mean and standard deviation (Mean±SD), and data with skewed distribution were described by median and interquartile range as M (P_{25}, P_{75}). The paired Student's t-test was employed to compare the $PM_{2.5}$ concentrations between two intervention periods, or the indoor and outdoor environment. The Linear mixed effect models were conducted to estimate the correlation between $PM_{2.5}$ exposure and cardiovascular indicators. The results were reported by the percentage change of indicators associated with an interquartile range (IQR) decreases of $PM_{2.5}$ exposure. The interpretation contribution rate of independent variables in the model were calculated by the determination coefficient R^2 of independent variables/ of the model.

In the linear mixed effect models, the "effective drug" variable is defined as one or more kinds of the effective drug had been taken by the subject (dichotomous variable). The kinds of drug need to be controlled were selected according to *Guidelines for Rational Drug Use of Coronary Artery Disease (2nd Edition)* (17) and the actual medication of the subjects (taken by more than 20% of the subjects). Whether the drug is effective was determined by searching the literatures on "Pubmed," "Web of Science," "China National Knowledge Infrastructure," "Wanfang" and "VIP" (before December 30, 2021). It needs to meet the following requirements: (a) there were two or more case-control trials or pre-and post-treatment control trials of cardiovascular disease patients treated with the drug, and the results of the trials were statistically significant; or (b) there was a case-control trial or pre-and post-treatment control trial of cardiovascular disease patients treated with the drug, and the results were statistically significant, and there was one or more animal experiment of the drug, and the results were statistically significant. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of literatures relevant to case control/pre-and post-control studies in patients with cardiovascular disease, and the CAMARADES Scales was used to assess the quality of literatures relevant to animal studies. Literatures with a score more than 6 points would be included in the summary.

Influencing factors of $PM_{2.5}$ exposure and cardiovascular indicators need to be considered as independent variables in the linear mixed effects models. It includes the "effective drug," age, gender and BMI, as well as temperature and relative humidity. The stepwise elimination method based on the principle of minimization of Akaike's Information Criterion (AIC) was adopted for the validity of models. We screened three additional independent variables on the basis of preserving key variables ($PM_{2.5}$ exposure and the "effective drug"). The model was established for each indicator respectively, given the influencing factors differences.

The parameters of the model were tested by bilateral t-test, with statistical significance of 0.05. The "lme4" package and "r2glmm" package in the R (Version 4.0.3) was separately used for linear mixed effect model and R^2 calculation.

2.5. Quality control

The monitoring instruments were cleaned and calibrated before sampling. Instrument condition review was done at the end of the first and last day of each intervention. The blood samples were collected by the nurses. Blood lipid indicators were detected on the same day, and samples were stored at −80°C before further detection. The detection process was controlled strictly in accordance with the testing procedures and the requirements of the chips/kits.

The subjects of the study were trained by professional personnel before recording the questionnaire themselves. Questionnaires were re-checked at the end of the first and last day of each intervention for ensuring recording accuracy. Questionnaire and data input were done by two personnel, and then reviewed and analyzed by special personnel.

3. Results

3.1. The general characteristics of the subjects

The residences of the subjects were all located within 5 km of the hospitals, in apartment buildings built from 2003 to 2015, with an area between 45.1 and 96.0 m^3. The windows of the rooms were made of plastic steel or aluminum alloy to ensure the sufficient air tightness. The average age of the subjects was 65.3 ± 5.2 years old, and the ratio of male to female was 14:10. The average BMI of the subjects was 26.0 ±2.4 kg/m^2. The drug use during the intervention is shown in Table 1.

TABLE 1 The general characteristics of the participations.

Items	Categories	Result
Age (Mean±SD)		65.3 ± 5.2 years
Gender (n)	Male	14
	Female	10
BMI (Mean±SD)		26.0 ± 2.4 kg/m^2
Drug Use (n)		
	Aspirin	18
	Statins	18
	ACEI/ARB	14
	Clopidogrel	13
	β-blockers	7
	Ca-channel blockers	5

3.2. Air purification effect and individual $PM_{2.5}$ exposure level

The 72 h average indoor $PM_{2.5}$ concentration in the real-intervention period was 40.58% of the outdoor. It was significantly reduced by 40.04% when compared with the sham-intervention period. The change of individual $PM_{2.5}$ exposure level was consistent with indoor concentration. During the real-intervention period, the individual $PM_{2.5}$ exposure level was reduced by 22.72% when compared with the sham-intervention period. The use of air purifiers in residences can effectively reduce the indoor $PM_{2.5}$ concentration, and then the individual $PM_{2.5}$ exposure (Table 2).

3.3. Drug to be controlled and their effects on indicators

According to the questionnaire survey, 6 kinds of drug were taken by more than 20% of the subjects during the intervention period: statins, β-blockers, Ca-channel blockers, clopidogrel, aspirin and ACEI/ARB. Based on literatures review (Supplementary Tables S1–S6) (18–77), the effects of these 6 kinds of drug on the indicators of inflammation, coagulation, plaque stability and blood lipids were determined, as shown in Table 3.

3.4. Model selection and interpretation contribution rate of variables

In this study, each cardiovascular indicator was selected by minimizing AIC in the linear mixed effect analysis model, except for CHO and LDL-C. Based on the previous association research of blood lipid indicators, the influence of age, gender and BMI variables were greater than that of ambient temperature and RH. And the AIC values of CHO and LDL-C models ("log (**Indicator**) ~**PM$_{2.5}$+Age+Gender+BMI+ED+ (1|ID)**" and "log (**Indicator**) ~**PM$_{2.5}$+Gender+BMI+Temp+ED+ (1|ID)**") were similar, which were 12.74 vs. 12.21 and 47.03 vs. 46.54, respectively, so "log (**Indicator**) ~**PM$_{2.5}$+Age+Gender+BMI+ED+ (1|ID)**" was selected as the model. The final selection of linear mixed effect models for each cardiovascular indicator is shown in Supplementary Table S7.

The determination coefficient R^2 of the independent variables of each model and its interpretation contribution rate in the model were calculated (Supplementary Table S7), we found that in the models corresponding to IL-6, TNF-α, FIB, CD62P, ICAM-1, ET-1, MMP-9, CHO, TG and AIP, the contribution rate of "effective drug" to the interpretation of the model was greater than that of $PM_{2.5}$ exposure, and the contribution rate of "effective drug" to the interpretation of IL-6, TG and AIP models was more than 58%. In the model corresponding to the CRP, CD40L, NO, HDL-C and LDL-C, the interpretation contribution rate of $PM_{2.5}$ exposure to the model was slightly greater than that of "effective drug." In the model corresponding to MMP-2, the interpretation contribution rate of $PM_{2.5}$ exposure to the model was much greater than that of drug intake (60% vs. 3%).

3.5. Effects of $PM_{2.5}$ reduction on inflammation indicators

The levels of TNF-α, CRP and FIB were decreased with each IQR decrease (22.51 μg/m^3) of $PM_{2.5}$ exposure on lag0 when the subjects used the "real" air purifier, but the changes were not statistically significant. And CRP level of the subjects was significantly reduced by 20.93% (95%CI: 6.56%, 33.10%), 23.44% (95%CI: 2.77%, 39.39%) and 24.11% (95%CI: 4.21%, 39.69%) for each $PM_{2.5}$ exposure IQR decrease, on lag1, lag01, and lag02 (Figure 2).

3.6. Effects of $PM_{2.5}$ reduction on coagulation indicators

There was no statistically significant change in coagulation indicators when the individual $PM_{2.5}$ exposure was decreased by each IQR on lag0, lag1, lag2, lag01, and lag02. Except that ET-1 level was significantly reduced by 5.64% (95%CI: 0.83%, 10.23%) for each $PM_{2.5}$ exposure IQR decrease on lag1 (Figure 3).

TABLE 2 Comparison of indoor, outdoor and individual exposure to $PM_{2.5}$ concentrations.

Intervention	Scene	$PM_{2.5}/\mu g/m^3$ (Mean±SD)	Mean difference with sham/$\mu g/m^3$ (95% CI)	Mean difference with outdoor /$\mu g/m^3$ (95% CI)
Real	Indoor	26.24 ± 11.26	−17.52* (−31.93, −3.09)	−38.44* (−51.78, −25.09)
	Outdoor	64.67±34.45	4.66 (−21.98, 31.31)	—
	Individual	32.65 ± 13.18	−9.60 (−21.84, 2.63)	—
Sham	Indoor	43.76 ± 29.11	—	−16.25* (−23.55, −8.95)
	Outdoor	60.01 ± 36.90	—	—
	Individual	42.25 ± 28.82	—	—

*$p < 0.05$.

TABLE 3 Effects of 6 kinds of drug on cardiovascular indicators.

	Statins	β-blockers	Ca-channel blockers	Clopidogrel	Aspirin	ACEI/ARB
IL-6	•[a]	•	•		•	•
TNF-α	•	•	•	•	•	•
CRP	•	•	•	•	•	•
FIB	•	•				•
CD62P	•			•	•	
CD40L	•			•		
ICAM-1	•					•
NO					•	
ET-1	•	•				
MMP-2	•		•	•		
MMP-9	•		•	•		•
CHO	•	•			•	
TG	•	•				
HDL-C	•					
LDL-C	•	•			•	
AIP	•	•				

[a] •Based on literatures review, the effects of drug on the indicators were determined.

3.7. Effects of $PM_{2.5}$ reduction on plaque stability indicators

There was no significantly change in plaque stability indicators. And while the level of MMP-9 showed a downward trend for each IQR decrease of $PM_{2.5}$ exposure on lag0, lag1, lag2, lag01 and lag02, the level of MMP-2 level showed an opposite trend ($p > 0.05$) (Figure 4).

3.8. Effects of $PM_{2.5}$ reduction on blood lipid indicators

The levels of CHO, HDL-C and LDL-C increased associated with each IQR decrease of $PM_{2.5}$ exposure on lag0, lag1, lag2, lag01 and lag02. But only the increase of HDL-C was significant on lag0, lag1 and lag01, which was 5.10% (95%CI: 0.69%, 9.05%), 3.71% (95%CI: 0.92%, 6.60%) and 6.48% (95%CI: 2.58%, 10.24%) respectively. Although with no statistical significance, the level of AIP showed a decreasing trend on lag1 and lag01 ($p = 0.06$ and $p = 0.07$, respectively) with the decrease of $PM_{2.5}$ exposure. There was no significant change in the level of TG (Figure 5).

4. Discussion

Most of previous air purifiers intervention studies of the elderly did not consider the role of medication, leading to bias in results. In this study, the use of 6 conventional SCAD

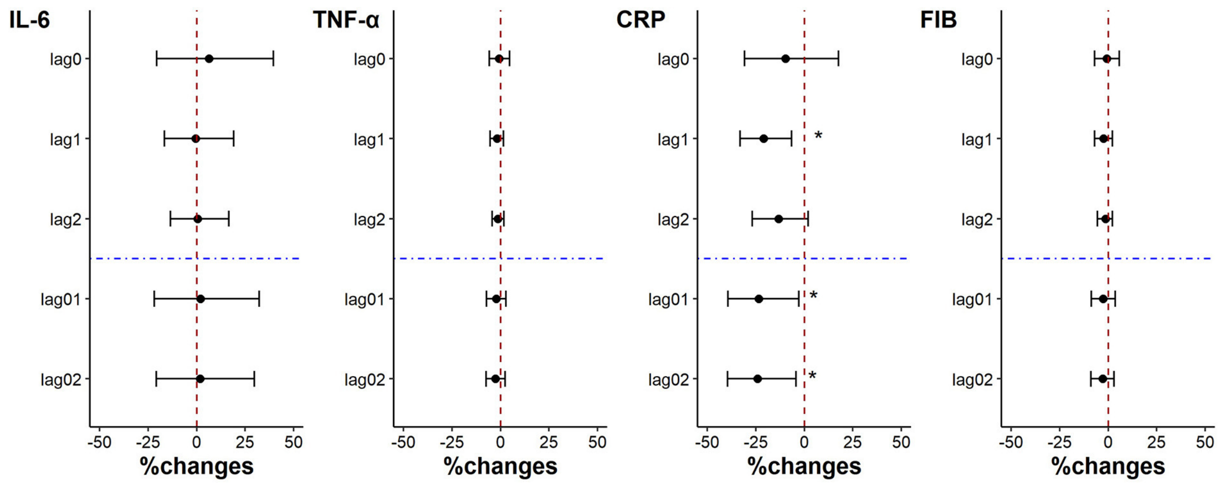

FIGURE 2
Percent changes in inflammation indicators associated with an IQR decrease in $PM_{2.5}$ exposure. *p < 0.05.

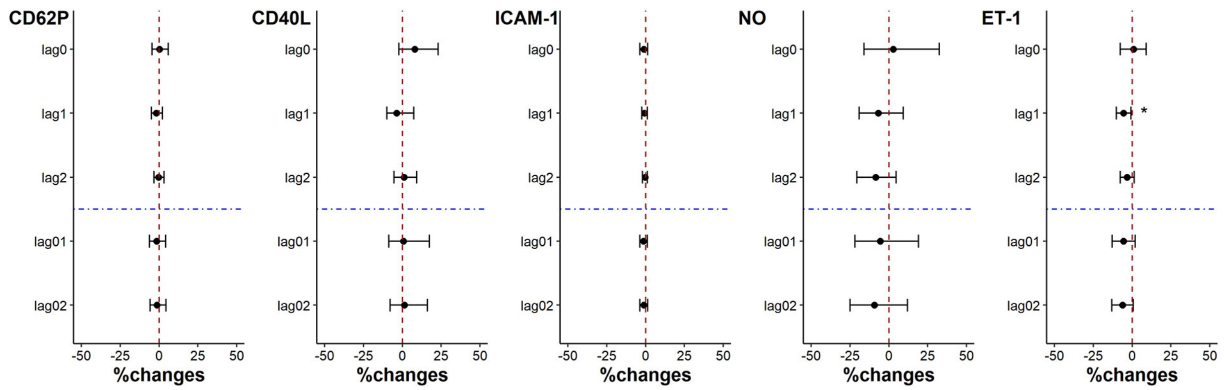

FIGURE 3
Percent changes in coagulation indicators associated with an IQR decrease in $PM_{2.5}$ exposure. *p < 0.05.

drugs (statins, β-blockers, Ca-channel blockers, ACEI/ARB, clopidogrel and aspirin) was combined and included into the linear mixed effect model in the form of one "effective drug" variable to analyze the influence of $PM_{2.5}$ exposure on indicators, so as to establish a set of evaluation methods for the health protection effect of air purifier on patients with SCAD. And through a randomized crossover intervention study with small sample size, using the established evaluation method, it was found that the use of "true" air purifier to reduce the $PM_{2.5}$ exposure level of patients with stable CAD had a certain protective effect on the levels of inflammatory indicator CRP and lipid indicator HDL-C under the control of the influence of drugs. But there were no significant effects on other inflammation and lipid indicators, or on coagulation and plaque stability indicators. It is suggested that CRP and HDL-C may be sensitive indicators of the acute effect of $PM_{2.5}$ exposure on SCAD patients, and it is more worthy of attention in the air purifier intervention trials for stable CAD patients. Therefore, the method established in this study provided methodological reference for relevant studies, and the results of the intervention study broadened the understanding on health protection for patients with stable CAD using the air purifier, which has an important public health significance.

Inflammation is recognized as a key step in the development of CAD. Clinical studies have indicated that inflammation indicator CRP is a risk biomarker of atherosclerosis, which can mediate atherosclerosis at different stages (78). Elevated CRP level can predict the occurrence of cardiovascular events (79). In

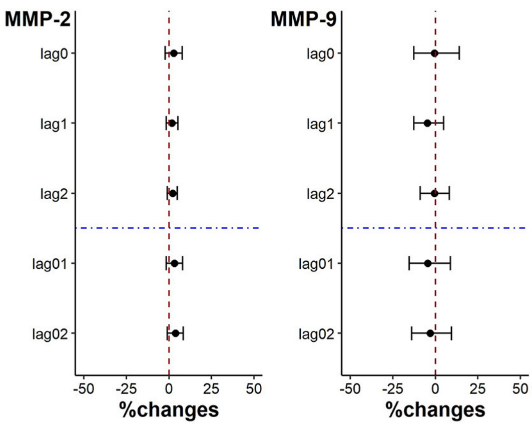

FIGURE 4
Percent changes in plaque stability indicators associated with an IQR decrease in $PM_{2.5}$ exposure.

previous intervention studies of air purifiers for healthy adults, a significant association was found between the decrease of CRP and $PM_{2.5}$ exposures levels (8, 9), confirming the health protection of air purifiers. However, no significant association has been found in studies for the elders, including those with cardiovascular disease (7). This study found that CRP level in patients with SCAD significantly decreased by 20.93 to 24.11% when the daily exposure to $PM_{2.5}$ was reduced by 22.51 $\mu g/m^3$ on day lag1, lag01, and lag02. After the interference of drug use was controlled, the air purifiers were found to have a protective effect on CRP levels of the subjects. In addition, the study revealed that the interpretation contribution rate of drug use to the analysis model corresponding to CRP was similar with that of $PM_{2.5}$ exposure, which further illustrates the necessity of controlling the drug use of the subjects in the air purifier intervention studies for patients with SCAD and even patients with cardiovascular diseases who need to take drugs daily.

Blood lipid is one of the risk factors to be controlled in patients with CAD. The meta-analysis (14) showed that for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ long-term exposure, the levels of CHO and LDL-C were increased significantly by 4.53 and 5.36%, respectively, with no significant change in HDL-C and TG levels. In a large cohort study conducted by Wu et al. (80) on middle-aged women (42–52 years old), it was found that the HDL-C level changed significantly by -0.7% when the average yearly concentration of $PM_{2.5}$ was increased by 3 $\mu g/m^3$, but the correlation between the average daily concentration of $PM_{2.5}$ and HDL-C level was not statistically significant. At present, there are only a few population-based studies on the acute effects of $PM_{2.5}$ exposure on blood lipid indicators, and there is no effective evidence to prove a significant correlation between $PM_{2.5}$ exposure and changes in blood lipid indicators, which may be due to the failure to control the effects of drug use on blood lipid. In this study, it's showed that the interpretation contribution rate of drug use to the model of HDL-C was similar to that of $PM_{2.5}$ exposure. And under controlling the drug effects, we analyzed the association between exposure to $PM_{2.5}$ and acute effect of HDL-C in patients with SCAD. The AIP of the subjects in this study tended to improve with the decrease of $PM_{2.5}$ exposure ($p = 0.06$ and 0.07), which proved, together with the results of HDL-C, that air purifiers used to reduce $PM_{2.5}$ exposure might have a positive effect on the improvement of the quality of lipid-related indicators in patients with SCAD. These findings not only illustrate the necessity of considering drug use in relevant studies, but also provide experimental epidemiological evidence for the research of the association between $PM_{2.5}$ exposure and acute effect of blood lipid indicators.

In the environmental health studies of SCAD patients, medications have a greater impact on cardiovascular indicators than environmental factors, so it's important to control their interference with the results. Stratified analyses by single kind of drug usage are usually used for this purpose (2). However, this stratified analysis is too simple considering that SCAD patients often require multiple drugs to control disease progression. The approach used in this study was to integrate multiple medications into an "effective drug" variable, which not only allows for a comprehensive consideration of single and combination drug use, but also reduces the sample size required for such studies.

The intervention study considered the influence of daily drug use on cardiovascular indicators of the patients with SCAD, and revealed the real protective effect of air purifiers on the patients with SCAD after reducing $PM_{2.5}$ exposure level. However, compared with other air purifier intervention trials, the study is an experimental epidemiological study with small sample size, which may have limitation on the research results. The limitation had been noted, and individual measurements had been used to more precisely evaluated $PM_{2.5}$ exposure levels of each study subject, which in turn could increase the accuracy of $PM_{2.5}$ exposure-response evaluation results. In addition, the small sample size limits the stratified analysis for different drug use. If the sample size is expanded, the interference effect of various drug on the results of $PM_{2.5}$ impacts can be analyzed in depth. When considering the influence of drug on cardiovascular indicators, only six kinds of conventional drug for coronary heart disease were controlled in the study. With the development and application of new drug, as well as the new discovery of the effect of drug on cardiovascular indicators, it will be necessary to conduct in-depth studies and to reveal the protective effect of air purifiers on people with cardiovascular diseases by expanding the sample size and increasing the control of the effects of other drug in the future.

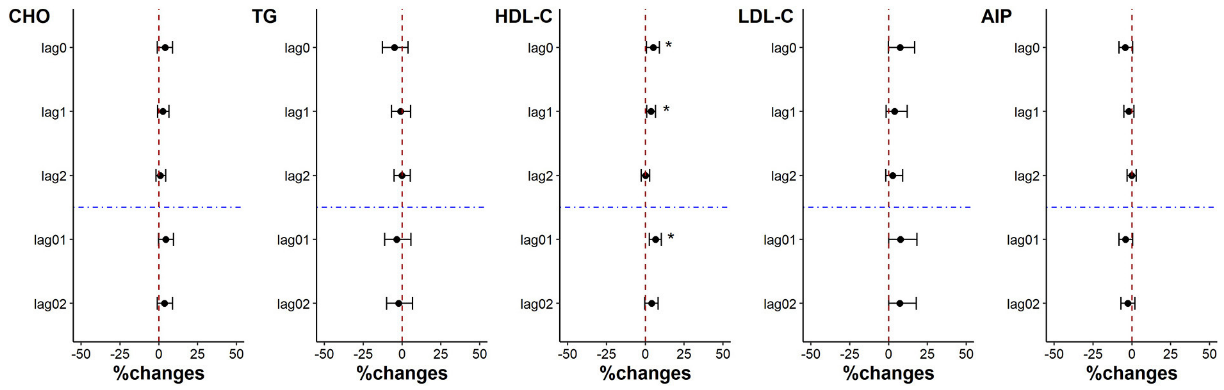

FIGURE 5
Percent changes in blood lipid indicators associated with an IQR decrease in $PM_{2.5}$ exposure. *$p < 0.05$.

5. Conclusions

In the evaluation method established in this study, the way to control the influence of drug use can provide methodological reference for future research in related fields, and the comprehensive analysis of the protective effects of air purifiers on cardiovascular system from multiple indicators of inflammation, coagulation, plaque stability and blood lipid can also provide scientific basis for screening sensitive indicators of air purification protection for patients with SCAD. In addition, through a randomized crossover intervention study with small sample size, the study found that the use of air purifier had a clear protective effect on patients with SCAD, in the case of daily routine medication management for disease management, and could significantly improve patients' inflammation indicator CRP and blood lipid indicator HDL-C. It shows that using air purifiers is one of the effective measures to protect the health of patients with SCAD in $PM_{2.5}$ polluted weather.

Data availability statement

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

Ethics statement

The study was approved by the Ethics Committee of National Institute of Environmental Health, Chinese Centre for Disease Control and Prevention and all participants provided their written informed consent.

Author contributions

ZL, QW, NL, CX, YL, and DX: conceptualization and methodology. ZL and NL: project administration. ZL, NL, CX, YL, JZ, LL, HZ, YM, and FH: investigation. ZL and CX: formal analysis. ZL: visualization and writing–original draft. DX: writing–review and editing, supervision, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1082327/full#supplementary-material

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EDITED BY
Ruoyu Wang,
University of Edinburgh,
United Kingdom

REVIEWED BY
Getrude C. Ah Gang,
Universiti Malaysia Sabah, Malaysia
Salvatore Bernardo Durante,
Alberta Hospital Edmonton, Canada

*CORRESPONDENCE
Sam S. S. Lau
✉ samlau@hkbu.edu.hk

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Brief repeated virtual nature contact for three weeks boosts university students' nature connectedness and psychological and physiological health during the COVID-19 pandemic: A pilot study

Sam S. S. Lau[1,2,3,4]*, Sharron S. K. Leung[1,5], Jonathan W. C. Wong[4,6], Terence C. P. Lee[1,2], Stephen R. Cartwright[1,2], Janet T. C. Wong[1], Jackie Man[1,3], Ethan Cheung[1,3] and Regene P. W. Choi[1]

[1]Research Centre for Environment and Human Health, School of Continuing Education, Hong Kong Baptist University, Kowloon, Hong Kong SAR, China, [2]College of International Education, Hong Kong Baptist University, Kowloon, Hong Kong SAR, China, [3]Multidisciplinary Research Centre, School of Continuing Education, Hong Kong Baptist University, Kowloon, Hong Kong SAR, China, [4]Institute of Bioresources and Agriculture, Hong Kong Baptist University, Kowloon, Hong Kong SAR, China, [5]Division of Nursing Education, School of Continuing Education, Hong Kong Baptist University, Kowloon, Hong Kong SAR, China, [6]Department of Biology, Hong Kong Baptist University, Kowloon, Hong Kong SAR, China

The COVID-19 pandemic and its associated uncertainties and restrictions have adverse impacts on university students' mental wellbeing. Evidence shows that virtual nature contact has mental health benefits. However, little is known about the potential beneficial health impacts of virtual nature contact during times of social distancing, when access to the natural environment is restricted. This pilot study aimed to examine the effectiveness of a 3-week virtual nature contact in improving nature connectedness and reducing psychophysiological stress. A sample of 56 university students in Hong Kong was randomly assigned to control and nature interventions using 2-D video played for 15 min three times a week for 3 weeks. Nature connectedness, perceived restorativeness and psycho-physiological wellbeing were measured. Our findings show significant changes in psychological stress levels after nature interventions compared with the baseline, including increased happiness and stronger emotions of comfort and relaxation. When compared with the control group, the results show the nature intervention group has significantly higher levels of nature connectedness, happiness, and positive affect, but no significant effects on other psychological and physiological variables (e.g., cardiovascular responses). Our preliminary findings highlight the potential use of virtual nature contacts in bolstering university students' wellbeing at times of pandemic or when in-person visit to the natural environment is not feasible.

KEYWORDS

COVID-19 pandemic, virtual nature contact, mental health, nature connectedness, restorativeness

1. Introduction

The COVID-19 pandemic poses an unprecedented threat to global health. People experience distress from contracting this highly contagious virus, and pandemic health-control measures and the economic impact of the pandemic have an adverse impact on mental health (1). In the first year of the pandemic, the Global Burden of Disease 2020 study reported a 27.6% increase in the prevalence of major depressive disorder and a 25.6% increase in the prevalence of anxiety (2). As revealed in a meta-analysis, there is increasing concern about the general population's mental health during the COVID-19 pandemic. That analysis showed that the prevalence of stress was approximately one-third (29.6%) in a sample of 9,047 people from five studies, the prevalence of anxiety was 31.9% in a sample of 63,439 people from 17 studies, and the prevalence of depression was 33.7% in a sample of 44,531 people from 14 studies (3). In Hong Kong, young adults were particularly susceptible to stress, with approximately half (46%) of the population aged 18–24 reported feeling stressed, compared with less than one third (31%) of the general population (4). Another study's findings revealed that age as a risk factor for stress was further magnified during the COVID-19 pandemic, as young people across 26 countries and areas experienced higher levels of stress than older people (5). According to a territory-wide epidemiological study on youth mental health in Hong Kong (6), among 594 participants aged 15–24, 12% reported moderate to severe levels of stress. Overall, 22.8 and 22.5% of that study's participants reported moderate to severe levels of depression or anxiety symptoms, respectively. Fu et al. (7) reported that 41.1% of 89,588 college students showed anxiety symptoms. The COVID-19 pandemic and its associated uncertainties and restrictions on daily activities are damaging the mental health and wellbeing of adolescents. Another study shows that social distancing and social isolation reduced university students' perceived peer support, increased their perceived loneliness, and decreased their sense of hope, thus increasing their depressive symptoms (8). Werner et al. (9) reported that school lockdowns and closures increased loneliness and social stress and negatively impacted students' mental wellbeing. These findings have revealed an urgent need to address the overwhelmingly common stress problem in adolescents. There is a pressing need to develop effective stress interventions that are accessible to adolescents during the pandemic.

Stemming from Wilson's (10) biophilia hypothesis predicting the innate desire to connect with nature, a growing body of empirical research has cultivated staunch support for nature's benefits for mental and physical wellbeing (11–16). Li et al. (17) explored the link between exposure to nature and adolescents' moods in a real-life setting by recording the participants' locations for four consecutive days and matching the resulting data to their mood states. They revealed that increased exposure to nature throughout the day was significantly associated with decreased depression, anger, fatigue and overall negative mood. Another study suggested that the stress reduction property of nature works in two ways: it increases a person's distance from stressors and it restores a person's adaptive resources (18). In addition, attention restoration theory attempts to explain the mechanism of nature exposure in restoring human cognitive states (19, 20). One meta-analysis demonstrated that experiencing the components of nature requires little mental effort and hence can replenish a person's mental resources (21). A systematic review supported the benefits of interactions with nature in children and adolescents to their emotional wellbeing, stress, and overall mental health (22). Experimental evidence has also illustrated that nature exposure has promising results for improving mental wellbeing. Wilderness expeditions have been reported to be associated with improved self-esteem in adolescents (23, 24). Taking a nature walk significantly increases nature connectedness and positive affect compared to a control group in individuals with clinically diagnosed depression and anxiety (25). After a forest visit, the participants in another study reported lower levels of stress, fatigue, and irritation (26). Kotera et al. (27) compiled findings from six randomized controlled trials of forest-bathing and found the significant effects of forest-bathing on reducing depression and anger.

In the face of a threat, stress arousal contributes to activating a top-down mechanism from the brain to the body through the release of stress hormones, which elicit physiological responses, including cardiovascular functioning, to prepare the body to overcome threats (27). One study of laboratory stress tasks yielded results supporting the psycho-physiological nature of stress (28). Significant associations between perceived stress and increased heart rate, respiratory sinus arrhythmia, and cortisol levels were found in adolescents when performing a social stress task. Cardiovascular responses have also been well studied [e.g., Thayer et al. (29)]. It was reported that there is a positive association between stress and increased blood pressure that lasts even after the stressor disappears (30). Kim et al. (31) conducted a meta-analysis investigating how stress can be reflected in heart rate variability (HRV). The results from 37 studies consistently pointed to a significant change in HRV in response to stress, characterized by a decrease in the high frequency band and an increase in the low frequency band. With support from the literature, physiological changes, particularly cardiovascular responses, were deemed to be robust subjective measurements of stress. According to the stress recovery theory proposed by Ulrich and colleagues (32, 33), humans' physiology and psychology are evolutionarily adapted to the natural environment; thus, nature can relieve both physiological and psychological stress. Previous studies have demonstrated the benefits of spending time in nature for alleviating hypertension, reducing oxidative stress and stress hormones, and improving cardiac and pulmonary functions and emotional response (34). Furthermore, another study reported that a green schoolyard lowered students' physiological stress indicators, including blood pressure levels and HRV, and were associated with better mood and wellbeing (35). However, a systematic review of nature-based interventions on psycho-physiology stress recovery concluded that the evidence for physiological stress reduction with nature exposure is equivocal (36).

Recent research in nature-based intervention has turned the researchers' focus to the virtual nature experience, which is partly driven by the rapid urbanization of modern society, with an increasing number of people living in cities with limited nature nearby (37–39). According to the United Nations (UN), 55% of the world's population lives in urban areas, a percentage that is expected to increase to nearly 70% by 2050 (40). The increased accessibility of virtual natural environments *via* smartphones and virtual reality (VR) devices facilitates the virtual delivery of nature-based interventions (41, 42). Virtual nature provides nature exposure in an inexpensive, convenient, and less time-consuming manner than *in vivo* nature exposure (41, 43), and virtual nature can be experienced by individuals with mobility constraints (39). Browning et al. (42) reported that compared to a group of people who had an outdoor nature experience, a group that viewed short nature videos in VR experienced increased perceived restorativeness and positive mood. In addition, increasing research has explored the effectiveness of applying VR nature experiences in a wide range of healthcare applications, from pain management to depression (44–46). Valtchanov et al. (47) conducted a study with 22 participants and found a restorative effect of virtual forest immersion with VR akin to that of real-life nature exposure, resulting in increased positive affect and lower stress.

Unlike research into the benefits of virtual nature to ameliorate psychological stress, research into the benefits of virtual nature to ameliorate physiological stress has not yielded unambiguous results (48). The sound of nature can be crucial in recreating a dynamic natural setting for stress recovery (49, 50), as one group that experienced virtual nature with sound showed more parasympathetic activation than a group whose virtual nature experience did not include sound (51). Van den Berg et al. (52) illustrated that respiratory sinus arrhythmia, which is an indicator of parasympathetic activity, increased in a group of 46 students after they viewed photos of green spaces. However, a study with 30 participants failed to find a significant difference in systolic blood pressure and heart rate when comparing the effects of forest-environment and urban-environment VR experiences (48). Anderson et al. (53) concluded that there was no significant difference in objective physiological stress indicators, including electrodermal activity and HRV, after watching a 360° virtual nature video.

The prolonged COVID-19 pandemic and its associated prevention measures, such as citywide lockdowns, social-distancing rules, school closures, and working from home, have triggered mental and emotional stress and have limited people's ability to explore nature and experience green space *in vivo* (54). A virtual nature option would allow people who are unable to go outside to gain the benefits of nature exposure during the pandemic (55), and it might be an easily accessible alternative to *in vivo* nature exposure. However, there is a paucity of research examining the effects of virtual nature on the stress and health of adolescents during the COVID-19 pandemic (56). One preliminary study explored the plausibility of employing virtual nature as a stress-reduction intervention among COVID-19 frontline healthcare workers and found that the intervention had a significant stress-reducing effect (57).

To address the unmet need for an accessible and convenient stress-relief intervention amidst the COVID-19 pandemic, we aimed to conduct an exploratory study to examine the effect of virtual nature-based interventions on university students' psycho-physiological stress. Because our goal was to test an intervention that is easy to employ during the pandemic when social distancing measures were in place, we did not use specialized equipment or devices, but instead relied on a computer screen that played a 15-min 2-D video as an accessible method to obtain nature exposure at home. With most of the previous research adopting single interventions (42, 45–47, 55), we aimed to explore the effects of repeated nature exposure as a stress-reduction intervention package compared with control groups, with three types of virtual nature experience interventions conducted three times per week for three consecutive weeks. To explore the potential cumulative effects, follow-up assessments were conducted 2 weeks after the intervention period. When evaluating the effect of the virtual nature-based intervention, both physiological stress (particularly cardiovascular responses) and psychological stress were evaluated.

We hypothesized as follows: (a) Participants in the experimental group (virtual nature experience) will show lower levels of psychological and physiological stress responses after 3 weeks of interventions and during follow-up assessments compared with the baseline; and (b) Participants in the experimental group will show lower levels of psychological and physiological stress responses than the control group after 3 weeks of interventions and during follow-up assessments.

2. Materials and methods

2.1. Study design

Our study design involved a virtual experience-based pretest-posttest intervention with a control group. The independent variable was the virtual nature experience, whilst the dependent variables were the psychological and physiological health of university students. As part of a larger study investigating the influence of virtual nature exposure, this study aimed to examine the effects of a 3-week period of virtual nature experience on the psycho-physiological health.

2.2. Study population and sampling

Full-time students who were aged 18 years old or above and had the ability to comprehend our English-language questionnaire were recruited from a medium-sized university in Hong Kong. The exclusion criteria included self-reported mental illness, self-reported symptoms of disease, taking medicine, consuming caffeinated drinks and food, and consuming alcohol during the weeks of the study. Fifty-six participants were recruited, three of whom dropped out after registration due to other commitments, leaving an eligible sample of 53. All 53 participants completed the psychological measurements, and 28 participants agreed to the collection of data on the physiological stress variables. Because travel to the on-campus laboratory was required amidst the constraints of the fourth wave of COVID-19 in Hong Kong, we acquired a smaller sample of physiological stress variables than we would have acquired otherwise. The retention rate of the participants by the last week of the intervention was 84.5%. The study protocol was reviewed and approved by the Hong Kong Baptist University's Research Ethics Committee (REC/19-20/0306). All of the participants provided their prior informed consent. Convenience sampling was adopted through print advertisements and social media, including the school email network, Facebook, and Instagram, from December 2020 to November 2021. The participants were instructed to register and complete a demographic survey online. The eligible students who confirmed that they could attend all nine virtual nature experience sessions were then informed of arrangement of the interventions. To encourage retention, an incentive of HK$100 was offered to each participant who completed the study. The study was conducted between January and November 2021, during the fourth wave of COVID-19 pandemic, during which time Hong Kong had 12,436 confirmed cases (58), and 213 deaths as of 30 November 2021 (59). The Hong Kong government had adopted a dynamic zero-COVID policy, implementing strict anti-epidemic measures such as closing bars, schools, gym, cinemas, theme parks and sports venues; imposing a curfew for dine-in services; and adopting stringent travel restrictions.

2.3. Interventions and data collection procedure

The participants were randomly assigned to different groups: the experimental groups, which included the urban nature (n = 11), marine nature (n = 9), and forest nature (n = 11) groups; and the control groups, including a shopping mall (n = 9) and a city (n = 13). A 15-min video was the medium for delivering the virtual experience of the two groups. The videos were collected from various public sources using YouTube (www.youtube.com/). To ensure that the videos could be used without copyright limitations, we selected those labeled for non-commercial reuse only. Each exposure condition included sounds but lacked a narrative about the conditions depicted. Figure 1 shows the procedure of the interventions and the measurement undertaken at different time points. To assess the cumulative effects, the interventions were administered three times per week for 3 weeks, giving nine interventions in total. Each intervention lasting for 15 min was adopted which was about the lower end of the intervention duration (20 min) recommended by Coventry et al. (60). One-way blinding was employed to minimize bias; thus, the participants were not informed of which group they would be assigned to before the study. During the first intervention session, the participants watched the clips corresponding to the randomized groups. Before watching the videos, the participants were instructed to take 3 min of active rest to minimize the impact of commuting or other disturbances. After the active rest, an HRV monitor, oximeter, and blood pressure monitor were placed onto the participants, and remained in place throughout the intervention. Next, the videos corresponding to the participants' assigned groups were played. Afterwards, post-test measurements were taken. Before first intervention (T0), after the nine interventions (T1), 2 weeks after the nine interventions (T2), the participants were asked to complete a questionnaire measuring their psychological responses. Noting the potential sleeper effect [i.e., a delayed effect after discontinuing the intervention (61)], T2 was measured with an aim to investigate the retention effects of the intervention. The physiological measurements were as follows: shopping mall: n = 5; city: n = 5; urban nature n = 5; marine nature n = 6; forest nature n = 7.

2.4. Measurement and instruments

A survey was used to collect data on the participants' demographic factors, including age and gender. The participants' psychological and physiological responses to the interventions were measured. A pilot study of eight participants was conducted on the logistics of the interventions, the physiological measurement, and the readability and clarity of the questionnaire to improve the administration and implementation of the main study.

2.4.1. Psychological instruments

A self-reported questionnaire in English, which was approximately 15 min long, was administered to measure

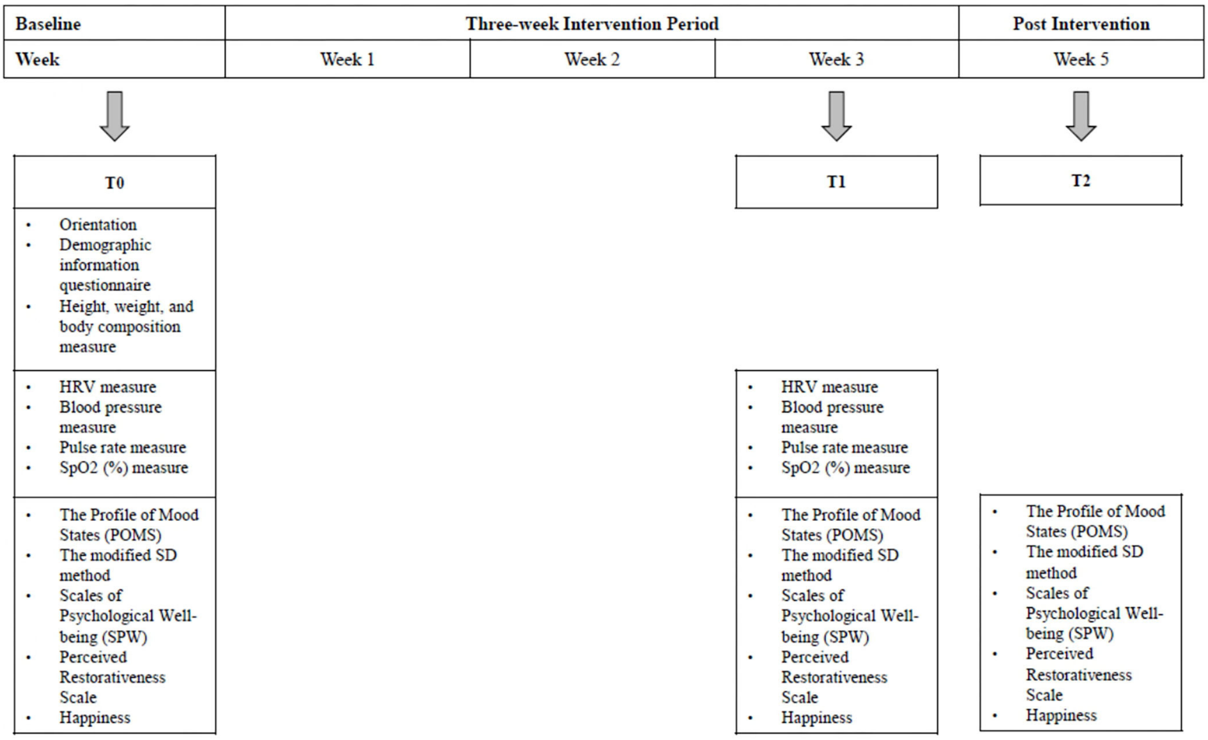

FIGURE 1
Measurements at different time points.

the participants' nature connectedness, stress, mood and psychological wellbeing.

Degree of Nature Connectedness. The degree of nature connectedness was measured by asking the respondents to indicate their degree of nature connected between themselves and nature using a score from zero to 100. The lowest self-reported degree of connectedness was represented by a score of zero, whereas a score of 100 indicated the highest degree of connectedness.

Profile of Mood State (POMS)-Short Form. Mood change was measured by the short form of POMS (62). The 37-item POMS was validated with a good internal consistency (Cronbach's $\alpha = 0.76$–0.95) (63); it presents respondents with various adjectives regarding mood states and asks them to rate how well the adjectives describe their mood on a five-point Likert scale (0 = not at all, 4 = extremely well). On this scale, psychological distress is categorized into six dimensions—tension, depression, anger, vigor, fatigue, and confusion—creating six subscales. The depression subscale is measured using eight items in this 37-item short form, with items including unhappy and blue. The vigor and confusion subscales are measured using six and five items, respectively, including items such as lively and active for vigor and confused and forgetful for confusion. Whilst the tension subscale consists of six items, including tense and on-edge, the anger subscale contains seven items, for example, angry and peeved. Finally, the fatigue subscale consists of five items, including worn-out and weary. The values of all of the items are added into a total mood score, with a lower score indicating a more stable mood profile. The Cronbach's α of the present study were 0.94, 0.96, and 0.97 at baseline, week 3 and week 5, respectively.

The Modified Semantic Differential (SD) Method. The modified SD method (64) was used to evaluate participants' subjective emotions. The respondents were asked to evaluate their degree of emotion on a spectrum with semantically bipolar adjectives, for example, "comfortable–uncomfortable." Three sets of opposing words were included, "comfortable–uncomfortable," "natural–artificial," and "relaxing–awakening." Items are rated on a 13-point scale ranging from −6 (*very artificial*) to +6 (*very natural*), with a higher score indicating more positive emotional conditions.

Scale of Psychological wellbeing (SPW). The SPW is a validated instrument derived from Ryff's model of psychological wellbeing (65) which contains six core dimensions, including autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, and self-acceptance. The SPW has a good internal consistency (Cronbach's $\alpha = 0.86$–0.93), test–retest reliability (Cronbach's $\alpha = 0.81$–0.85), and good validity (65). The scale includes 18 items, with each item evaluated using a 7-point Likert scale (1 = *strongly disagree* to 7 = *strongly agree*). Each subscale consists of three items. Questions 1, 2, and 5 measure self-acceptance, whilst questions 3, 7, and 10 measure purpose in life. Items measured on the Personal Growth subscales are found in questions 11, 12, and 14, whilst questions 6, 13, and 16 measure items on the Positive Relation with Others subscales. Questions 15, 17, and 18 belong to the Autonomy subscale, and questions 4, 8, and 9 belong to the Environmental Mastery subscale. Questions 1, 2, 3, 8, 9, 11, 12, 13, 17, and 18 require reverse scoring, as the statements are oppositely worded to the direction of the subscale. The recording formula is the number of scale points plus one, minus the answer of the respondent. For example, if the participant answers 3 *(agree a little*) to Question 1, the recording formula is 7 + 1 – 3 = 5. The subscale scores are calculated by summing the response values of the items corresponding to the subscales. A higher score indicates better psychological wellbeing. The Cronbach's α of the present study were 0.81, 0.85, and 0.85 at baseline, week 3 and week 5, respectively.

Perceived Restorativeness Scale (PRS). The PRS, developed by Hartig et al. (66), is a 26-item self-report validated scale for assessing the restorative quality of a particular environment. The scale was later shortened by Pasini et al. (67) to 11 items that capture factors such as Fascination, Being Away, Coherence, and Scope. Participants are asked to rate how well the statements describe their experience, on a 11-point scale, ranging from 0 (not at all) to 10 (completely/very much). Each factor was measured by three items, other than the Scope subscale, which was measured by two items only. An example of a Fascination subscale item is "In places like this it is hard to be bored." Items on the Being away subscale include "Places like that are a refuge from nuisances", "In places like this it is easy to see how things are organized" and "That place is large enough to allow exploration in many directions" are the example items for the Coherence and Scope subscales, respectively. A higher mean score indicates a higher level of perceived restorativeness. The scale is invariant across nationality and gender, suggesting good validity (67). The reliability of the short version of the PRS was previously reported as Cronbach's $\alpha = 0.79$ (68). The Cronbach's α of the present study were 0.92, 0.94, and 0.91 at baseline, week 3 and week 5, respectively.

Happiness. To evaluate the participants' happiness, we used a single item scale (69) that has been shown to be a valid and reliable tool. The participants were asked to indicate how happy they felt at the moment on an 11-point scale ranging from 0 (not happy) to 10 (very happy).

2.4.2. Physiological measurements

The average pulse rate, systolic blood pressure, and diastolic blood pressure were measured using a wireless portable blood pressure monitor (OMRON Smart Elite+). The average peripheral oxygen saturation (SpO2) was measured with an oximeter (O2Ring, US). In addition to the physiological indicators at a single time point, we collected data on HRV, which is a measure of the cardiac control exerted by the central autonomic nervous system (ANS) and a biomarker for stress for its association with emotional regulation ability (29). Various studies have demonstrated that HRV is significantly increased in response to stress in healthy participants (31). The converging evidence provides a strong basis for using HRV as an indicator of psychological stress. Therefore, we measured the participants' HRV using a wireless wearable HRV monitor (Polar H10 Heart Rate Sensor). HRV was represented by RMSSD, which is the square root of the mean of the sum of the squares of difference between adjacent to normal and normal intervals (31). The automatically generated Baevsky's stress index from the HRV monitor device was also used. This index is a geometric measurement of HRV, in which higher values indicate reduced variability and higher sympathetic cardiac activation, and hence higher cardiovascular system stress (70).

2.5. Statistical analysis

Our statistical analyses were performed using SPSS Statistical Package version 27 (SPSS Inc., Chicago, IL, USA). Descriptive statistics of the participants' demographics were calculated. The data were checked for normality by evaluating skewness, kurtosis, histogram, and normal plot, all of which confirmed a normal distribution. Three missing values were found to be missing at random with no outliers. The three experimental groups, namely, the urban nature group, marine nature group and forest nature group, were combined into the virtual nature group, whilst the two control groups, namely, the shopping mall group and city group, were combined into the urban group. Baseline data were compared between groups to detect the baseline difference. Paired sample *t*-tests were performed to compare the changes in psycho-physiological stress responses after 3 weeks of virtual nature experiences to the baseline in the nature group. In addition, to remove the placebo effect, stress responses after 3 weeks of virtual nature experiences were compared with stress responses in the control groups using an independent sample *t*-test. The assumptions of both tests were checked prior to the analyses. *P*-values of < 0.05 were used as the threshold to reject the null hypothesis.

3. Result

Among the total sample of 53 participants (73.6% female), the mean age was 20.3 years (SD = 1.2). The mean scores and standard deviations of the participants' psychological and physiological stress are reported in Tables 1, 2, respectively. None of the psycho-physiological stress variables showed significant differences between the virtual nature group and the

TABLE 1 Mean scores and standard deviations of the psychological stress of the virtual nature group and urban group at baseline (T0), week 3 (T1), and week 5 (T2).

	Virtual nature group			Urban group		
	T0	T1	T2	T0	T1	T2
Psychological stress variables						
Nature connectedness	67.1 (18.6)	74.9 (14.9)	74.2 (16.2)	56.6 (19.9)	47.6 (22.4)	51.8 (23.8)
Total mood disturbance (POMS)	40.3 (23.3)	32.9 (24.8)	31.6 (24.3)	31.1 (19.5)	35.9 (21.5)	36.2 (25.4)
Perceived restorativeness (PRS)	19.8 (4.9)	21.3 (4.3)	21.1 (3.8)	19.9 (4.5)	18.3 (5.9)	17.8 (5.2)
Happiness	6.7 (2.1)	7.7 (1.9)	7.9 (1.5)	7.6 (1.60)	7.3 (2.0)	7.4 (1.8)
Psychological well-being (SPW)	84.0 (13.1)	84.1 (15.4)	88.9 (16.5)	84.9 (11.5)	84.7 (10.8)	83.6 (11.7)
Degree of emotion: comfortable to uncomfortable	8.2 (2.5)	9.2 (2.4)	8.9 (2.5)	8.4 (2.7)	7.6 (2.7)	8.1 (2.3)
Degree of emotion: relaxed to aroused	8.3 (1.8)	9.4 (2.3)	8.47 (2.55)	7.8 (2.7)	7.8 (2.4)	8.0 (1.8)
Degree of emotion: natural to artificial	7.7 (2.4)	9.6 (1.9)	8.9 (1.8)	6.9 (3.0)	6.0 (2.5)	7.1 (2.5)

TABLE 2 Mean scores and standard deviations of the physiological stress variables in the virtual nature group and urban group ($N = 28$).

	Virtual nature group		Urban group	
	T0	T1	T0	T1
Average SpO_2 (%)	97.3 (0.6)	97.2 (0.65)	97.3 (0.7)	97.4 (0.8)
Average pulse rate	75.3 (11.1)	78.9 (11.4)	78.1 (12.8)	81.2 (13.9)
RMSSD	43.1 (22.2)	65.1 (87.4)	41.6 (23.1)	43.5 (47.3)
Stress index	10.3 (4.8)	8.9 (4.8)	11.0 (5.8)	11.2 (4.7)
Systolic blood pressure	−1.0 (10.7)	2.2 (10.7)	−1.4 (14.7)	4.6 (10.5)
Diastolic blood pressure	−2.4 (6.8)	−3.7 (8.6)	−1.8 (10.7)	0.6 (11.0)

urban group at the baseline, as revealed by the independent t-test, $p > 0.05$.

3.1. Effects of the interventions on the participants' psychological and physiological stress over time

It was hypothesized that participants in the virtual nature-based interventions would show improved psychological and physiological stress compared to the baseline. A paired t-test was conducted to compare the effects of the 3 weeks of virtual nature interventions on the participants' psycho-physiological responses with the baseline. The assumptions of the paired t-test were not violated. Table 3 summarizes the results of the paired and independent t-tests.

As shown in Figure 2, the participants in the virtual nature group showed significantly higher levels of nature connectedness after 3 weeks of intervention than the baseline, $t_{(25)} = -2.29$, $p = 0.03$. In addition, the participants in the virtual nature group reported significantly higher levels of happiness at week 3 than the baseline, $t_{(25)} = -2.34$, $p = 0.03$, as depicted in Figure 3. Significant increases over the baseline in terms of the degree of relaxed and natural emotions at week 3 were also found as follows: relaxed: $t_{(25)} = -2.31$, $p = 0.03$; natural: $t_{(25)} = -3.07$, $p = 0.005$. These results are further visualized in Figure 4. However, the degree of comfortable emotions, total mood disturbance, perceived restorativeness, and psychological wellbeing in the virtual nature group did not show significant differences at Week 3 compared to the baseline, $p > 0.05$. Our analyses also revealed no significant difference in any of the physiological stress variables at week 3 compared to the baseline, $p > 0.05$.

3.2. Effects of the interventions on the participants' psychological and physiological stress vs. the urban group

To test the second hypothesis that the participants who received virtual nature experiences would show lower levels of psychological and physiological stress responses than the

TABLE 3 Between-subject and within-subjects comparison of the psycho-physiological stress variables at T0, T1, and T2.

	Independent T-tests			Paired T-tests	
	T0	T1	T2	T0–T1	T0–T2
Psychological stress variables ($n = 53$)					
Nature connectedness	$t_{(51)} = -1.95$	$t_{(45)} = -5.01^{***}$	$t_{(33)} = -3.31^{**}$	$t_{(25)} = -2.29^{*}$	$t_{(18)} = -1.17$
Total mood disturbance (POMS)	$t_{(51)} = -1.53$	$t_{(45)} = 0.43$	$t_{(33)} = 0.55$	$t_{(25)} = 1.62$	$t_{(18)} = 2.19^{*}$
Perceived restorativeness (PRS)	$t_{(51)} = 0.08$	$t_{(45)} = -1.97$	$t_{(33)} = -2.20^{*}$	$t_{(25)} = -1.46$	$t_{(18)} = -1.86$
Happiness	$t_{(51)} = 1.68$	$t_{(45)} = -0.66$	$t_{(33)} = -0.81$	$t_{(25)} = -2.34^{*}$	$t_{(18)} = -3.31^{**}$
Psychological wellbeing (SPW)	$t_{(51)} = 0.25$	$t_{(45)} = 0.15$	$t_{(33)} = -1.07$	$t_{(25)} = -0.19$	$t_{(18)} = -1.48$
Degree of emotion: comfortable to uncomfortable	$t_{(51)} = 0.24$	$t_{(45)} = -2.17^{*}$	$t_{(33)} = -1.02$	$t_{(25)} = -2.11$	$t_{(18)} = -0.96$
Degree of emotion: relaxed to aroused	$t_{(51)} = -0.89$	$t_{(45)} = -2.33^{*}$	$t_{(33)} = -0.63$	$t_{(25)} = -2.31^{*}$	$t_{(18)} = -0.16$
Degree of emotion: natural to artificial	$t_{(51)} = -1.07$	$t_{(45)} = -5.73^{***}$	$t_{(33)} = -2.45^{*}$	$t_{(25)} = -3.07^{**}$	$t_{(18)} = -1.33$
Physiological stress variables ($n = 26$)					
Average SpO_2 (%)	$t_{(26)} = 0.09$	$t_{(26)} = 0.63$		$t_{(17)} = 0.27$	
Average pulse rate	$t_{(26)} = 0.60$	$t_{(26)} = 0.48$		$t_{(17)} = -0.85$	
RMSSD	$t_{(26)} = -0.17$	$t_{(26)} = -0.72$		$t_{(17)} = -1.05$	
Stress index	$t_{(26)} = 0.33$	$t_{(26)} = 1.20$		$t_{(17)} = 0.93$	
Systolic blood pressure (before–after)	$t_{(26)} = -0.08$	$t_{(26)} = 0.57$		$t_{(17)} = 0.74$	
Diastolic blood pressure (before–after)	$t_{(26)} = 0.20$	$t_{(26)} = 1.15$		$t_{(17)} = -0.48$	

T0: Baseline, T1: Week 3, T2: Week 5.
$^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

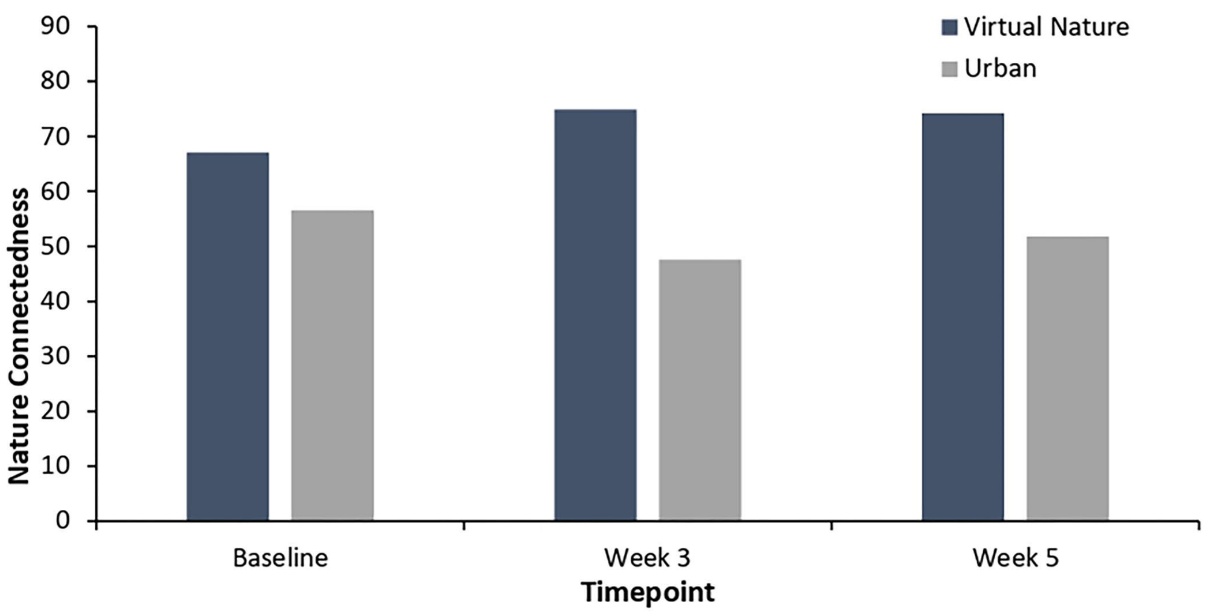

FIGURE 2
Nature connectedness in the virtual nature group and urban group from baseline to week 5. Levels of nature connectedness in the virtual nature group were higher than in the urban group in weeks 3 and 5. There was an increase in nature connectedness in weeks 3 and 5 over the baseline.

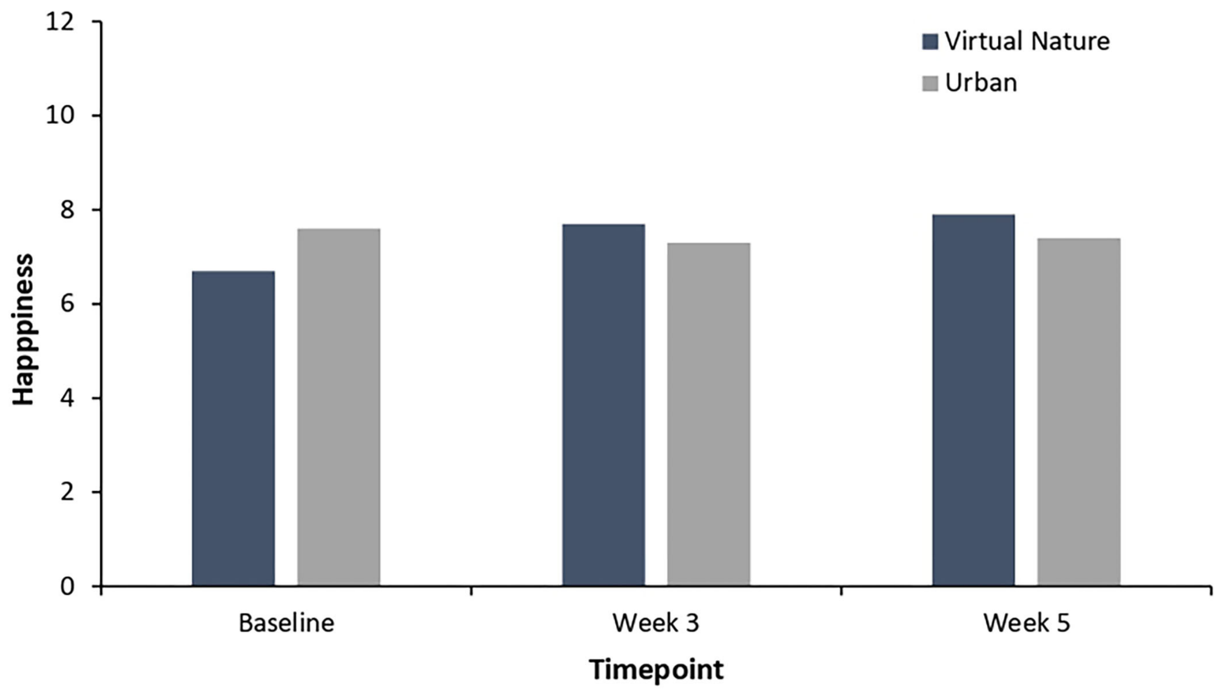

FIGURE 3
Happiness in the virtual nature group and urban group from baseline, week 3 and week 5. Levels of happiness in the virtual nature group were higher than in the urban group in week 3 and week 5. There was an increase in happiness in week 3 and week 5 over baseline.

participants in the urban group, independent *t*-tests were conducted to compare the stress variables at Week 3 in the virtual nature group vs. the urban group. Levene's test of equality of variance suggested that the assumption of homogeneity of variance had not been violated, with $p > 0.05$ in all variables at Week 3. The assumptions for the independent *t*-test were met, and hence the results can be interpreted accurately.

Table 3 illustrates the results from the independent *t*-test comparing psycho-physiological stress in the virtual nature group with that in the urban group at Week 3 and at the follow-up. As seen in Figure 2, the participants reported significantly higher levels of nature connectedness after 3 weeks of virtual nature experience than the participants in the urban group did at Week 3: $t_{(45)} = -5.01$, $p < 0.001$. Additionally, as shown in Figure 4, a significantly higher degree of natural emotion was found in the virtual nature group than in the urban group by the end of Week 3, $t_{(45)} = -5.73$, $p < 0.001$. The degree of comfortable and relaxed emotions was also significantly higher in the virtual nature group than in the urban group after 3 weeks as follows: comfortable, $t_{(45)} = -2.17$, $p = 0.04$; relaxed, $t_{(45)} = -2.33$, $p = 0.03$. Despite the significant within-subject change in happiness shown in Figure 3, there was no significant difference between the groups at Week 3 and follow-up. However, as shown in Figure 5, for total mood disturbance, perceived restorativeness, and psychological wellbeing, the difference between the virtual nature and urban groups at Week 3 did not reach statistical significance, $p > 0.05$. None of the physiological stress variables measured at Week 3 showed significant differences between groups, $p > 0.05$.

3.3. Retention effects of the interventions on participants' psychological stress vs. the urban group

A follow-up assessment of the participants' psychological variables was performed 2 weeks after the intervention period. Compared to the baseline using paired *t*-tests, significant differences were found in happiness, $t_{(18)} = -3.31$, $p = 0.004$, and total mood disturbance, $t_{(18)} = 2.19$, $p = 0.042$. The increased degree of positive emotions, including comfortable, relaxed, and natural feelings at the end of the intervention, were not sustained 2 weeks after the intervention, $p > 0.05$. The participants' nature connectedness, perceived restorativeness, and psychological wellbeing reported at the 2-week follow-up did not significantly differ from the baseline, $p > 0.05$.

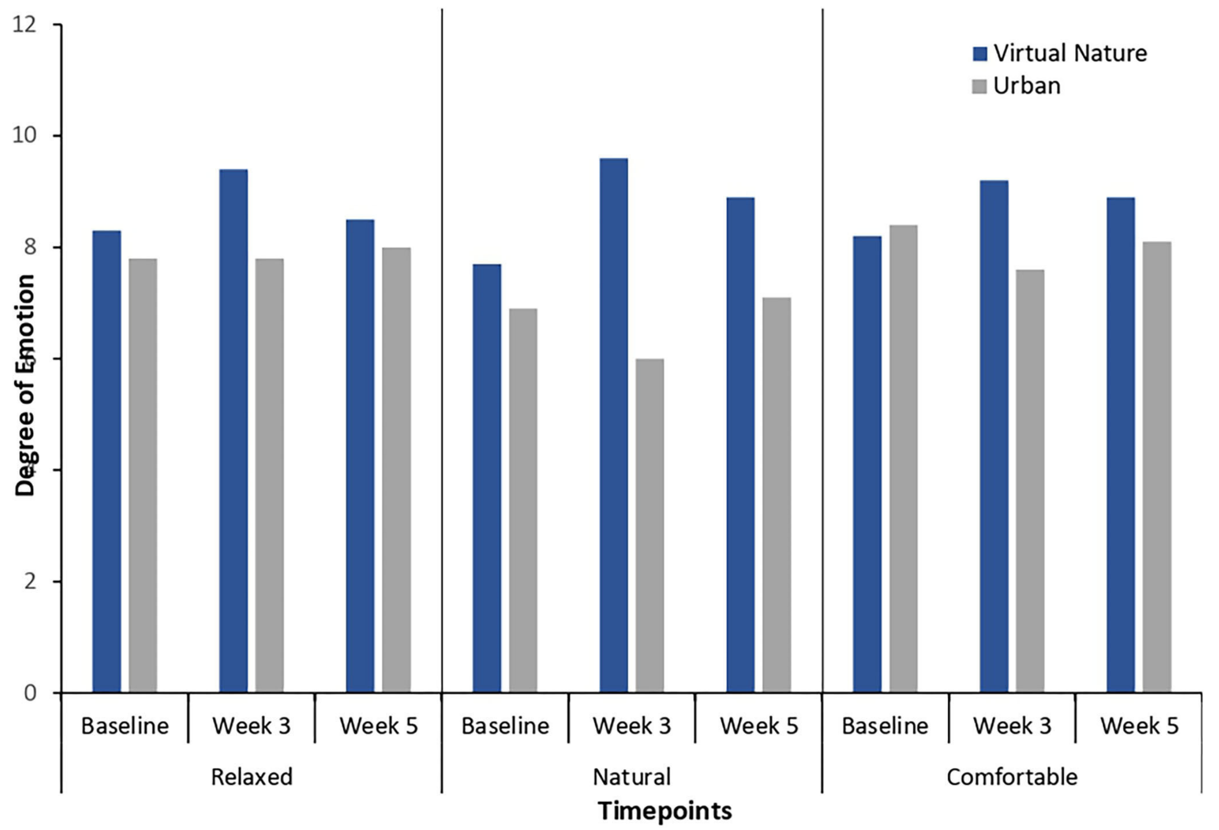

FIGURE 4
Degree of relaxed, natural, and comfortable mood at baseline (T0), week 3 (T1), and week 5 (T2) in the virtual nature group and urban group. The increase in relaxed, natural mood in week 3 from the baseline in the virtual nature group reached statistical significance. Although there was a trend of increase in comfortable mood in week 3 from the baseline, that change was not statistically significant. Moreover, the levels of relaxed, natural, and comfortable mood in the virtual nature group were higher than those in the urban group in week 3. Although the differences did not reach statistical significance, there was a greater trend of a more relaxed and comfortable mood in the virtual nature group than in the urban group at the week 5.

A comparison of the groups at follow-up was made using independent t-tests. Whilst Levene's test for equality of variance confirmed that the variables' variance did not differ significantly between the groups at the follow-up, $p > 0.05$, our assumptions were validated. When compared to those in the urban group, our results demonstrated that the heightened nature connectedness of the virtual nature group over the urban group remained during the follow-up, $t_{(33)} = -3.31$, $p = 0.002$, along with the increased emotions of feeling natural, $t_{(33)} = -2.45$, $p = 0.02$. The boost in degree of comfortable and relaxed emotions seen at the end of the 3-week intervention, however, was not sustained after 2 weeks, $p > 0.05$. Despite the absence of significant differences in perceived restorativeness at Week 3, the participants in the virtual nature group reported significantly higher levels of perceived restorativeness at the follow-up than at the baseline, $t_{(33)} = -2.20$, $p = 0.04$. Total mood disturbance, happiness, and psychological wellbeing at the follow-up did not significantly differ from the baseline.

4. Discussion

In light of the increased attention being paid to the mental health of adolescents during the COVID-19 pandemic, we aimed to evaluate the effect of a simple virtual nature-based intervention, i.e., watching a 2-D video, on reducing psycho-physiological stress in university students. This study provides evidence to add to the existing literature on the effectiveness of brief virtual nature-based intervention on the wellbeing of the university students during the pandemic. Our findings show that watching 15-min videos of three nature-based scenes, including urban nature, marine nature and forest nature, for 3 weeks resulted in psychological benefits for the participants, namely, increased happiness, along with comfortable, relaxed, and natural emotions. However, no influence was found on physiological stress. Despite increasing research into the adoption of VR technology in nature-based interventions that emphasize a

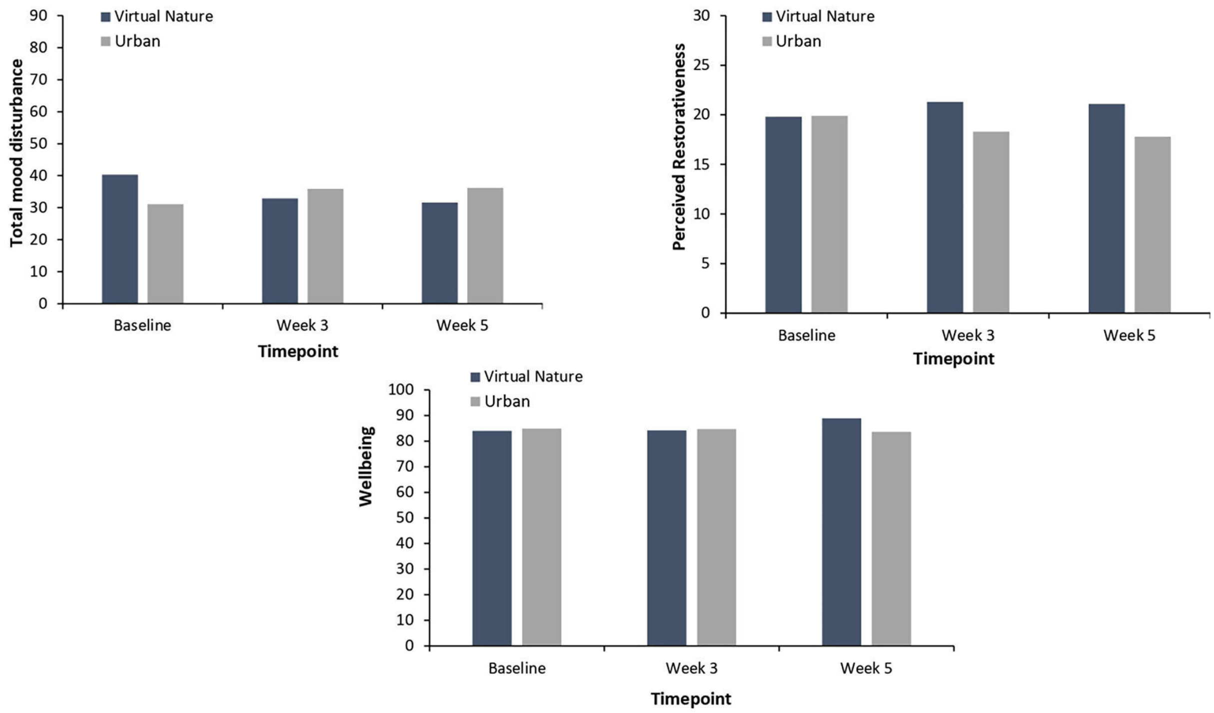

FIGURE 5
Levels of perceived restorativeness, total mood disturbance, and psychological wellbeing of the virtual nature group and urban group at baseline, week 3 and week 5. No significant difference was found between the groups in week 3 and the week 5. Moreover, no significant changes were found in either group between baseline and week 5.

fuller immersion in a simulated natural environment, we demonstrate that a simple 2-D video can be an effective, low-cost, convenient alternative to *in vivo* nature experiences during the pandemic.

4.1. Virtual nature and psychological stress

Previous studies have demonstrated that virtual nature delivered by various methods increases positive affect and reduces stress (46). Our findings are somewhat consistent with studies that have previously reported the hedonic effects of virtual nature exposure (42, 47), although support for a reduction in negative affect is less clear. Consistent with the recent literature, enhancements in positive affect and happiness were found after 3 weeks of the virtual nature-based intervention compared to the urban group and the baseline. Similarly, Keltner et al. (71) researched the emotional changes in study participants in six countries after they viewed short clips of natural history television content, and reported significant increases in positive feelings, including awe, contentedness, and joy; this change was significantly different from that observed in the control group. Whilst the literature has primarily adopted single viewings of nature videos, this study may add to the current understanding of the psychological effects of repeated viewings.

Our results showed that the intervention had no effect on psychological wellbeing as measured by SPW. Because Ryff's SPW measure of psychological wellbeing focuses heavily on eudaimonia, which is characterized by self-acceptance and fulfilling one's life purpose (65), the lack of change in psychological wellbeing might be attributable to the relatively constant nature of eudaimonia. In comparison to research that has successfully improved eudaimonic wellbeing (65), a 3-week intervention protocol may be too brief to exert effects on the participants' eudaimonia. Meanwhile, the participants' total mood disturbance only showed significant changes from the baseline during the follow-up, but not at the end of Week 3. Thus, this finding should be treated with great caution. Notably, because of the exploratory nature of this study, it included a more comprehensive group of variables than previous studies, allowing the measurement of multiple facets of psychological wellness. Given the multitude of outcome variables, this study had a higher likelihood of obtaining mixed results. Frost et al. (72) systematically reviewed 21 studies of the psychological effects of virtual nature immersion. They reported that 33% of the studies provided evidence supporting a reduction in negative effects, whilst 38% of the studies either failed to observe changes or observed an increase in negative affect. The evidence base for the psychological impact of virtual nature experiences remains inconclusive and warrants further research.

Coinciding with the significant improvement in positive mood, the experimental videos successfully cultivated strong nature connectedness in the participants during all weeks and at the follow-up. A study on 863 participants in China investigated the links between nature exposure, nature connectedness, and mental wellbeing (73) and found that nature connectedness moderated the associations between nature exposure, as measured by visitation frequency, nearby greenspace and park quantity, and mental wellbeing. Similarly, another recent study revealed that nature connectedness and nature restorativeness mediated the relationship between nature exposure and quality of life in 924 Lithuanians (74). The increase in nature connectedness over the control group and baseline following a virtual nature experience is consistent with the well-established evidence of how nature exposure affects mental wellbeing by eliciting nature connectedness. The concurrent increase in nature connectedness and positive affect provides primary support for increasing positive affect with 2-D videos that induce nature connectedness.

Nature exposure research has established the close association of perceived restorativeness and nature connectedness (75). A mediation analysis carried out by McAllister et al. (76) supported the proposition that perceived restorativeness is a mediator of nature experience and affect. However, despite the significant between-group difference in nature connectedness during Week 3 and at the follow-up in this study, the participants' perceived restorativeness only showed a significant difference at the follow-up. The reason for this discrepancy is unclear, one plausible explanation may be related to the spatial characteristics of the nature intervention. Tabrizian et al. (77) demonstrated that the permeability and arrangement of vegetation moderated the restorativeness of a green space by affecting the environment's perceived safety. A more dense and enclosed green space is associated with lower perceptions of safety and restorativeness. Therefore, future research in virtual nature should consider considering spatial characteristics which may influence the perception of the environment.

4.2. Virtual nature and physiological stress

Our findings suggest that 3 weeks of virtual nature exposure has no significant effect on any of the physiological variables. According to a systematic review by Frost et al. (72), 10 virtual nature studies that measured physiological indicators of stress, ranging from salivary cortisol to heart rate variability, returned mixed results. In line with our results, the blood pressure and HRV of that study's participants' did not display significant changes after watching 360° or VR videos of nature (48, 53). Nukarinen et al. (78) concluded that unlike their real-life nature group, the participants in their virtual nature group did not show significant restoration in terms of HRV and pulse rate. In contrast, some researchers have found evidence supporting the proposition that virtual nature experiences can lower a person's heart rate (79, 80) and HRV (51). For instance, Alyan et al. (79) conducted a study with 20 participants in Finland who were asked to go on virtual forest walks. They found a significant decrease in heart rate and skin conductance level, along with lower levels of depression and confusion in POMS. The nonsignificant findings of this study might be because the nature exposure was not immersive enough to translate psychological changes into physiological changes. Another possible explanation for the lack of significant changes in the physiological variables in the current study could be that the outcome measurements emphasized the physiological indicators of stress reductions, mainly cardiovascular stress responses. It could be argued that the psychological changes observed in this trial were mainly hedonic in nature, including an increase in happiness and positive affect, like comfortable and relaxed feelings. Psychosomatic research suggests that happiness and joy can also increase blood pressure (81), which is inconsistent with reduced blood pressure during relaxation. Notwithstanding the well-established evidence of real-life nature exposure on physiological stress, the physiological influence of virtual nature remains inconclusive.

5. Study limitations and future research

Although the current exploratory research provided some preliminary findings regarding the benefits of virtual nature experience on nature connection and health, the study has several limitations. First, there may have been a selection bias in the sampling, as students who were either more stressed or more interested in nature experiences than others were more likely to participate in the study. However, an incentive of $100 HKD (i.e., $12.78 UDS) would be able to attract students to participate regardless of their stress levels or interest level in nature experience. Noting from a large population study of 4,960 adults in England by Martin et al. (82) with the findings showed that trait connectedness to nature moderated the relationships between nature contacts and psychological wellbeing, future studies could consider measuring participants' personal inclination to connect with nature, e.g., how often they visit nature. Second, there was an imbalance amongst the virtual nature group and the urban group in that the numbers of controlled participants did not match those in the intervention groups. An unequal sample size of the two groups might have a different probability of resulting in type one or two errors (83). Third, it should be acknowledged that the sample size is small for a conclusive interpretation of the interventions' effects. Future research is required to replicate the study with a larger sample size, and with equally sized control and experimental groups, to capture the effectiveness of the virtual nature experience with a higher degree of confidence. Fourth, the participants' preference for natural environments was not measured in the study. Other research showed a significant correlation between the participants' appreciation of various natural environments and the improvement in their mood after experiencing them in VR (84). Future trials could take this into consideration to enhance the experience. Fifth, in the current study design, the content of the videos in each group was the same throughout the 3-week intervention period. It is unclear whether the repetition might have caused the participants to become bored with or tired of the intervention. The evidence suggests that there is a positive association between the psycho-physiological benefits of nature exposure and species richness and habitat diversity (85). Further research is needed to explore whether videos of various natural environments, or videos of various scenes of the same natural environments, can be used to maximize the participants' perception of biodiversity. Sixth, this study focused on the results of pre-post-intervention comparison of a 3-week virtual nature experience only, but without investigating the continuous changes of the physiological factors (such as cardiovascular variables) which were rather fluctuated as expected. The fuller picture of the benefits of the virtual nature contact could be further explored in future studies when the continuous changes of these variables are investigated. Seventh, because the intervention was self-administered in the participants' homes due to the COVID-19 pandemic and university campus closures, the above-referenced fluctuations are likely to have been influenced by other confounding factors that are unaccounted for, warranting future research. Future studies could randomize the control group and experimental group with participants of balanced gender according to the levels of participants' personal inclination to connect with nature in order to reduce the potential bias.

6. Implications

The COVID-19 pandemic has brought a rapid increase in stress, and psychopathology such as anxiety and depression (2, 3). Smith et al. (86) compared the difference of nature relatedness between actual nature and virtual nature experiences and found no significant differences between them. As technology advances, researchers have adopted different methods to deliver virtual exposure to nature, including 2-D videos, 360° VR viewing, and interactive computer-generated VR. However, there has been only limited research into how the effectiveness of these stimulations vary. Yeo et al. (87) compared the effectiveness of these three virtual nature delivery modes for lowering negative affect and increasing positive affect and found that despite the fact that interactive computer-generated VR provided the highest level of nature connectedness and increase in positive affect, all of the conditions achieved a significant reduction in negative affect that did not differ between the simulation forms. As three-dimensional VR technology becomes prevalent, more research studies have employed VR than have employed 2-D videos as the medium to deliver nature exposure (42, 44, 88). Nonetheless, the potential benefits of a more accessible and generalisable form of virtual nature should not be undervalued when developing stress reduction interventions with clinical implications.

This study demonstrates that with the objective of exploring an accessible method to obtain regular nature exposure during the pandemic that requires no special equipment to self-administer, watching 2-D videos of nature could be an adequate form of delivery. Samus et al. (89) reported that in 261 participants, having a private garden with high biodiversity predicted strong nature connectedness, which in turn predicted more positive emotions during New Zealand's 2020 COVID lockdown. Hence, maintaining a good level of nature connectedness is crucial to maintaining wellbeing during stressful times or when mobility is limited. The implications of the restorative effects of virtual nature have been explored in patients with chronic pain, cancer, and dementia (44). Promising results were found in a pilot study of nature-based VR experiences on 24 healthcare professionals during COVID-19 in the United States (90), with a significant alleviation of emotional distress and boost in focus reported.

7. Conclusions

Our exploratory study provides preliminary findings in supporting the positive effect of a 3-week virtual nature experience on nature connectedness, happiness, and positive affect during the COVID-19 pandemic. The need to facilitate virtual nature contact opportunities for youth is underscored during times of crisis, when outdoor nature-based activities are limited. Virtual nature contact might be a simple self-help tool for stress relief that does not require a visit to an outdoor natural environment nor specialized equipment like VR. Future studies with larger samples that make comparisons with real-life nature exposure are warranted to validate the effectiveness and clinical significance of virtual nature experience interventions to target stress reduction.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Hong Kong Baptist University's Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualisation and study design, coordination of the study, and funding requisition: SLa. Development of the study methodology: SLa, SLe, JoW, TL, and SC. Data collection: SLa, JM, JaW, and EC. Data analysis: SLa, JM, EC, and RC. Writing up of the manuscript: SLa and RC. All authors have read and agreed to the published version of the manuscript and review of the manuscript.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1057020/full#supplementary-material

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EDITED BY
Zhiming Yang,
University of Science and Technology
Beijing, China

REVIEWED BY
Chunkai Zhao,
South China Agricultural University, China
Wafa Orman,
University of Alabama in Huntsville,
United States

*CORRESPONDENCE
Sheng Xu
✉ shenghsu@163.com

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Effect of air pollution on adult chronic diseases: Evidence from a quasi-natural experiment in China

Yan Li[1], Sheng Xu[2]*, Jinghua Yin[3,4] and Guan Huang[5]

[1]College of Management, Guangdong AIB Polytechnic, Guangzhou, China, [2]School of Health Management, Southern Medical University, Guangzhou, China, [3]School of Insurance, Guangdong University of Finance, Guangzhou, China, [4]Department of Economics, Jinan University, Guangzhou, China, [5]Wenlan School of Business, Zhongnan University of Economics and Law, Wuhan, China

We utilize a quasi-experiment derived from China's Huai River policy to investigate the effect of air pollution on adult chronic diseases. The policy led to higher pollution exposure in cities north of the river boundary because they received centralized coal-based heating supply from the government during winter, whereas cities in the south did not. By applying a geographic regression discontinuity design based on distance from the Huai River, we determine that a 10 $\mu g/m^3$ increase in fine particulate matter ($PM_{2.5}$) raises chronic diseases rates by 3.2% in adults, particularly cardiorespiratory system diseases. Furthermore, the same effects are observed on multiple chronic disease rates, but the rates are reduced to 1.3%. The effect of pollution exposure varies depending on age, gender, and urban/rural status. Our findings imply that reducing 10 $\mu g/m^3$ of the average nationwide level of $PM_{2.5}$ concentration will save 27.46 billion CNY (4.16 billion USD) in chronic disease costs.

KEYWORDS

air pollution, chronic diseases, winter heating policy, quasi-natural experiment, regression discontinuity design

1. Introduction

The prevention and treatment costs of chronic noncommunicable diseases account for the majority of public health expenditure. The last decades have seen an increase in the fraction of chronic noncommunicable disease prevention and treatment expenditure in China's medical expenditure. In 2003, the economic burden of chronic noncommunicable diseases in China was only 858.05 billion Chinese yuan (CNY) (130.01 billion USD),[1] accounting for 71.45% of the total economic burden of all diseases (1). By 2015, the economic cost of chronic noncommunicable diseases has reached 3682.8 billion CNY[2] (558 billion USD), accounting for 80% of the total economic burden of all diseases. In response to this, numerous attempts have been made to determine the causes of chronic diseases, including medical conditions, habits, genetics, and the environment (2, 3). Some studies have focused on the effect of air pollution on chronic diseases (4), However, most studies are limited to exploring the determinants of a single disease, making aggregating the total effect of air pollution on chronic diseases under the same framework difficult due to differences in context, methodologies, and pollutant measures across studies. Moreover, the causal relationship between air pollution and adult chronic diseases remains largely unexplored.

In the past few decades, as a rapidly growing developing economy, China's air quality has deteriorated to a certain extent with the increase of industrial pollution emissions.

1 For comparison, we use the annual average exchange rate between USD and CNY in 2010: 1 USD for 6.6 CNY in this study.

2 See https://www.sohu.com/a/306526685_120099842 (in Chinese).

Simultaneously, as a large population country, China has the largest number of chronic patients in the world, and the prevalence of adult chronic diseases is rising with economic development. Therefore, China provides a unique opportunity to study the relationship between air pollution and adult chronic diseases. In the present work, we investigate in particular the causal relationship between air pollution and adult chronic diseases.

This study contributes to two strands of the literature. First, we build upon previous work that estimates the effect of air pollution on health. In contrast with a large number of studies that focused on mortality (5–8), migration (9), labor supply (10), body weight (11, 12), mental health (13), and children health (4, 14, 15), our study extends this work to encompass adult chronic diseases. Given the lack of research in this area, the total cost of air pollution is underestimated. Additional evidence from the cost of chronic diseases due to air pollution will be beneficial to policy makers and researchers to accurately calculate the total benefits of environmental regulation. Second, chronic diseases have considerably increased public health expenditure. Many previous studies have focused on complex and diverse determinants, including income (16), obesity (17), early life environment (18), genetics (2), and medical conditions (3). This study builds upon the growing literature by providing a new determinant of interest, namely, air pollution.

The primary challenge in identifying causal effect is that air pollution is likely to be endogenous due to omitted variable bias. For example, confusion factors related to economic activities, such as income, are among the determinants of health, while economic activities are also highly correlated with air pollution. To overcome the endogeneity of air pollution, the current study utilizes the regression discontinuity (RD) approach based on a quasi-natural experiment of China's Huai River policy. This policy creates discontinuous variation in air pollution by providing a coal-based centralized heating infrastructure only in cities north of the Huai River and no equivalent system for cities to the river's south.

Using the Huai River RD design, we find a statistically significant and economically positive effect of fine particulate matter ($PM_{2.5}$) on chronic diseases. In particular, a 10 $\mu g/m^3$ increase in average $PM_{2.5}$ concentrations increases the rates of chronic diseases by 3.2% among adults. Taking advantage of a rich survey questionnaire, we define multiple chronic disease dummy variables when respondents answered two chronic diseases. We determine that a 10 $\mu g/m^3$ (19.7%) increase in average $PM_{2.5}$ concentrations increases the probability of having multiple chronic diseases by 1.3%. Moreover, these effects are nearly significant throughout an adult's life cycle, although the magnitude is different. In addition, these effects vary across urban–rural status and gender interaction groups, depending on the level of air pollution exposure. Our results are robust to varying specifications, including different controls, functional forms for the RD polynomial, bandwidth selection, sample selection, and placebo checks.

The Huai River effects are economically meaningful. Our estimate indicates that a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations induces a total annual cost of 27.46 billion CNY (4.16 billion USD), or 0.234% of China's gross domestic product (GDP), in terms of additional medical expenditure for chronic diseases. Notably, these values were derived from 2003 data. As GDP rises, the medical expenditure for chronic diseases in China increases.[3] Several studies have found that the social mortality cost of a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration is 48 billion USD (316.8 billion CNY) (7), the cost of obesity and being overweight is 18.9 billion CNY (2.86 billion USD) (11), the cost of mental illnesses is 12.68 billion USD (83.68 billion CNY) (13), and the total cost of medical expenditures is 75 billion CNY (11.36 billion USD) (19). Although the difference between the cost of chronic diseases due to air pollution and the cost of obesity due to air pollution estimated by Deschenes et al. (11) is the closest, directly comparing them is meaningless because our calculation is derived from China's data in 2003, while the values calculated by Deschenes et al. (11) are based on 2016 data. As China's economy grew rapidly from 2003 to 2016, a prediction can be made that if we use 2016 data to calculate the cost of chronic diseases, then the cost of chronic diseases caused by air pollution will be considerably greater than the cost of obesity. However, disregarding the effect of chronic diseases will certainly underestimate the overall health cost of air pollution.

The remainder of this paper is organized as follows. Section 2 presents the literature review and background information regarding the Huai River policy, and lays out the RD design. Section 3 describes the data sources. Section 4 presents our major findings, including those of the validity, robustness, and heterogeneous tests. Finally, Section 5 concludes the study.

2. Literature review and empirical strategy

2.1. Literature review

Air pollution is a fundamental determinant affecting population health. A large body of literature shows links between air pollution and exacerbations of respiratory diseases, preterm birth, infant mortality, low birth weight, neurodevelopmental disorders, deficits in lung growth, and possibly the development of asthma (20). In view of this fact, the medical mechanism of air pollution effects has always been a research focus. Several studies explore the medical mechanism of air pollution effects and believe that air pollution effects can be mediated by oxidative stress, chronic inflammation, endocrine disorders, and genetic and epigenetic mechanisms throughout the life cycle (21). Another research focus is the health costs of air pollution. Recent studies also estimate the cost of air pollution on a variety of health outcomes, including cardiorespiratory mortality, obesity, mental health, respiratory symptoms, asthma exacerbations, and asthma hospitalizations (4–8, 11, 12, 14, 15). The challenge associated with estimating the health costs of air pollution is that air pollution is likely to be endogenous due to omitted variable bias. There are different ways to solve the endogenous of air pollution in the literature in studying the health outcomes of air pollution. In order to address the endogenous of air pollution on body weight, Deryugina et al. (7) use changes in local wind direction as an instrumental variable for air pollution to estimate the life-years lost due to pollution exposure. Thermal inversion is another useful instrumental variable for air pollution. The strategy to instrument

3 Hu et al. (1) calculated the economic burden of chronic noncommunicable diseases in China in 2003. Health expenditure generally increases with GDP growth, and thus, our estimate is low bound.

for air pollution using thermal inversion was first proposed by Arceo et al. (5), to evaluate the influence of air pollution on infant mortality in Mexico City. Subsequently, the strategy was used to explore the impact of air pollution on children's respiratory health (15), adult obesity (11), and mental illness (13). Another way to deal with the endogenous of air pollution is to use the exogenous variation of air pollution generated by policies, such as China's Huai River policy, which leads to higher pollution exposure in cities north of the river boundary, because they get centralized coal-fired heating from the government in winter, while southern cities do not. Almond et al. (22) first exploit RD design based on Huai River policy and find that the Huai River policy led to higher total suspended particulate levels in the north. This identification strategy has been subsequently used to explore the effects of air pollution on mortality, life expectancy (6, 23), and willingness to pay for clean air (24) in China. Although various health costs of air pollution have been estimated in the literature, the overall chronic disease and multiple chronic disease costs of air pollution have not received much attention under the condition of fully solving endogenous air pollution. We then extend the previous literature by using the Huai River RD design to investigate the cost of chronic diseases caused by air pollution.

2.2. Background

China's winter centralized heating system began in 1958. However, the government only provides centralized heating to northern cities due to energy and financial constraints (22, 23). The north–south boundary of China roughly runs along the Huai River and the Qinling Mountains. The government uses this line because it is also the line where the average temperature in January is about 0°C; however, it is not used for other administrative purposes (8, 24). Cities to the north of the river boundary receive centralized heating from the government every winter. By contrast, no centralized heating is provided by the state to southern China. Most centralized heating systems in the north are coal-fired. The incomplete combustion of coal during the heat generation process will lead to the release of air pollutants, particularly particulate matter. Many studies have found that the Huai River policy has led to an increase in the total level of suspended particulate matter in the northern region (22, 23).

The Huai River policy divides northern and southern cities into treatment and control groups, respectively. Coal consumption enables us to compare the difference in air pollution concentration between the two groups. This scenario provides a quasi-natural experimental environment for researchers to estimate the effect of air pollution on health by using the discontinuity of air pollution caused by coal burning in the Huai River.

This approach provides us with a useful research strategy for two reasons. First, some factors that affect health, such as economic level, education level, and resource differences, will be controlled because the Huai River Line is a geographical boundary rather than an economic and administrative boundary. This strategy enables us to identify the causal effects of air pollution on health. Second, the difference in pollution caused by the policy has always existed since its implementation in 1958. The pollution effect captured by this approach may be extremely significant due to the long-term cumulative effect of air pollution.

2.3. Empirical Strategy

Considering the effects of economic factors on health and the correlation between air pollution and these economic confounding factors, endogeneity may be produced by omitted variables between air pollution and chronic diseases among adults. To address this problem, we utilize the Huai River RD design. We estimate the effects of winter heating on air pollution and health by using an RD design based on distance from the Huai River. We examine whether discontinuous changes exist in air quality and chronic diseases among adults at the Huai River boundary.

In particular, we first estimate the first stage of air pollution by using an RD design created by the Huai River heating policy following Equation (1):

$$PM_c = \varphi_0 + \varphi_1 North_c + f\left(distance_c\right) + \varphi_2^{'} X_c + \varepsilon_c \quad (1)$$

Where PM_c indicates the $PM_{2.5}$ concentration ($\mu g/m^3$) in county c; and $North_c$ is a dummy variable for the north that takes the value of 1 if the county is in the north of the Huai River and 0 otherwise. The key independent variable, i.e., the running variable, $distance_c$ is the distance between county c and the Huai River. We use positive values of $distance_c$ for distances north of the Huai River and negative values for distances south of the river. The function f is a polynomial in $distance_c$ whose coefficients are estimated in the regression. X_c is a covariate, and it includes temperature, relative humidity, cumulative precipitation, and sunshine duration. A potential problem with the Huai River RD design is that the space boundary is extremely long from the west to the east of China. Therefore, factors not observed in the east and west dimensions may confuse RD estimates. To solve this problem, our covariates also include the longitude quartile bin, which flexibly controls the systematic differences between the eastern and western dimensions. ε_c is the error term.

Second, the Huai River RD design utilizes the discontinuity in air pollution caused by coal-fired heating to estimate the effect of air pollution on health. We estimate the reduced form of the RD design to examine whether a discontinuous change exists in chronic diseases among adults at the Huai River boundary following Equation (2):

$$Health_{ic} = \alpha_0 + \alpha_1 North_{ic} + f\left(distance_{ic}\right) + \alpha_2^{'} Z_{ic} + \varepsilon_{ic} \quad (2)$$

Where i indicates observation; and $Health_{ic}$ denotes health status measures, particularly the indicators for chronic diseases, multiple chronic diseases, and subcategories of chronic diseases. The chronic diseases indicator take the value of 1 if i suffers from at least one chronic disease and 0 otherwise. $North_{ic}$ takes the value of 1 if i is located in county c in the north of the Huai River and 0 otherwise. $distance_{ic}$ indicates the distance from county c where individual i lives to the Huai River. Z_{ic} is a vector of observed covariates that potentially affect health, including not only X_c but also demographic and health behavior characteristics. The coefficient of interest, α_1, measures a discontinuous change in health at the Huai River boundary.

Finally, some counties may have less air pollution due to environmental protection measures, although they are located in the north of the Huai River. We reestimate using a fuzzy RD framework with a two-stage least squares (2SLS) regression specified by Equations (3) and (4).

$$PM_{ic} = \varphi_0 + \varphi_1 North_{ic} + f\left(distance_{ic}\right) + \varphi_2^{'} X_{ic} + \varepsilon_{ic} \quad (3)$$
$$Health_{ic} = \beta_0 + \beta_1 PM_{ic} + f\left(distance_{ic}\right) + \beta_2^{'} Z_{ic} + \varepsilon_{ic} \quad (4)$$

Equations (3), (4) are the first and second stages, respectively, in a 2SLS system of equations. PM_{ic} refers to the exposure average concentration of $PM_{2.5}$ sustained by individual i residing in county c. The other variables are as described above. We use $North_{ic}$ as the instrument variable (IV) for PM_{ic}. We estimate the effect of $PM_{2.5}$ on health by using the fuzzy RD approach. The parameter of interest is β_1, which measures the effect of $PM_{2.5}$ exposure on chronic diseases after controlling for available covariates.

3. Data sources

We obtain chronic disease data from the China Family Panel Studies (CFPS), which is a nationwide and comprehensive social tracking survey project. CFPS aims to reflect the changes in China's society, economy, population, education, and health by tracking and collecting data at the individual, family, and community levels. We utilize rich questions and answers on chronic diseases in the CFPS 2010 wave, which is a baseline survey[4] that includes the interviews of 14,960 households and 42,590 individuals from 162 counties/districts in 25 provinces, representing 95% of the population in China. CFPS is conducted by the Social Science Research Institute of Peking University. It uses implicit stratification, multiple stages [county/district (six-digit code),[5] village/community, and household], multiple levels, and probability sampling in proportion to population size.

CFPS has four advantages for our research. First, accurate information about the geographic location of the sample from the county is crucial for our identification strategy. CFPS documents the geographic location and interview date of all the respondents, enabling us to match the health characteristics of the respondents accurately with the external air pollution data. Second, for our research content, CFPS provides detailed information about chronic diseases through the questions and answers and classification codes in the health questionnaire. Third, the survey covers men and women of different ages in rural and urban areas of China, enabling us to conduct rich heterogeneity analysis. Fourth, the survey not only provides health information but also detailed information on socioeconomic and demographic characteristics, enabling us to control a wide range of covariates.

We use three types of health measures. The first is chronic diseases, which is obtained from the questionnaire question "Have you ever suffered from any chronic disease diagnosed by your doctor in the last 6 months?" The variable of chronic diseases is assigned to 1 if the respondent suffers from at least one chronic disease and 0 otherwise. The second is multiple chronic diseases, which is obtained from the questionnaire question "What are the two most important chronic diseases you have been diagnosed with by your doctor?[6]" The result is assigned to 1 if the respondent answers two chronic diseases and 0 otherwise. The third is the subcategories of chronic diseases, which are obtained from the names and classification codes of the chronic diseases answered by the respondents.

For the running variable and longitude covariate, we first use ArcGIS to obtain the longitude and latitude of 162 counties surveyed in CFPS from the map of China. Second, we make a distance variable based on the locations of the county and the Huai River. In particular, we use ArcGIS to measure the shortest distance from the county centroids to the nearest point on the Huai River.[7]

Local governments in China are strongly encouraged to reduce air pollution in China, and the central government uses air quality readings to assess the environmental performance of local governments, and thus, researchers are concerned that local governments may manipulate data. Previously, several studies have investigated China's air pollution data and found a suspicious pattern in the distribution of reported data[8] (25, 26). Although previous studies have shown that the satellite-based aerosol optical depth (AOD) retrieval pollution data and ground-based monitoring station measures exhibit no statistical difference (9, 27, 28), AOD-based data have higher accuracy than ground-based pollution data, which are more easily affected by weather conditions, because the former has a certain correction function for pollution diffusion caused by changes in meteorological conditions (29). To eliminate errors and improve accuracy, our data on air pollution are from satellite-based AOD retrievals. We obtain the AOD data from the $PM_{2.5}$ concentration[9] calculated by the Atmospheric Composition Analysis Group of Dalhousie University through sensors and processed using ArcGIS software. Wang et al. (30) showed that high ambient $PM_{2.5}$ concentration is considered closely related to China's huge primary energy consumption, particularly coal consumption.

The weather data are obtained from the Daily Data Set of China's Surface Climate Data on the China Meteorological Science Data Sharing Service Website, which releases the daily weather variables of more than 800 meteorological stations in China. We use the inverse distance weighting method to convert the weather data from stations to counties and select a radius of 200 km. Weather data include temperature, relative humidity, cumulative precipitation, and sunshine duration. This dataset has been used in previous studies (9, 11, 13).

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4 CFPS conducted four consecutive tracking interviews in 2012, 2014, 2016, and 2018. Our RD design uses the cross-section data of CFPS 2010.

5 The three administrative levels, i.e., province, city, and county, are respectively marked as two-digit, four-digit, and six-digit codes in China. See http://www.stats.gov.cn/tjsj/tjbz/tjyqhdmhcxhfdm/.

6 If the respondent has multiple chronic diseases, then the two most important diseases should be provided. If the respondent has only one chronic disease, then the answer to the second disease should be "not applicable".

7 This distance ranges from 2 km to 2200 km, and the mean distance is 560 km.

8 Chen et al. (9) found that AOD-based pollution data in China are closely matched with data from ground-based monitoring stations.

9 $PM_{2.5}$ refers to particles with an equivalent aerodynamic diameter of 2.5 μm or less in ambient air.

Air pollution and weather data were collapsed at the county level average in 2010 to match the CFPS baseline survey and meet the requirements of the Huai River RD design for cross-sectional characteristics. We compile a dataset from three data sources: the CFPS 2010 wave, air pollution, and weather data. Demographic variables (e.g., age, gender, minority, urban/rural status, and income) and health behavior variables (i.e., whether the respondent smokes regularly, drinks heavily, and eats excessive amounts of red meat), are obtained from the CFPS 2010 wave.

4. Empirical results

4.1. Major results

We begin investigating the effectiveness of the Huai River RD design. An essential test is whether systematic differences exist in observable determinants at the Huai River boundary. The RD design's identifying assumption is that observable determinants change smoothly at the boundary. Table 1 provides the summary statistics of county-level and individual-level observable covariates and evidence for the validity of the RD design. Columns 1 and 2 report the sample mean and standard deviation for the north and south of the Huai River. Column 3 reports the mean difference between the north and the south along with the associated standard errors. Notably, this statistic shows a simple difference, which is not necessarily a discontinuous difference at the boundary. In Column 4, we report whether a discontinuous change occurs at the Huai River boundary by using local linear regression, our primary RD specification in the empirical analysis, to approximate the size of the discontinuity estimated for the covariates with the bandwidth selected using the common mean square error (MSE) method proposed by Calonico et al. (31), Calonico et al. (32), and Calonico et al. (33) with a triangular kernel and report the standard errors in brackets. We do not find a statistically significant discontinuity for a wide range of observable determinants at the river boundary, confirming the internal validity of our research design.

We then present the RD results on the effect of the Huai River policy. The RD method allows for a transparent graphical representation of the effects of interest. We start from this analysis and then present the parametric and nonparametric estimation results. Before we proceed to the formal regression analysis, we provide a graphical analysis of the first stage of the RD design based on the regression results of Equation (1) and the reduced form of the RD design based on the regression results of Equation (2).

Figure 1A presents a graphical analysis of the first stage of the RD design. The points are the unconditional average values of $PM_{2.5}$ across 100 km bins to the south and north of the Huai River boundary. The distance between counties and the boundary, $distance_c$, is shown on the horizontal axis. The vertical line at $distance_c = 0$ indicates the location of the boundary. The northern counties are displayed on the right side of the vertical line, while the southern counties are presented on the left side. The solid and dashed lines are the regression fit and associated confidence intervals, respectively, based on the quadratic polynomial regression of $PM_{2.5}$ exposure on the separately estimated distance from the Huai River. As evident from the figure, the discontinuity of $PM_{2.5}$ concentration increases at the boundary, suggesting that the heating policy has caused higher pollution levels in the northern counties of the Huai River boundary. Similar findings have been reported in previous studies, such as Ebenstein et al. (6) and Ito and Zhang (24).

The right and left columns of Figure 1B display chronic disease and multiple chronic disease rates, respectively around the Huai River boundary, as estimated by the reduced form of the RD design. The figures indicate a discontinuous decrease in the adult chronic disease rate at the boundary, followed by a steady decrease. Visually, the discontinuous jumps in Figure 1B are around 6.9% and 4.8% for chronic diseases and multiple chronic diseases, respectively. These findings are consistent with the reduced form regression results presented in the next section. The figures depict an apparent dependency of the proportions of chronic disease and multiple chronic disease rates in adults on their location relative to the Huai River boundary. Although transparent graphics initially show the RD effect of interest, different regression methods and RD specifications, such as the choice of the order of the polynomial and the bandwidth, may exert a substantial effect on RD estimates.

In the major estimates, we use a polynomial f that is either linear or quadratic in $distance_i$ by applying parametric and nonparametric regression methods. In the robustness checks, however, we also probe the sensitivity of the results to alternative RD specification.

Table 2 presents the first stage estimation results for $PM_{2.5}$ when using parametric and nonparametric regression methods. The first two columns are the results when using a parametric method, while the last two columns are the results when using a nonparametric regression method. We report our estimates from local quadratic and linear regressions.[10] The results in all regressions include weather and longitude covariates. The estimates are robust to different regression methods, the choice of polynomial for the running variable, and the inclusion of weather and longitude covariates. Table 2 suggests a discontinuous change in $PM_{2.5}$ at the Huai River between 27 and 30 $\mu g/m^3$. This magnitude is consistent with the visual evidence presented in Figure 1A. Following the work of Imbens and Lemieux (34) and Gelman and Imbens (35), we use the results from the local linear nonparametric regression application of the RD design as our baseline results.[11] Column (4) presents our baseline results, which report the nonparametric estimates discontinuity at the Huai River by using the triangle kernel local linear regression and bandwidth selected by the common MSE-optimal bandwidth selector. Column (4) suggests a significant increase in $PM_{2.5}$ at the Huai River. At the boundary, $PM_{2.5}$ concentration rises by about 28.58 $\mu g/m^3$.

Table 3 provides the reduced-form and second-stage results for health outcomes when using parametric and nonparametric regression methods. Covariates from Table 1 were included in all regressions. Columns (1)–(4) report that the parametric regression approach and the sample locations are restricted to within 500 km of the Huai River. As mentioned earlier, this method can be regarded as an informal way to implement local regression by manually limiting bandwidth. Column (1) presents the reduced-form parametric estimation results when using a quadratic polynomial for f. These

10 The first two columns of reports come from the RD method, which limits the samples to 500 km of Huai River. This method can be regarded as an informal approach for implementing local quadratic and linear methods by manually limiting bandwidth.

11 Gelman and Imbens (35) suggested that the parametric RD methods have several undesirable statistical properties, and local linear regression based on data near RD cutoff may produce the most robust estimation.

TABLE 1 Summary statistics of observables for the north and south of the Huai River.

Variable	North (1)	South (2)	Differences in means (3)	RD estimates (Nonparametric) (4)
Weather and longitude				
Temperature (°C)	11.095 (3.701)	18.404 (2.766)	−7.309*** [0.512]	0.272 [0.318]
Relative humidity (%)	61.904 (6.607)	73.646 (5.097)	−11.742*** [0.925]	−2.146 [1.583]
Precipitation (mm)	664.104 (278.597)	1447.153 (466.230)	−783.048*** [60.713]	35.448 [103.188]
Sunshine duration (h)	2190.358 (300.363)	1520.847 (354.240)	669.511*** [51.722]	115.746 [278.569]
Longitude	115.506 (6.887)	113.721 (6.412)	1.785* [1.045]	1.916 [4.548]
Demographic and health behavior characteristics				
Age	45.160 (16.146)	45.924 (16.698)	−0.764*** [0.180]	−1.211 [0.738]
Gender	0.481 (0.500)	0.489 (0.500)	−0.008 [0.005]	0.003 [0.020]
Minority	0.952 (0.214)	0.872 (0.334)	0.080*** [0.003]	−0.009 [0.008]
Urban/rural status	0.413 (0.492)	0.524 (0.499)	−0.112*** [0.005]	−0.017 [0.030]
Income (10,000 yuan)	0.777 (1.552)	1.184 (2.372)	−0.407*** [0.022]	−0.069 [0.072]
Smoking regularly	0.309 (0.462)	0.287 (0.452)	0.022*** [0.005]	0.004 [0.023]
Drinking regularly	0.048 (0.214)	0.044 (0.205)	0.004* [0.002]	−0.002 [0.011]
Excessive red meat consumption	0.009 (0.096)	0.019 (0.137)	−0.010*** [0.001]	−0.004 [0.003]
Consumption of puffed/fried food	1.252 (0.984)	1.339 (1.335)	−0.088*** [0.013]	0.000 [0.048]

Weather measurements were calculated as a county's average reading in the CFPS survey year. Columns (1) and (2) report the mean values of the north–south samples of the boundary, and Column (3) reports the raw differences between the mean of the two samples by using *t*-test. The results in Column (4) are the nonparametric estimated discontinuity at the Huai River obtained using local linear regression and the bandwidth selected using the common MSE method with a triangular kernel. The optimal bandwidth is chosen separately for each variable. In Columns (1) and (2), standard deviations are reported in parentheses. In Columns (3) and (4), standard errors are reported in brackets. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

results are consistent with Figure 1B, and they provide evidence that a statistically significant discontinuous increase occurs in the rates of chronic diseases and multiple chronic diseases for adults at the Huai River boundary. Column (3) uses a linear polynomial. Columns (2) and (4) report the second-stage (2SLS IV) parametric estimation results. Nonparametric estimates from the reduced-form and second-stage (fuzzy RD) regressions are reported in Columns (5)–(8). Columns (5)–(8) provide the results when using triangle kernel local quadratic and linear regressions, respectively, and the bandwidth selected by the common MSE-optimal bandwidth selector.

Two characteristics of the results in Table 3 should be noted. First, the RD effects on chronic diseases and multiple chronic diseases are highly statistically significantly positive for different regression methods and RD specifications, implying that our conclusions are robust and not strongly affected by the choice of function form. Second, the coefficients estimated by the 2SLS IV method are smaller than the reduced-form estimates. Such finding is not surprising given that many counties have good air quality although they are located north of the Huai River because of regulatory measures. Therefore, the reduced-form estimate overvalues the effect of the Huai River policy.

As mentioned earlier, we use the results from the local linear nonparametric regression application of the RD design as our baseline results. The fuzzy RD approaches suggest a substantially smaller estimate of the health effects of $PM_{2.5}$. Column (8), which reports the estimates from the nonparametric fuzzy RD approach, suggests that an additional 10 $\mu g/m^3$ sustained exposure to $PM_{2.5}$ is associated with a statistically significant increase in the probability of suffering from chronic diseases and multiple chronic diseases by 3.2 and 1.3%, respectively.

We also report the results of the change in subcategories of chronic diseases at the Huai River boundary. Our primary division is chronic diseases of the cardiorespiratory system, neuropsychiatric system, motor system, digestive system, and all other chronic diseases, which we have identified using the chronic disease classification codes recorded by CFPS and the Chinese coding

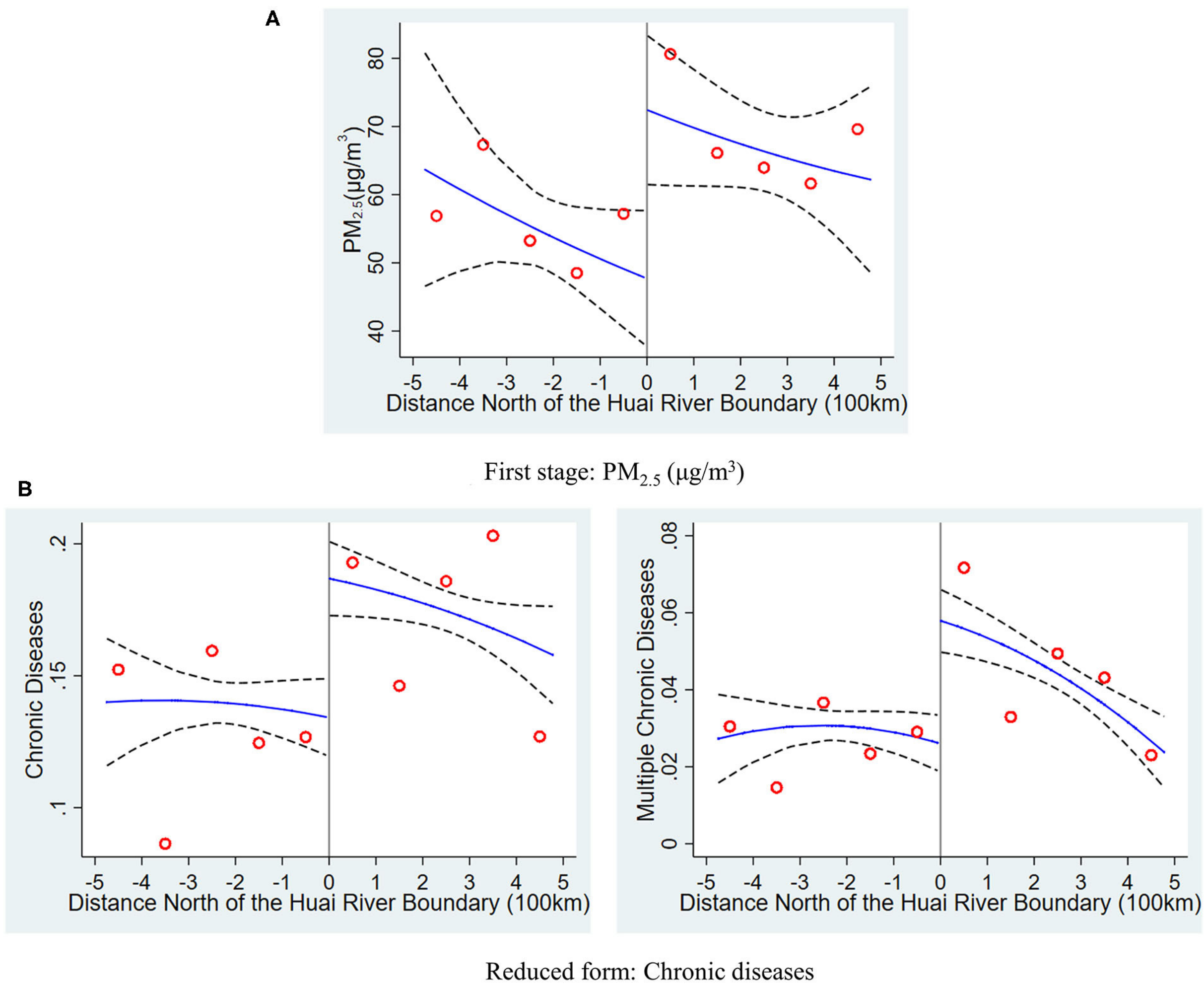

FIGURE 1
Distribution of pollution exposure and chronic diseases at the Huai river boundary. The graphs show the average value of $PM_{2.5}$ exposure and rates of chronic diseases north and south of the Huai River. The horizontal axis is the distance north (positive values) and south (negative values) from the sample location to the Huai River. The scatterplot in **(A)** is the means of $PM_{2.5}$ within 100 km bins, and the solid and dashed lines are the regression fit and associated confidence intervals, respectively, based on the quadratic polynomial regression of $PM_{2.5}$ exposure on distance from the Huai River estimated separately on each side of the river. The right and left columns of **(B)** present the results for at least one chronic disease and multiple chronic diseases, respectively, estimated in the same manner as shown in **(A)**.

scheme.[12] We presume that chronic diseases of the cardiorespiratory system are the most affected by air pollution, while chronic diseases of the neuropsychiatric and motor systems are also partially affected by air pollution. Chronic diseases of the digestive system and other chronic diseases will not be affected by air pollution. This prediction is borne out by the data: a statistically significant increase in chronic diseases of the cardiorespiratory system, neuropsychiatric system, and motor system rates is found at the Huai River by using different RD specifications. The RD estimation coefficient for chronic diseases of the cardiorespiratory system is the largest. By contrast, the change in rate of all the other chronic diseases at the Huai River is a decrease at the Huai River line. However, this decrease is not statistically significant.

To make our conclusion more intuitive, we consider the following counterfactual policy. The policy changes coal-fired heating into natural gas, wind energy, or solar energy. Ma et al. (36) estimated that 15.5% of North China's $PM_{2.5}$ emissions came from coal burning in power plants during winter.[13] Assuming that coal-fired power generation in northern winter is used for heating.[14] Therefore, if the output of existing coal burning power plants is replaced with wind power or solar power, $PM_{2.5}$ will be reduced by 15.5%. This result implies a reduction in $PM_{2.5}$ concentration by 7.86 $\mu g/m^3$

12 The codes are provided by the Chinese Center for Disease Control and Prevention.

13 Ma et al. (36) developed an emission inventory for 2013 by using up-to-date information on energy consumption and emission controls. They simulated the contribution of coal combustion to the total concentration of $PM_{2.5}$ in 74 major cities across the country. Notably, this study is about emissions from coal burning power plants in northern China during winter, not overall coal usage.

14 Evidently, this situation is different from the reality, because most of the heating is directly generated by a coal-fired boiler in an apartment building. Building accurate emissions is frequently challenging, and thus, we would like to emphasize that our calculation should be interpreted as a rough estimation.

TABLE 2 RD estimates of the effect of the Huai River policy on $PM_{2.5}$.

	Dependent variable: $PM_{2.5}$ in $\mu g/m^3$			
	Parametric estimates		Nonparametric estimates	
	(1)	(2)	(3)	(4)
North	29.917** (12.983)	27.118*** (8.591)	27.094** (11.489)	28.580*** (9.786)
Weather	Yes	Yes	Yes	Yes
Longitude	Yes	Yes	Yes	Yes
Polynomial	Quadratic	Linear	Quadratic	Linear
Size of bandwidth (100 km)	[−5 5]	[−5 5]	[−5.205 5.205]	[−4.026 4.026]
Observations	85	85	162	162
Observations inside bandwidth			88	78
Bandwidth selection method			MSE	MSE
Kernel			Triangle	Triangle

This table provides the parametric and nonparametric estimates of the effect of the Huai River Policy on $PM_{2.5}$. In Columns (1) and (2), we report the parametric estimates of a dummy North = 1 for samples located to the north of the Huai River after controlling for quadratic and linear regressions in distance from the Huai River and its interaction with the dummy North, respectively. In Columns (3) and (4), we report the nonparametric estimate discontinuity at the Huai River by using triangle kernel local quadratic and linear regressions, respectively, and the bandwidth selected by the common MSE-optimal bandwidth selector. The results in all regressions include weather and longitude covariates. Standard errors are reported in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

for the average nationwide level of $PM_{2.5}$ concentration in our data (50.72 $\mu g/m^3$). The finding by Hu et al. (1) implied that China spends 858.054 billion CNY (130.01 billion USD) on treating chronic noncommunicable diseases every year. The application of the study's estimates suggests that the counterfactual policy will save 21.58 billion CNY (3.27 billion USD) in chronic disease costs. If the national average concentration of $PM_{2.5}$ is reduced by 10 $\mu g/m^3$, then the cost of chronic diseases will save 27.46 billion CNY (4.16 billion USD).

4.2. Robustness checks

We check the robustness and validity of our results against a variety of dimensions, such as functional forms for the RD polynomial, selection of bandwidth, sample selection, and placebo checks. Our robustness checks support the validity of the RD design, giving us confidence in the robustness of our results.

Although we control for the covariates listed in Table 1 in all regressions, one possible concern is that our RD estimates can be confused if covariates are discontinuous across the treatment threshold of the Huai River boundary. To address this concern, we examine the internal validity of our research design. If the variation near the Huai River boundary is real, then we expect that sample location characteristics, such as weather and longitude, and demographic and health behavior characteristics will not exhibit significant differences between the north and south of the Huai River. We use local linear regression and the bandwidth selected by the common MSE method proposed by Calonico et al. (31), Calonico et al. (32), and Calonico et al. (33) by using a triangular kernel, i.e., our major RD specification in the empirical analysis, to test for the continuity of sample characteristics at the Huai River boundary. The results are presented in Column (4) of Table 1 and the standard errors are in brackets. The RD estimates indicate that the discontinuous difference for the covariates is not statistically significant at the river boundary, confirming that observables that are close to the river boundary are identical on average.

In Table 4, we explore the robustness of the results to the selection of bandwidth to implement the parametric RD design by restricting the sample of locations, starting within 500 km of the Huai River in Column (1), which is primary analysis reported in Table 3, and then progressively narrowing the 100 km term to each subsequent selection of bandwidth as one moves from left to right. We report the results by using 2SLS IV estimates and controlling for a quadratic polynomial in distance from the Huai River and its interaction with a North dummy. The North dummy is the IV of $PM_{2.5}$. Supplementary Table A1 further reports the first stage estimation for $PM_{2.5}$. Although the results fluctuate to a certain extent, the discontinuity observed in chronic diseases, multiple chronic diseases, and subcategories of chronic diseases is significant at the level of 1%. This finding shows that our results are robust, even if we use samples that are closer to the Huai River.

Table 5 further explores the sensitivity of the nonparametric results to different bandwidth selection and kernel weighting methods. Column (1) reports the baseline regressions, and they are the same as those reported in Column (8) of Table 3. In the baseline regression, we use the triangle kernel local linear regressions and the bandwidth selected by the common MSE-optimal bandwidth selector. In Columns (2) and (3), we reestimate our MSE-optimal bandwidth results by using different kernel types (Epanechnikov and Uniform). To cross-validate the sensitivity of the results to different bandwidths, we use the same kernel local linear regressions as those in Columns (1)–(3) in Columns (4)–(6), but with an alternative bandwidth choice criterion. The common coverage error rate (CER) optimal bandwidth method proposed by Calonico et al. (32), Calonico et al. (37), and Calonico et al. (38) is used to estimate the effect of 10 $\mu g/m^3$ of $PM_{2.5}$ on health outcomes. The results are qualitatively similar across different bandwidth selection methods and choice of kernel type, suggesting that our findings are insensitive to the method used to generate our local linear regression estimates.

TABLE 3 RD estimates of the effect of the Huai River policy and 10 μg/m^3 of $PM_{2.5}$ on health outcomes.

	Parametric estimates				Nonparametric estimates			
	OLS	2SLS	OLS	2SLS	Reduced form	Fuzzy RD	Reduced form	Fuzzy RD
Dependent variables	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Chronic diseases	0.069*** (0.018)	0.021*** (0.006)	0.059*** (0.012)	0.019*** (0.004)	0.126*** (0.020)	0.044*** (0.007)	0.095*** (0.017)	0.032*** (0.006)
Multiple chronic diseases	0.048*** (0.010)	0.015*** (0.003)	0.027*** (0.007)	0.009*** (0.002)	0.068*** (0.012)	0.024*** (0.004)	0.061*** (0.011)	0.013*** (0.003)
Subcategories of chronic diseases								
Cardiorespiratory	0.055*** (0.012)	0.017*** (0.004)	0.035*** (0.008)	0.011*** (0.003)	0.080*** (0.012)	0.028*** (0.004)	0.064*** (0.011)	0.022*** (0.004)
Neuropsychiatric	0.011** (0.005)	0.003** (0.001)	0.006* (0.003)	0.002* (0.001)	0.019*** (0.006)	0.006*** (0.002)	0.012*** (0.004)	0.004*** (0.001)
Motor	0.024*** (0.009)	0.007*** (0.003)	0.018*** (0.006)	0.006*** (0.002)	0.060*** (0.011)	0.017*** (0.003)	0.039*** (0.009)	0.013*** (0.003)
Digestive	0.007 (0.009)	0.002 (0.003)	0.005 (0.007)	0.002 (0.002)	0.015 (0.010)	0.005 (0.003)	0.013 (0.009)	0.004 (0.003)
Other chronic diseases	−0.006 (0.010)	−0.002 (0.003)	0.006 (0.007)	0.002 (0.002)	−0.010 (0.011)	−0.003 (0.004)	−0.007 (0.010)	−0.002 (0.003)
Covariates	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Polynomial	Quadratic	Quadratic	Linear	Linear	Quadratic	Quadratic	Linear	Linear
Size of Bandwidth (100 km)	[−5 5]	[−5 5]	[−5 5]	[−5 5]				
Observations	17752	17752	17752	17752	33575	33575	33575	33575
Kernel					Triangle	Triangle	Triangle	Triangle
Bandwidth selection method					MSE	MSE	MSE	MSE

Each cell in the table represents a separate regression. This table shows parametric [Columns (1)–(4)] and nonparametric [Columns (5)–(8)] estimates of the effect of the Huai River Policy and 10 μg/m^3 of $PM_{2.5}$ on the listed outcomes. Columns (1) and (3) report the ordinary least squares (OLS) estimates of the coefficient on a north of the Huai River dummy. Columns (2) and (4) present the 2SLS IV estimates by using the "North of Huai River" as the IV. Columns (1)–(2) and (3)–(4) show the results after controlling for quadratic and linear polynomials in distance from the Huai River interacted with a north dummy by using the sample within 500 km of the Huai River, respectively. Columns (5) and (7) report the estimated discontinuity at the Huai River. Columns (6) and (8) present the estimates of the effect of 10 μg/m^3 of $PM_{2.5}$ on the listed outcomes that regarded distance from the Huai River as the running variable and $PM_{2.5}$ as the treatment variable, with the Huai River representing a "fuzzy" discontinuity at the level of 10 μg/m^3 of $PM_{2.5}$ exposure. Columns (5)–(6) and (7)–(8) show the results when using the triangle kernel local quadratic and linear regressions, respectively, and bandwidth selected by the common MSE-optimal bandwidth selector. Covariates from Table 1 were included in all regressions. Standard errors are reported in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

Overall, our parametric and nonparametric estimates for different bandwidths are qualitatively similar to those in our primary analysis and suggest that our core finding is insensitive to our bandwidth choice. Notably, the stability of the results in Tables 4, 5 further indicates that our major results in this study do not depend on parametric or nonparametric estimation methods.

In Table 6, we also report additional robustness checks for alternative specifications and sample the first stage estimation. We reproduce the analysis in Column (8) of Table 3 baseline estimates, in which we use the triangle kernel local linear regressions and the bandwidth selected by the common MSE-optimal bandwidth selector. We first examine the OLS estimates. In contrast with the equation estimated by OLS in Columns (1) and (3) of Table 3, Columns (2) and (3) in Table 6 report the traditional OLS equation that does not include a running variable for the distance from the Huai River and its interaction with the North dummy. Column (2) uses the full sample, while the sample within 500 km of the Huai River is used in Column (3). The traditional OLS estimates are remarkably smaller in magnitude compared with the baseline estimates of the health effects of $PM_{2.5}$. In particular, the OLS estimates show that the coefficient of $PM_{2.5}$ is between 0 and 0.003, and only the effect on chronic diseases is significant when using all samples. These estimates by conventional criteria can be explained by several reasons. One explanation is that under the non-RD design, the air pollution effect on health will be confused by economic factors, such as income, because air pollution exhibits a strong correlation with economic factors, which are also important determinants of health. Another primary explanation is the measurement error of air pollution. We cannot observe the precise air pollution exposure of each person, and thus, we can only use outdoor air pollution constructed from satellite observations to approximate actual personal pollution exposure. Many studies in the literature on the effect of air pollution have pointed out that allocating air pollution exposure at the regional level (the county level in the current study) to individuals will introduce classical measurement errors (5, 39–41). In turn, classical measurement errors will lead to the underestimation and confusion of air pollution effects.

Our baseline results include covariates for weather and longitude variables in flexible specifications to control for the confusion of weather and longitude location factors on our results and ensure that the Huai River policy affects health through air pollution rather than weather and location differences. In Column (4),

TABLE 4 Effect of alternative bandwidths on regression results, parametric estimates.

Dependent variables	IV Estimates of 10 $\mu g/m^3$ of $PM_{2.5}$			
	500 km (1)	400 km (2)	300 km (3)	200 km (4)
Chronic diseases	0.021*** (0.006)	0.039*** (0.007)	0.042*** (0.008)	0.026*** (0.005)
Multiple chronic diseases	0.015*** (0.003)	0.021*** (0.004)	0.024*** (0.005)	0.016*** (0.003)
Subcategories of chronic diseases				
Cardiorespiratory	0.017*** (0.004)	0.028*** (0.005)	0.028*** (0.005)	0.013*** (0.003)
Neuropsychiatric	0.003** (0.001)	0.006*** (0.002)	0.007*** (0.002)	0.005*** (0.002)
Motor	0.007*** (0.003)	0.014*** (0.004)	0.020*** (0.004)	0.012*** (0.003)
Digestive	0.002 (0.003)	0.006* (0.004)	0.006 (0.004)	0.006** (0.003)
Other chronic diseases	−0.002 (0.003)	−0.003 (0.004)	−0.005 (0.005)	−0.003 (0.003)
Covariates	Yes	Yes	Yes	Yes
Observations	17,752	15,910	12,956	6,566

This table shows the 2SLS IV estimates of $PM_{2.5}$ on the listed outcomes with the alternative size of bandwidth by using "North of Huai River" as IV after controlling for a quadratic polynomial in distance from the Huai River and its interaction with a North dummy. Column (1) presents the baseline regressions, which are the same as those reported in Column (2) of Table 3. The covariates from Table 1 are included in all regressions. Standard errors are reported in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

TABLE 5 Effects of alternative bandwidth selection and kernel weighting methods on regression results, nonparametric estimates.

Dependent variables	Bandwidth: MSE-optimal bandwidth			Bandwidth: CER-optimal bandwidth		
	(1)	(2)	(3)	(4)	(5)	(6)
Chronic disease	0.032*** (0.006)	0.031*** (0.006)	0.026*** (0.006)	0.023*** (0.005)	0.026*** (0.005)	0.020*** (0.005)
Multiple chronic diseases	0.020*** (0.004)	0.017*** (0.003)	0.013*** (0.003)	0.014*** (0.004)	0.079*** (0.040)	0.018*** (0.004)
Subcategories of chronic diseases						
Cardiorespiratory	0.022*** (0.004)	0.022*** (0.004)	0.010*** (0.002)	0.016*** (0.003)	0.016*** (0.003)	0.019*** (0.004)
Neuropsychiatric	0.004*** (0.001)	0.004*** (0.001)	0.002* (0.001)	0.005*** (0.002)	0.004*** (0.002)	0.004*** (0.001)
Motor	0.013*** (0.003)	0.012*** (0.003)	0.007*** (0.003)	0.012*** (0.003)	0.012*** (0.003)	0.014*** (0.003)
Digestive	0.004 (0.003)	0.004 (0.003)	0.000 (0.002)	0.003 (0.003)	0.003 (0.003)	0.007* (0.003)
Other chronic diseases	−0.002 (0.003)	−0.002 (0.003)	0.001 (0.002)	−0.005 (0.003)	−0.005 (0.003)	−0.001 (0.003)
Covariates	Yes	Yes	Yes	Yes	Yes	Yes
Observations	33575	33575	33575	33575	33575	33575
Kernel	Triangle	Epanechnikov	Uniform	Triangle	Epanechnikov	Uniform

This table shows the nonparametric estimates of the effect of $PM_{2.5}$ on the listed outcomes with the Huai River representing a "fuzzy" discontinuity in the level of $PM_{2.5}$ by using local linear regression different bandwidth selection and kernel weighting methods. Column (1) reports the baseline regressions, which are the same as those reported in Column (8) of Table 3. The table reports the bandwidth selection methods, i.e., one common MSE-optimal bandwidth selector or one common CER-optimal bandwidth selector. Covariates from Table 1 are included in all regressions. Standard errors are presented in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

we exclude weather and longitude variables and find that the magnitude and statistical significance of the estimation coefficient are essentially unchanged.

As mentioned earlier, we construct the individual sustained pollution exposure variable based on the $PM_{2.5}$ concentration in the residential county. A potential concern is that relocation to other

TABLE 6 Robustness of results to alternative specifications and samples.

	Baseline (1)	OLS (2)	OLS within 500 km (3)	No Covariates (4)	Hukou (5)	Prefecture level (6)
Chronic diseases	0.032*** (0.006)	0.003*** (0.001)	0.001 (0.001)	0.035*** (0.006)	0.035*** (0.006)	0.033*** (0.006)
Size of bandwidth (100 km)	[−2.749 2.749]			[−1.838 1.838]	[−2.415 2.415]	[−2.749 2.749]
Observations inside Bandwidth	12,044			5,927	10,582	12,044
Multiple chronic diseases	0.020*** (0.004)	0.001 (0.001)	0.000 (0.001)	0.019*** (0.004)	0.020*** (0.004)	0.021*** (0.004)
Size of bandwidth (100 km)	[−2.236 2.236]			[−2.656 2.656]	[−2.268 2.268]	[−2.236 2.236]
Observations inside bandwidth	10,217			12,044	9,859	10,217
Observations	33,575	33,575	17,752	33,575	30,898	33,575

This table presents the results of various robustness checks for alternative specifications and samples. Column (1) reports the baseline regressions, which are the same as those reported in Column (8) of Table 3. In Columns (3) and (4)–(6), we estimate the effect of $PM_{2.5}$ on the listed outcomes with the Huai River representing a "fuzzy" discontinuity at the level of $PM_{2.5}$ with a triangle kernel local linear regression and bandwidth selected by the common MSE-optimal bandwidth selector. Column (4) excludes weather, longitude, and demographic covariates. Column (5) excludes samples without local hukou registration. Column (6) collapses pollution data at the prefecture level, which typically includes 5 to 15 counties. In Columns (2) and (3), we report the OLS estimates of the association between $PM_{2.5}$ and the listed outcome. All the results report the effect of 10 $\mu g/m^3$ of $PM_{2.5}$ on these outcomes. Standard errors are presented in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

counties may be required to work or seek cleaner air. Such migration, if it occurs, can pose a potential challenge to our pollution exposure measurement, which assumes that the level of exposure to pollution is at the level observed at their hukou (obtained at one's city of birth). In addition, large-scale migration will also pose potential challenges to the RD design based on the Huai River boundary if migration occurs across boundaries. Although some studies have pointed out that migration is unlikely to affect our estimates significantly due to strict migration policies and low real migration rates across boundaries (6, 24), we still explore the potential effect of migration on the results by using two methods. First, we exclude samples without local hukou registration because data collection on migrant populations is notoriously difficult. The results are presented in Column (5), and they remain robust. Second, job-oriented migration has a considerable rate of mobility within a prefecture-level city, which typically contains 5–15 counties. That is, people may live in one county but work in another. We collapse the pollution data at the prefecture level for RD estimation. The results are presented in Column (6), and they remain robust. Supplementary Table A2 further reports the same robustness checks for cardiorespiratory and non-cardiorespiratory chronic diseases. The results fail to contradict the study's qualitative findings.

The asymptotic properties of parametric and nonparametric estimators depend on the order of the polynomial and the bandwidth, respectively. A trade-off exists between the bias and variance of estimates: higher-order polynomials and smaller bandwidths reduce bias but increase variance. Here, we explore the sensitivity of our results to higher-order polynomials.

Figure 2 plots the parametric estimates for the 2SLS effects of $PM_{2.5}$ on health outcomes by using the sample of locations within 500 km of the Huai River and the associated 95% confidence intervals when the order of the polynomial varies between linear and sextic. The RD-estimated effects on chronic diseases, multiple chronic diseases, and subcategories of chronic diseases, including cardiorespiratory, neurological, and motor systems, are nearly always significantly positive. Our results are robust to the choice of functional forms for the RD polynomial.

The strong correlation between the Huai River Policy and chronic diseases in adults documented in Table 3 is unlikely to have arisen by chance. As a check on the model, we implemented a series of placebo tests. To do this, we used the RD nonparametric approach to estimate a reduced form boundary effect at a randomly assigned latitude boundary. To avoid having the placebo estimate influenced by any jump at the true boundary, we repeated the test 1,000 times, enabling us to exclude the possibility that our estimates are driven to a significant extent by small sample bias within groups. We use a triangle kernel local linear regression and the bandwidth selected by the common MSE-optimal bandwidth selector to estimate the effect of boundary on chronic and multiple chronic diseases. This test has been used in previous studies (42).

Figure 3 plots the distribution of placebo estimates along with the true discontinuity value for chronic and multiple chronic diseases. Each placebo estimate was obtained by assigning a latitude boundary at random, computing a "false" running variable as the distance from the sample location to the placebo boundary. The distributions of the placebos are centered at 0, and the actual coefficient estimates are plotted as vertical lines. As the graphs become clear, the true boundary effect (the Huai River Policy) on chronic and multiple chronic diseases is less than that of most of the placebo estimates. These findings exclude the possibility that the baseline estimates only averaged a small sample bias. They indicate that the odds of finding the Huai River boundary effects to be as large as ours merely by chance are small, and thus, our major results are not likely to be systematic artifacts caused by spurious factors around the Huai River boundary.

4.3. Heterogeneous effects

In the previous sections, we estimated the average effect of the Huai River policy on chronic diseases in adults. However, this effect can be heterogeneous. In this section, we investigate whether heterogeneity effects of the Huai River policy exist on chronic diseases. In particular, we explore heterogeneous effects on age, gender, and urban/rural registration.

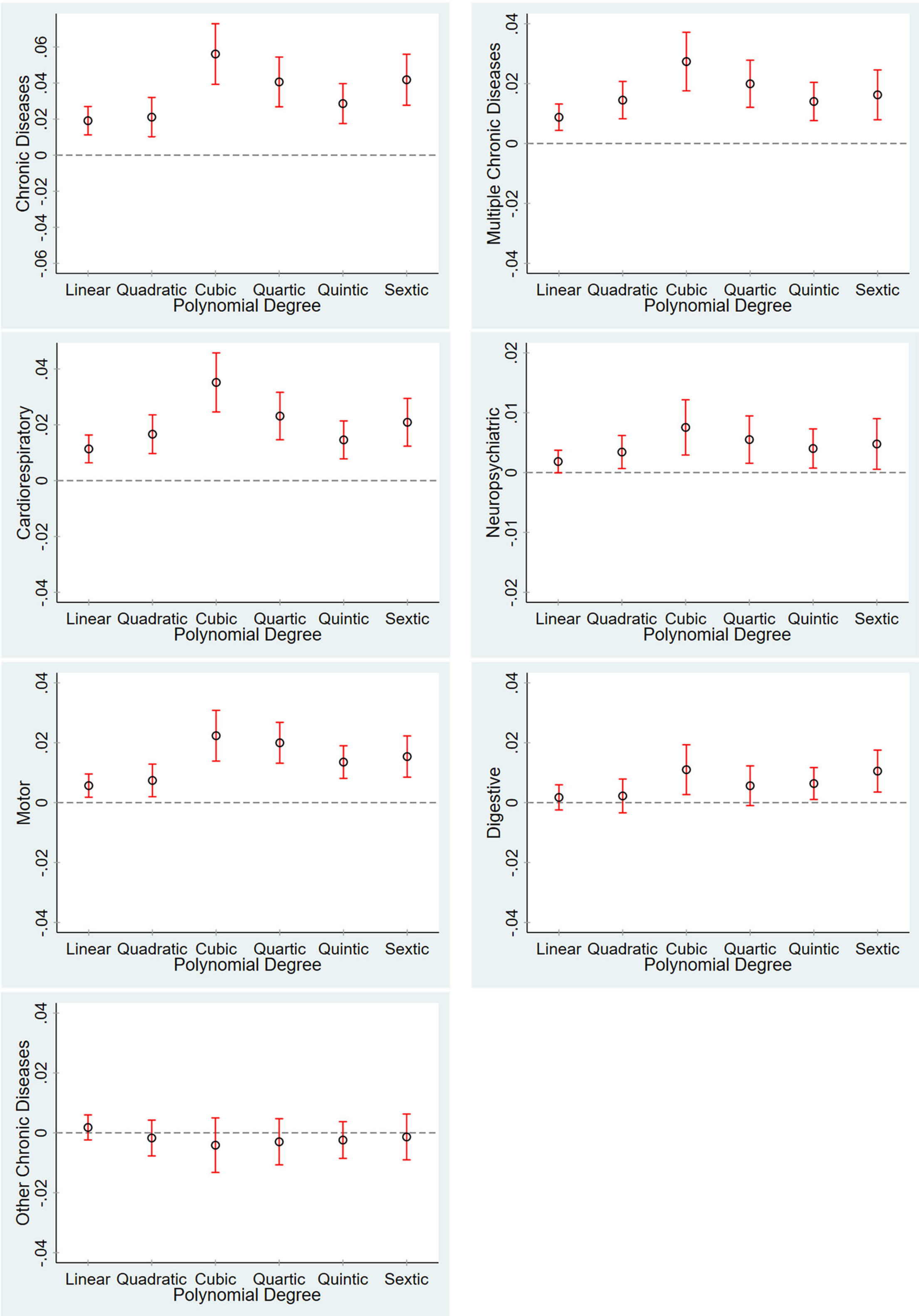

FIGURE 2
Robustness test for different RD polynomials. The graphs show the point estimates for the effect of $PM_{2.5}$ on health outcomes and the associated 95% confidence intervals when the degree of the polynomial used in regression varies between linear and sextic. All the graphs show the 2SLS IV estimates and include all the covariates listed in Table 1.

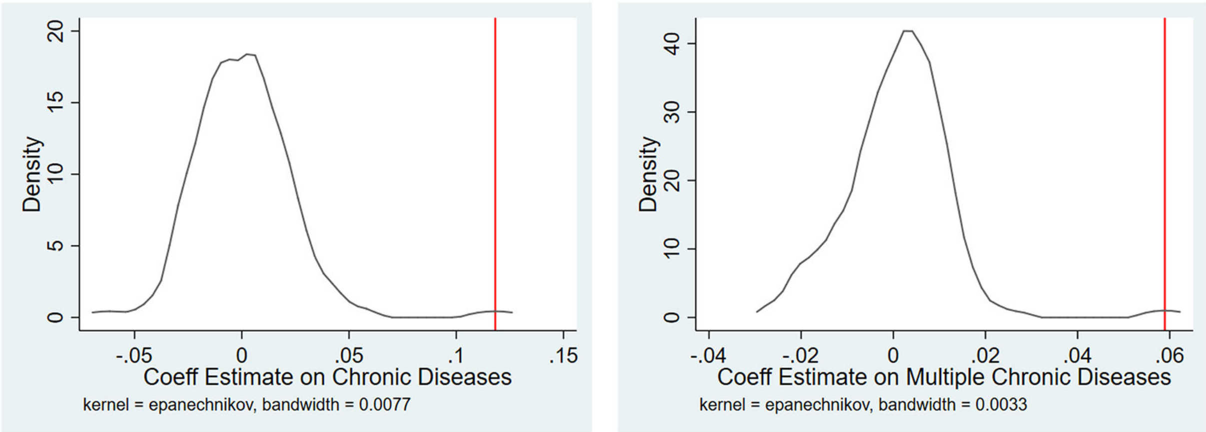

FIGURE 3
RD Estimates of the effect of the latitude boundary on chronic diseases, placebo estimates. The graphs show the distribution of the RD estimates by using a nonparametric method obtained from 1,000 random permutations of the boundary. Each placebo estimate assigned a false latitude boundary and then used a triangle kernel local linear regression and the bandwidth selected by the common MSE-optimal bandwidth selector to estimate the effect of the boundary on chronic and multiple chronic diseases. The vertical solid lines denote the actual estimates.

We first examine how air pollution effect differs between young and elderly populations. The resistance of people varies with age, and the resistance of the elderly is generally weaker than that of the young; accordingly, multiple chronic diseases are more common among the elderly (43). Therefore, differences may exist in the effect of air pollution on chronic diseases among age groups. The wide age span of the CFPS data enables us to consider the effects of air pollution throughout adulthood. Table 7 presents the parametric and nonparametric estimates of $PM_{2.5}$ exposure on chronic and multiple chronic disease rates separately for different age groups. The results of the subcategories of chronic diseases are reported in Supplementary Figure A1. As reported in Table 7, all the regressions include weather, longitude, and demographics other than age controls or covariates. We report the 2SLS IV estimates by using all the samples and the sample within 500 km of the Huai River and fuzzy RD estimates with a triangle kernel local linear regression. Our results show that the Huai River has significantly increased the prevalence of chronic diseases in adults aged 20–50 years. For multiple chronic diseases, the estimated coefficients are nearly significant throughout the adult life cycle, and magnitude increases with age. These results show that air pollution will not aggravate the prevalence of chronic diseases among the elderly, but will aggravate the incidence rate of multiple chronic diseases among the elderly. One explanation is that chronic diseases are extremely common among the elderly, and air pollution only aggravates the rate of suffering from multiple chronic diseases. For young people, regardless of whether chronic or multiple chronic diseases, air pollution has a significant positive effect on them, suggesting that $PM_{2.5}$ is an important determinant of health. Supplementary Figure A1 plots the change in subcategories of chronic disease rates at the Huai River throughout the adult life cycle by using the local linear regression estimates of the magnitude of discontinuity, including the 95% confidence interval. The results indicate that the increase in cardiorespiratory chronic diseases is statistically significant for a large range of the adult life cycle. These results help explain the study's central finding of a large effect of $PM_{2.5}$ on chronic diseases.

Second, we examined gender heterogeneity. Similar to Table 7, we report the parametric and nonparametric results and all the regressions, including weather, longitude, and demographics other than the age controls or covariates in Table 8. As indicated in Table 8, when estimated separately for men and women, evidence of consistencies across genders in the effect of $PM_{2.5}$ on chronic diseases and multiple chronic diseases seems to be strong. For example, in the preferred specifications for using local linear regression in Columns (3) and (6), we estimate that the rate of men and women with chronic diseases at the Huai River increased by 3.3%, respectively. Similarly, the rate of men and women with cardiorespiratory chronic diseases at the Huai River increased by 2.1 and 2.3%, respectively. The rate of men and women with motor chronic diseases at the Huai River increased by 1.4 and 1.1%, respectively. The results between different genders are similar in quality, which is consistent with the interpretation of the results driven by joint exposure to air pollution, rather than a false correlation with omitted variables.

Finally, regional heterogeneity may exist for two reasons. First, China's rural residents are considerably poorer than its urban residents. Given that income levels play an important role in food intake and the incidence of chronic diseases (44), urban residents may have a high prevalence of chronic diseases, confusing the effects of air pollution. We expect that the effect of air pollution on chronic diseases is insignificant in urban areas. Second, pollution in cities is more serious due to industrial agglomeration (45), and thus, the total air pollution exposure of rural residents may be significantly lower than that of urban residents. We expect that the effect of air pollution in urban areas will be greater.

Table 9 provides the 2SLS IV and local linear estimates of $PM_{2.5}$ on chronic and multiple chronic diseases by urban/rural-specific. We analyze our preferred specification by using local linear regression results reported in Columns (3) and (6). For chronic diseases, the effect of $PM_{2.5}$ is statistically significant in rural areas but not in urban areas. The different effects may be related to the income gap between urban and rural areas. Given the higher income level of urban residents and their excessive calorie intake,

TABLE 7 Effect of the Huai River policy on chronic diseases by age.

Age (years)	Chronic diseases			Multiple chronic diseases		
	2SLS		Fuzzy RD	2SLS		Fuzzy RD
	(1)	(2)	(3)	(4)	(5)	(6)
<20	0.011 (0.009)	0.005 (0.015)	0.014 (0.014)	−0.001 (0.004)	−0.000 (0.001)	−0.002 (0.002)
[20, 30)	0.012** (0.005)	0.027*** (0.008)	0.027*** (0.009)	0.002 (0.003)	0.007* (0.004)	0.006* (0.003)
[30, 40)	0.015* (0.007)	0.019** (0.009)	0.027*** (0.009)	0.008** (0.003)	0.011** (0.005)	0.011*** (0.004)
[40, 50)	0.031*** (0.008)	0.043*** (0.012)	0.052*** (0.012)	0.007* (0.004)	0.010 (0.006)	0.013* (0.007)
[50, 60)	0.012 (0.009)	0.022 (0.014)	0.027** (0.014)	0.010** (0.005)	0.016** (0.008)	0.017** (0.008)
[60, 70)	0.012 (0.012)	−0.002 (0.019)	0.014 (0.017)	0.020*** (0.007)	0.028** (0.012)	0.031** (0.012)
[70, 80)	0.021 (0.017)	0.018 (0.023)	0.042* (0.023)	0.026** (0.011)	0.029* (0.016)	0.052*** (0.016)
≥80	−0.004 (0.030)	0.024 (0.042)	0.075* (0.038)	0.023 (0.017)	0.027 (0.027)	0.046 (0.028)
Covariates	Yes	Yes	Yes	Yes	Yes	Yes
Polynomial	Quadratic	Quadratic	Linear	Quadratic	Quadratic	Linear
Size of bandwidth (100 km)	All	[−5 5]		All	[−5 5]	
Kernel			Triangle			Triangle
Bandwidth selection method			MSE			MSE

Each cell in the table represents a separate regression. In Columns (1)–(2) and (4)–(5), we report the 2SLS IV estimate of $PM_{2.5}$ on the listed outcomes by using "North of Huai River" as the IV, after controlling for a quadratic polynomial in distance from the Huai River and its interaction with a North dummy. In Columns (3) and (6), we estimate the effect of $PM_{2.5}$ on the listed outcomes with the Huai River representing a "fuzzy" discontinuity at the level of $PM_{2.5}$ with a triangle kernel local linear regression, respectively, and the bandwidth selected by the common MSE-optimal bandwidth selector. Covariates from Table 1 other than age are included in all regressions. Standard errors are presented in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

urban residents have a higher rate of chronic disease. This income-driven chronic disease effect may be sufficient to offset the effect of air pollution. Consequently, the estimated coefficient of urban samples is insignificant. For multiple chronic diseases, the estimation coefficient is significantly positive across urban and rural areas. However, compared with rural area residents, urban area residents have a higher risk of multiple chronic diseases during adulthood. This comparison supports the effect of total exposure to air pollution on chronic diseases and the argument that cities are more exposed to air pollution.

Although we do not find evident gender heterogeneity from Table 8, gender heterogeneity may be confused by urban–rural differences. For example, differences exist in the amount of physical labor between men and women in rural China, but it may not exist in cities. More manual work (physical activities) can reduce the incidence of many diseases (46, 47), leading to gender heterogeneity being different between rural and urban samples. To test this hypothesis, we further divide the rural and urban samples into four subsamples based on gender and estimate the effect of the Huai River policy on the rural male, rural female, urban male, and urban female populations. As reported in the graph on the right of Figure 4, no significant gender difference is found in the effect of the Huai River policy on multiple chronic diseases in urban samples, but differences are observed in rural samples. In particular, the effect of $PM_{2.5}$ on rural women is statistically significant, but the effect on rural men is insignificant. This comparison supports the conjecture that differences exist in the amount of physical labor between rural men and women. In addition, gender difference in rural samples may also be explained by the difference in total exposure to air pollution between men and women. Women are mostly engaged in outdoor agricultural production (e.g., work on the field), while men are mostly engaged in non-agricultural work in rural China. Given the nature of their work, the total exposure to air pollution of rural women may be significantly higher than that of rural men. The same results are found for cardiorespiratory chronic diseases, as presented in the graph on the left of Supplementary Figure A2.

4.4. Mechanism tests

Two main conclusions can be drawn from the results obtained so far. First, air pollution increases the risk of chronic diseases in adults. Second, in addition to cardiorespiratory system diseases, a statistically significant increase in chronic diseases of the neuropsychiatric system and motor system rates is also found at the Huai River by using different RD specifications. Many studies show that air pollution has a direct impact on cardiorespiratory diseases (6, 23). In this section, we mainly explore the possible channels of air pollution affecting the neuropsychiatric system and motor system diseases. First, air pollution may affect neuropsychiatric system diseases

TABLE 8 Heterogeneous effect of the Huai river policy on chronic diseases by gender.

	Men Only			Women Only		
	2SLS		Fuzzy RD	2SLS		Fuzzy RD
	(1)	(2)	(3)	(4)	(5)	(6)
Chronic diseases	0.016*** (0.005)	0.020*** (0.008)	0.033*** (0.008)	0.015*** (0.005)	0.021*** (0.008)	0.033*** (0.008)
Multiple chronic diseases	0.009*** (0.003)	0.009** (0.004)	0.014*** (0.004)	0.011*** (0.003)	0.019*** (0.005)	0.023*** (0.005)
Subcategories of chronic diseases						
Cardiorespiratory	0.011*** (0.003)	0.015*** (0.005)	0.021*** (0.005)	0.009*** (0.003)	0.018*** (0.005)	0.023*** (0.005)
Neuropsychiatric	0.001 (0.001)	0.005** (0.002)	0.006*** (0.002)	0.002 (0.001)	0.002 (0.002)	0.002 (0.002)
Motor	0.006** (0.002)	0.006 (0.004)	0.014*** (0.004)	0.007** (0.003)	0.009** (0.004)	0.011*** (0.004)
Digestive	0.000 (0.003)	0.001 (0.004)	0.002 (0.004)	0.001 (0.003)	0.003 (0.004)	0.006 (0.005)
Other chronic diseases	0.002 (0.003)	−0.001 (0.004)	−0.002 (0.004)	−0.001 (0.003)	−0.003 (0.005)	−0.003 (0.005)
Covariates	Yes	Yes	Yes	Yes	Yes	Yes
Polynomial	Quadratic	Quadratic	Linear	Quadratic	Quadratic	Linear
Size of Bandwidth (100 km)	All	[−5 5]		All	[−5 5]	
Kernel			Triangle			Triangle
Bandwidth selection method			MSE			MSE

This table replicates the RD estimates in Table 7, but estimated by gender. Covariates from Table 1, other than gender, are included in all regressions. Standard errors are presented in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

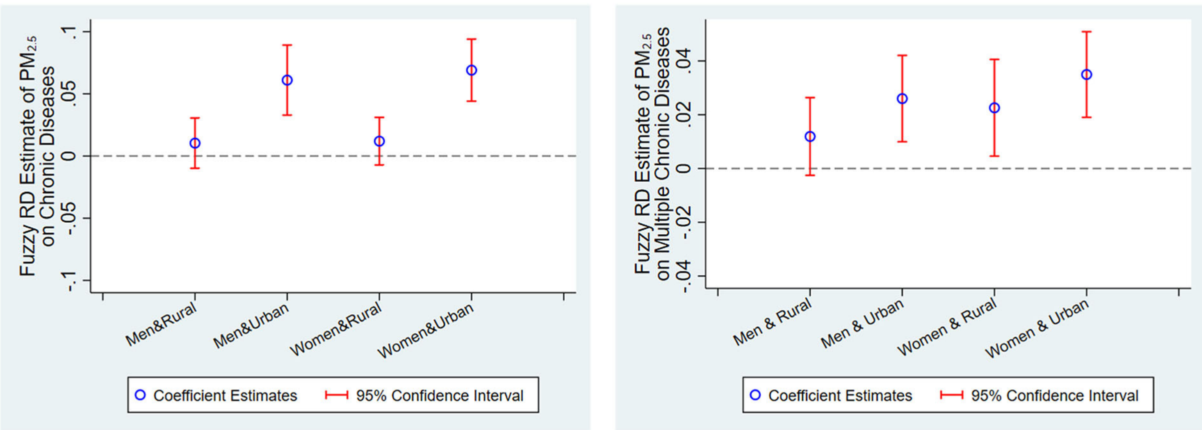

FIGURE 4
Heterogeneous effect of additional 10 $\mu g/m^3$ exposure to $PM_{2.5}$ on chronic diseases by gender and urban/rural status. These graphs present fuzzy RD nonparametric point estimates of the effect of additional 10 $\mu g/m^3$ exposure to $PM_{2.5}$ on chronic and multiple chronic diseases, regarding distance from the Huai River as the running variable and $PM_{2.5}$ as the treatment variable, with the Huai River representing a "fuzzy" discontinuity at the level of pollution exposure by gender and urban/rural status and the associated 95% confidence intervals. The discontinuities are estimated using a triangle kernel local linear regression and the optimal bandwidth is chosen by the common MSE-optimal bandwidth selector. Each point estimate includes all the covariates, other than gender and urban/rural status, listed in Table 1.

such as mental health directly through the induction of systemic or brain-based oxidative stress and inflammation. The biological pathway of fine particulate matter inducing oxidative stress and inflammation is that they will lead to the disorder of cytokine signal transduction, which can lead to depression, anxiety, cognitive dysfunction, and other mental illness (48). Second, air pollution may also affect neuropsychiatric system diseases through sleep disorders, which can lead to depression and anxiety. For motor system diseases, air pollution may affect it through behavioral responses. Many studies find that people are likely to stay indoors to avoid air pollution, thereby increasing sedentary behaviors and reducing outdoor physical activities (49), which causes diseases of the motor

TABLE 9 Heterogeneous effect of the Huai river policy on chronic diseases by urban/rural status.

	Urban only			Rural only		
	2SLS		Fuzzy RD	2SLS		Fuzzy RD
	(1)	(2)	(3)	(4)	(5)	(6)
Chronic diseases	0.026*** (0.005)	0.051*** (0.010)	0.004 (0.010)	0.012*** (0.006)	0.005 (0.007)	0.028*** (0.007)
Multiple chronic diseases	0.017*** (0.003)	0.028*** (0.006)	0.034*** (0.007)	0.006* (0.003)	0.009** (0.004)	0.012** (0.005)
Subcategories of chronic diseases						
Cardiorespiratory	0.010*** (0.004)	0.031*** (0.007)	0.036*** (0.008)	0.012*** (0.003)	0.010** (0.005)	0.008** (0.004)
Neuropsychiatric	0.002* (0.001)	0.003 (0.002)	0.004** (0.002)	0.001 (0.001)	0.004* (0.002)	0.006** (0.002)
Motor	0.010*** (0.003)	0.015*** (0.005)	0.018*** (0.004)	0.005* (0.003)	0.004 (0.004)	0.010*** (0.004)
Digestive	0.002 (0.003)	0.007 (0.005)	0.008 (0.005)	−0.001 (0.003)	−0.001 (0.004)	−0.001 (0.003)
Other chronic diseases	0.006** (0.003)	0.010* (0.006)	0.007 (0.007)	−0.003 (0.003)	−0.008* (0.004)	−0.009** (0.004)
Covariates	Yes	Yes	Yes	Yes	Yes	Yes
Polynomial	Quadratic	Quadratic	Linear	Quadratic	Quadratic	Linear
Size of bandwidth (100 km)	All	[−5 5]		All	[−5 5]	
Kernel			Triangle			Triangle
Bandwidth selection method			MSE			MSE

The results report the discontinuity in the listed outcomes by urban/rural status in the same manner as those reported in Tables 7, 8. Covariates from Table 1, other than urban/rural status, are included in all regressions. Standard errors are presented in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

TABLE 10 Potential mechanisms of the Huai River policy on chronic diseases.

	2SLS		Fuzzy RD
	(1)	(2)	(3)
Sleep time	0.026 (0.017)	0.020 (0.027)	−0.075** (0.034)
Physical activity frequency	−0.024 (0.021)	−0.166** (0.072)	−0.110* (0.060)
Covariates	Yes	Yes	Yes
Polynomial	Quadratic	Quadratic	Linear
Size of bandwidth (100 km)	All	[−5 5]	
Kernel			Triangle
Bandwidth selection method			Mserd

Each cell in the table represents a separate regression. The dependent variables are and sleep time and physical activity frequency. Physical activity frequency is expressed in terms of how often an individual engages in fitness or participates in physical activity, ranging from 1 (1 time in a few months) to 5 (almost daily). Sleep time is expressed as the number of hours of sleep on weekdays. Standard errors are presented in parentheses. *Significant at 10% level; **Significant at 5% level; ***Significant at 1% level.

system. We explore differences in sleep time and physical activity frequency to explain the effects of air pollution on chronic diseases of the neuropsychiatric system and motor system. To gain some insights into these factors, we use rich questions and answers about exercise and sleep in the CFPS. Like the above specification, we report the results of parametric and nonparametric estimates.

Table 10 presents the fuzzy RD estimates of $PM_{2.5}$ exposure on the frequency of physical activity and sleep time of adults. We start with sleep time in Table 10. We find that higher concentrations of air pollution can lead to a reduction in sleep time, and when using our preferred specifications, Column (3), this effect is significant. As mentioned earlier, Column (3) uses the optimal bandwidth method, while Columns (1), (2) show insignificant positive results due to manual bandwidth restriction. We then examine the effect of $PM_{2.5}$ on physical activity. The survey asked how often an individual engages in fitness or participates in physical activity, ranging from 1 (1 time in a few months) to 5 (almost daily). Since only 6,140 observations report a valid range, these estimates should be interpreted with caution. Nevertheless, we find a stable negative effect of $PM_{2.5}$ on physical activity frequency, indicating that less outdoor exercise to avoid air pollution is a possible channel for the air pollution effect.

5. Conclusions

Although the previous literature has examined the shorter lifespan caused by airborne particulate matter, limited evidence is available regarding the effect of air pollution on chronic diseases. We used an RD design based on distance from the Huai River to estimate the chronic disease consequences of the indoor heating policy. A fuzzy RD estimate finds that sustained exposure to additional 10 $\mu g/m^3$ $PM_{2.5}$ is associated with a reduction of 3.2 and 1.3% in at least one chronic disease and multiple chronic disease rates, respectively.

Various robustness checks and placebo regressions using false latitude boundary support our findings. Our findings suggest that the effect of air pollution differs depending on urban or rural status, gender, and age. In particular, women who work outdoors in agricultural production in rural areas are more sensitive to air pollution. For age heterogeneity, the coefficient of estimation of multiple chronic diseases is nearly significant throughout the adult life cycle, and its size increases with age. For young people, regardless of whether they are suffering from chronic diseases or multiple chronic diseases, air pollution exerts a significant positive effect on them, indicating that $PM_{2.5}$ is an important determinant of health.

The results of this study have powerful policy implications. We demonstrate that negative effect of air pollution on chronic diseases. Considering that the annual cost of chronic diseases in China is 858.054 billion CNY (130.01 billion USD), the estimates of this study imply that reducing 10 $\mu g/m^3$ of the average nationwide level of $PM_{2.5}$ concentration will save 27.46 billion CNY (4.16 billion USD) in chronic disease costs.

In addition, in pursuing economic development, developing countries are prone to disregard emission restrictions on pollutants, leading to the deterioration of air quality and the increase in the economic burden of diseases. Whether health risks caused by air quality reduce labor productivity and human capital, which, in turn, hinders economic development, further research is necessary. More broadly, the results of this study are of enlightening significance for environmental regulations, economic incentives, and labor policies.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: http://www.isss.pku.edu.cn/cfps/.

Author contributions

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

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Conflict of interest

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

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Supplementary material

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Muhammad Tanveer,
Imam Muhammad ibn Saud Islamic University, Saudi Arabia

*CORRESPONDENCE
Charli Sitinjak
✉ p112562@siswa.ukm.edu.my

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Model predicting social acceptance behavior to implement ELV policy: Exploring the role of knowledge toward ELV policy on social acceptance in Malaysia

Hasani Mohd Ali[1], Charli Sitinjak[2,3]*, Muhamad Helmi Md Said[1], Jady Zaidi Hassim[1], Rozmi Ismail[2] and Vladimir Simic[4]

[1]Faculty of Law, National University of Malaysia, Bangi, Malaysia, [2]Centre for Research in Psychology and Human Well-Being, Faculty of Social Sciences and Humanities, National University of Malaysia, Bangi, Malaysia, [3]Fakultas Psikologi, Universitas Esa Unggul, West Jakarta, Indonesia, [4]Faculty of Transport and Traffic Engineering, University of Belgrade, Belgrade, Serbia

Effective management of end-of-life vehicles (ELVs) represents a sound strategy to mitigate global climate change. ELVs are contaminants that pollute water, air, soil, and landscape. This waste flow must be adequately treated, but no proper rule oversees the disposal of ELV waste in Malaysia. This study aims to determine the extent of implementing the ELV policy and the social readiness in implementing environmentally friendly ELV disposal in Malaysia. The questionnaire seeks public input on critical ELV concerns such as public perception of the phenomena, environmental and safety standards, and recycling and treatment facilities. This research uses a cross-sectional design with 448 respondents in the survey. Fit models in structural equation modeling are evaluated using a variety of goodness-of-fit indicators to ensure an actual hypothesis. This study's advantages include the availability of representative samples and allowing for comparable and generalizable conclusions to larger communities throughout Malaysia. It is found that personal experience is significantly correlated with social readiness. The cause of ELV vehicles knowledge was the vital mediator, along with recycling costs knowledge. Thus, knowledge regarding ELV management costs is the most decisive mediation variable to predict public acceptance. The recommended strategy to reduce resentment and rejection of ELV policy is to disseminate information about the negative ELV impact on environmental and social sustainability.

KEYWORDS

end-of-life vehicles, contaminant, social acceptance, waste management, environmental sustainability, structural equating modeling

1. Introduction

Malaysia is one of the Southeast Asian nations with the most significant automobile sector. Malaysia has the third-highest automobile production rate in the Association of Southeast Asian Nations (ASEAN), behind Thailand and Indonesia, according to the Organization Internationale des Constructeurs d'Automobiles (OICA). Since the founding of PROTON in 1985 and PERODUA in 1993, the automobile sector in Malaysia has developed; this is a visible manifestation of the Malaysian government's national vehicle initiative (1).

The large production of vehicles in Malaysia positively affects the economy. However, the increasing mobility of automobiles utilized by Malaysians has led to urban air pollution, posing a severe threat to this warning (2–4). Even in 2019, the World Air Quality Index (WAQI) recorded a regional air pollution index of 299, making Malaysia the nation with the most significant amount of air pollution, followed by South Africa (217), Indonesia (207), India (194) and China (178) (5). This is a severe threat to Malaysian society, as the high levels of air pollution created by automobiles can lead to various health issues.

Air pollution is primarily caused by automobile emissions, especially in urban areas. Carbon monoxide (CO), nitrogen oxides (NOX), hydrocarbons, and sulfur oxides are produced mainly by automobile emissions (6–8). According to existing studies, carbon monoxide is the most prevalent contaminant, and over 70% of all carbon monoxide gases are generated by motor vehicles (9). Carbon monoxide is an odorless, tasteless, and non-irritating gas that has a lethal effect on humans despite its lack of color, odor, and taste (10–12).

Sulfur dioxide is an odorless gas with an offensive odor. The combustion of sulfur-containing fossil fuels produces sulfur oxide (13–15). This oxide contributes to acid rain and secondary particle production. Indirectly, the amount of sulfur emitted is proportional to the amount of sulfur in the fuel, primarily diesel (16–18). Automobile exhaust emissions also contain sulfur oxide, which is the primary source of sulfuric acid and the most prevalent form of acid deposition (19). Recent European research indicates that emission diesel contains sulfur in the form of particles and gases; hence reducing sulfur in diesel fuel will reduce particulates. Human exposure to dangerous substances is predicted to rise in densely populated metropolitan regions. This happens near busy traffic hubs in urban areas, where urban characteristics can lead to poor air dispersion, causing pollution hot spots (19–21).

Particulates (PM) and nitrogen dioxide (NO_2) emitted from vehicle exhaust are often the primary sources of urban air pollution that negatively affect the health of people (22, 23). In 2016, on-road vehicles accounted for ∼39 and 20% of the total NOx and CO emissions in the European Union (EU), and it was determined that passenger vehicles were the largest source of NOx and CO emissions from road transport (24). In addition to CO and total hydrocarbons (THC), diesel-powered vehicles have been recognized as the primary source of excessive NOx emissions in the EU (25–27).

Malaysia released 2,210,634 metric tons of carbon monoxide, 889,890 metric tons of nitrogen oxide, 257,457 metric tons of sulfur dioxide, and 26,789 metric tons of particulate matter in 2018 (28). PM10, which comes from power plants, accounts for 36% of the pollution; the remaining 63% comes from the industry; 16% comes from automobile exhaust; and 15% comes from residential, commercial, non-energy, and agricultural use (29). In 2018, 95.6% of Malaysia's carbon monoxide emissions came from automobiles (28).

Considering that the high number of automobiles has negatively impacted environmental and social sustainability, implementing the end-of-life vehicle (ELV) policy in Malaysia can be viewed as a solution for fostering the automotive industry's growth (30–32). As a nation that manufactures its automobiles, Malaysia is obligated to pay special attention to the impact of vehicles that contribute to the gradual contamination of the environment. The government made multiple attempts to formulate legislation to minimize car congestion on metropolitan highways in Malaysia, but they were discontinued due to widespread opposition.

ELV management and its recycling system are made up of several activities involving several processes. Effective and efficient ELV management is critical for maintaining the quality of the automotive industry's environment, economy, and ecosystem. As a result, ELV management has become a primary concern for authorities and researchers. In recent years, researchers have focused on reviewing relevant studies to understand better the dynamics of ELV management and the most appropriate recycling systems. Until now, most studies on ELV management and recycling systems have only focused on specific components such as ELV maintenance processes, demolition techniques, ELV management infrastructure, and ELV transportation facilities, but no one has focused on researching the social side to see the acceptance and public perception of ELV management.

For the first time, this study focuses on ELV review from a social standpoint as judged by personal experience, knowledge comprised of three factors (i.e., knowledge of the causes of ELV, knowledge of technological techniques, and recycling costs), as well as social readiness for implementing ELV. This study provides a comprehensive view of the Malaysian community's readiness for implementing the ELV policy. It has been discovered that knowledge can significantly increase the community's readiness to accept and implement ELV policies, even if their experience with ELV is still low.

The remainder of this paper is structured as follows. Section 2 provides a review of some related works. Section 3 presents the materials and methods. Section 4 shows the results. Section 5 gives a discussion of the results. Sections 6 and 7 provide managerial recommendations and research implications. Section 8 offers conclusions.

2. Literature review

2.1. Vehicles as a source of air pollution

Automobiles are the primary source of air pollution around the globe. The transportation industry is a significant contributor to traffic pollution. Besides, ELVs are eight times more likely to contribute to the increase in air pollution than new vehicles, and 15-year-old trucks contribute 10 times more to air pollution than new trucks (33, 34).

Large quantities of CO, THC, NOX, and hazardous chemicals such as fine particles and lead are emitted by motor vehicles (25–27). Private cars, motorcycles, light, and heavy vehicles all play a significant role in Malaysia's declining air quality, particularly in urban areas (33). These vehicles' emissions can negatively affect human health and the environment. This has led to the problem of severe air pollution accompanying the lives of urban residents (35, 36). Historically, air pollution concerns have been confined to metropolitan areas, but in recent years they have spread to impair the health of rivers, lakes, and forests (6, 19, 20). The impact of motor vehicle gases is beginning to have a highly negative influence on human health. This has led to concerns that motor vehicles have a catastrophic effect on global changes, which could alter the climate (37–39).

Sulfur oxides, CO, NOX, and THC are harmful gases to human health (40–42). CO is produced when fossil fuels are burned incompletely (43, 44). If humans inhale CO, they may have poisoning symptoms, including headaches, dizziness, nausea, vomiting, and loss of consciousness (27, 35, 45). CO was ligated to hemoglobin significantly more strongly than oxygen (33, 46). This demonstrates that persons exposed to CO to a certain degree frequently experience severe poisoning caused by the human body's loss of oxygen over a prolonged time. Additionally, CO is closely associated with global warming (47).

NOX is a traffic-related contaminant since automobile engines emit it (48, 49). As it penetrates deeply into the lungs, it irritates the respiratory system, causing respiratory illnesses, coughing, wheezing, dyspnea, bronchospasm, and even pulmonary edema when inhaled at high concentrations (50). It appears that concentrations >0.2 ppm cause these adverse effects in humans, whereas concentrations >2.0 ppm influence T-lymphocytes, specifically the CD8+ cells and NK cells that trigger our immune response (51). According to reports, prolonged exposure to high quantities of nitrogen dioxide can cause chronic lung illness.

Sulfur dioxide (SO_2) is a toxic gas generated mainly by the combustion of fossil fuels and industrial processes. The annual SO_2 standard is 0.03 ppm (50, 51). It affects humans, animals, and plants. Those susceptible, such as those with lung illness, the elderly, and youth, are more likely to sustain injury. The primary health issues associated with SO_2 emissions in industrialized areas are respiratory irritation, bronchitis, mucus production, and bronchospasm because sulfur dioxide is a sensory irritant and penetrates deeply into the lung, where it is converted into bisulfite and interacts with sensory receptors, causing bronchoconstriction. In addition, redness of the skin, damage to the eyes (lacrimation and corneal opacity), and mucous membranes, as well as a worsening of cardiovascular disease, have been noted (52, 53).

In 2020, it was recorded that 31.2 million motor vehicles were registered in Malaysia, demonstrating that the automotive industry in Malaysia has multiplied. However, in the same year, the Road Transport Department reported that there are at least 60,000 inactive vehicles across the country whose registration expired more than 3 years, a matter of great concern (54). The development of the automotive industry can make Malaysia increasingly competitive with other developed countries in the automotive industry, stimulating economic growth in Malaysia. Nevertheless, there has been one problem behind the success: the more vehicles there are, the higher the risk of environmental pollution. According to 2019 statistics, CO produced by vehicles has been recorded as the worst pollution in Malaysia, accounting for 70.4% of the total pollution occurring. Abandoned vehicles that have not been used can also threaten the sustainability of the environment. This risk derives from waste materials such as electronic components, lithium batteries, lead acid batteries, used engine oil, engine coolant, etc. When left without proper management, these waste materials will result in indirect environmental pollution (33).

The Public Complaints Bureau received numerous complaints from 2014 to 2017 regarding abandoned vehicles in Malaysia, where 15,019 cases of abandoned vehicles were totaled for the year (54). However, there has been an increase in the number in 2019, when the Road Transport Department informed that there are at least 60,000 abandoned vehicles across the country (54). The facts and statistics on abandoned vehicles are highly concerning since they not only affect environmental degradation but can also impact the welfare of the country's community; i.e., social sustainability. Many abandoned automobiles are parked in public places such as roadsides, parking lots, and other areas where they can annoy the public. Vehicles parked on the side of the road contribute to visual pollution. This pollution is an aesthetic issue that can interfere with a person's ability to enjoy a sight or vista (55). Destructive natural changes have disrupted an individual's visual area, resulting in visual pollution. As a result, the abandoned vehicle might produce visual pollution in the surrounding population, resulting in distraction, eye fatigue, a reduction in the diversity of opinions, and loss of identity.

2.2. ELV policy in Malaysia

The ELV policy is a source of contention in Malaysia. Many people rejected this policy but the Malaysian Institute of Road Safety Research, which highlighted possible hazards in passenger vehicles older than 12 years, gradually implemented it. There were almost four million cars in Malaysia older than 10 years old in 2017, which is expected to rise to 9.97 million by 2020. According to the research of Azmi and Tokai (56), the rapid growth of ELVs in Malaysia will lead to new problems with environmental pollution. Moreover, an ELV policy can contribute to long-term environmental control while also boosting safety in more modern vehicles (57). Furthermore, if Malaysia adopts the ELV policy, the country's economy will expand and the new car assessment program for Southeast Asian Countries will be more successful (1).

As one nation that produces automobiles, the Malaysian government has not yet established an ELV legislation. This is evidence that there is no desire from the automobile industry sector to implement the ELV policy, even though the total industry volume has reached 500,000 vehicles during the past decade (1).

Malaysians have been interested in ELV policy since 2009 (30). The Ministry of International Trade and Industry had evaluated this regulation progressively at the time, even though it was not included in the initial policy. This policy had several essential elements, including annual car inspections for 15 years. However, the public quickly criticized this regulation, so it was quickly abandoned. The ELV policy was then recreated in 2014 (30). However, it was not explicitly specified, and the word was substituted with Voluntary Vehicle Inspection (VVI). The Malaysian government's intention when introducing VVI was to reduce carbon intensity in metropolitan Malaysia by 40%.

In 2014, the National Automotive Policy (NAP) also began emphasizing the roadworthiness of automobiles to guarantee that they were safe to operate. As part of formulating future ELV laws, NAP introduced the Automotive Remanufacturing Roadmap and the Authorized Treatment Facilities Roadmap (57).

In 2016, the Malaysian government also launched the "cash-for-clunkers" initiative, which gave a cash rebate system to reduce the number of ELVs on the road (58). However, the rejection came not only from the community but also from the minister of transportation, who delivered a reaction that was unsupportive of giving instructions that every regulation must be further considered before implementation because it can have detrimental effects on several parties. Additionally, the 4R program was launched in 2016 (59). This program offers "Reuse, Recycle, Remanufacture, and Repair Service and Spare Parts" and has attracted the participation of 34 Malaysian enterprises. The objective of the 4R program in Malaysia is to promote the automobile sector and discourage the use of older vehicles (60).

Malaysia launched a new automotive policy in February 2020 (61). This policy emphasizes the growth of the automotive manufacturing sector, engineering, and technology. However, precise directions for ELV management are no longer discussed. Local automotive ambitions to transform Malaysia into an automotive manufacturing hub in ASEAN have resulted in the abandonment of ELV-related negotiations and a singular concentration on production and market expansion. According to Karagoz et al. (62), the management of ELV can only be successful if a single government enacts ELV-related policies. Besides, ELV management must incorporate the entire ecosystem, from the last vehicle owners to related centers and facilities for dismantling, recycling, and remanufacturing.

Malaysia may take lessons from advanced jurisdictions in regulating ELVs. For example, the European Parliament approved Directive 2000/53/EC on ELVs (i.e., ELV Directive). As a result, all EU member states adopted it in regulating the environmentally friendly ELV management process that prioritizes the reuse, recycling, and recovery of ELVs (63).

Germany is among the member states of the EU that have successfully adopted the Directive into their legal system. As a result, the recycling rate of ELVs in the country reaches 87.7%, exceeding the reuse and recycling target set by the ELV Directive (64).

Apart from Germany, Ireland can also be an excellent example in the disposal and management system of ELVs. The recycling rate and recovery of ELVs in Ireland show an 87.43% recycling rate and a 95.21% recovery rate in 2019. It is estimated that 160,000 cars are disposed of each year in Ireland, most of which are between 10 and 16 years old (65). Any last vehicle owner will receive a certain amount of payment when disposing of an ELV. However, insufficient disposal fees were paid in the late 1990's and early 2000's, leading to an increase in abandoned vehicles (65). However, according to Farrell (66), experts in vehicle disposal predicted that in 2022, the value of an ELV would rise. The increase can be seen from November and December 2021, when the value of an ELV increased significantly to more than €320 compared to the average ELV value in 2020, which is as much as €100. This increase is very significant (66). It can encourage car users and owners to dispose of their ELVs responsibly. Additionally, ELV must dispose of and processed only at locations that have been registered following Irish government regulations.

Raja Mamat et al. (31), surveyed the factors that can lead to success in establishing an end-of-life vehicle management system in Malaysia without considering the performance level of local ELV management. The subsequent study conducted by Abu Kassim et al. (1) analyzed only the public's response to the probability of implementing the ELV management policy. However, it did not include any information on the current practice of ELV management in Malaysia. Therefore, it can be outlined that no study has been done on the readiness of the Malaysian public to accept an ELV policy.

2.3. End-of-life vehicles process

There are two different kinds of ELV: natural and premature (67). Premature vehicles have reached the end of their useful life sooner than expected. This could be because of a fire, theft, flood, destruction, or damage from an accident. In this case, often a part can be used again before going on to the next step. Natural ELV, on the other hand, is a vehicle that has reached the end of its useful life (59–68).

When taking apart an ELV, the first step is to take out the batteries, liquids, and other potentially dangerous parts. Then, high-value parts are dismantled, and parts that still work are sold directly to secondary markets. The remaining parts of the vehicle are then forwarded to recyclers and processors. After removing the iron, the non-ferrous scrap can be separated using the solid medium separation process (69, 70).

The ELV processing is split into two parts: disassembly and destruction during the process and recycling and energy recovery after the process (71, 72). Parts with high economic value are picked out in traditional ways in a typical disassembly process. These parts are resold or fixed up. On the secondary market, usable parts can be sold directly to users (71, 73).

The evolving manufacturing technique may pose a certain issue. For example, the ELV Directive requires a 95% recovery rate from ELV and an 85% recycling rate. However, recent changes in vehicle material composition indicate a gradual replacement of ferrous metals traditionally used in the automotive industry with plastics and composites, to reduce vehicle weight, fuel consumption, and CO_2 emissions. As a result, the share of recyclable materials decreases while the share of materials that are difficult (and thus expensive) to recycle increases (74).

For the shredding process, the body of the car and any broken parts will be sent to a crushing plant, where they will be broken down into smaller pieces that are easier to handle. The ELV will be pressed down before it goes into the shredder. The leftover pieces of the car, called automobile shredder residue (ASR), are then separated by type. Magnets are used to separate metals from other types of materials (75, 76).

2.4. Knowledge predicting social acceptance

Knowledge is a significant factor in a person's acceptance. Knowledge factors are deemed capable of explaining an individual's acceptance and can functionally contribute to greater acceptance by enhancing an individual's understanding of the rules and their intended purpose. The more an individual's awareness about regulations, the greater the likelihood they will comply. In such circumstances, understanding the rules positively affects a person's ability to receive without a response. According to Sitinjak et al. (67), a high environmental regulation knowledge correlates with solid support for their implementation. Similarly, Modoi and Mihai (77), demonstrated that the objective level of information could positively influence social and economic attitudes, as well as acceptance of ELV policy. On the other hand, according to Baldassarre et al. (78), the higher the public's awareness of the impact of ELV on the environment, the greater the positive influence on society's acceptance of ELV regulation.

In the instance of air pollution, knowledge might indirectly affect individuals' acceptance of efforts to safeguard the surrounding environment by highlighting the risks and advantages of successfully implementing the rules. Marvi et al. (79) revealed that a person's acceptance of environmental regulations was heavily influenced by social perceptions, environmental attitudes, and personal experiences. Furthermore, it was discovered that environmental knowledge positively correlates with acceptance, especially when viewed from the perspective of education level (80, 81). Education has a more significant effect on people's desire to protect and maintain their environment. Conversely, the less education a person has, the more difficult it is to convince them to accept the norm (78).

3. Materials and methods

The research was conducted in several parts of Malaysia, such as Pahang, Selangor, Melaka, Perlis, Pulau Pinang, Johor, Kedah, Negeri Sembilan, Terengganu, Perak, Kelantan, Sabah, Sarawak, and the Guild Region. The collection of areas is used for data gathering since there are many cases of old vehicles remaining in operation and even left unattended on the periphery of the road and public parking lots without suitable treatment.

3.1. Study design

This research uses a cross-sectional design. The cross-sectional method is used by researchers because all variables are measured and observed at the same time in this study design, making it easier for researchers to conduct research and obtain relevant results (82). Krejcie and Morgan (83), suggested that the minimum required total sample size was 384 if the population was up to 1 million. In this research, 448 respondents took part in the survey. This survey selected respondents who were 18 or older and in possession of a valid driver's license using a systematic random sampling method. In this study, all enumerators and trained personnel explained the goal of the survey to selected respondents. Only respondents who provided written authorization were permitted access to the research. Respondents' socio-demographic backgrounds (age, gender, race, education, employment, income, vehicle ownership, etc.), knowledge (ELV causes, recycling techniques, recycling costs), and readiness were collected in their houses. The survey sheets filled out by respondents are then examined by using SPSS and WAR-PLS. The human research committee of Universiti Kebangsaan Malaysia has approved this study (UKM PPI/111/8/JEP-2021-595).

3.2. Study instrument

To address the issues raised in this study, the Trans-Disciplinary Research Grant Scheme (TRGS) team from the Faculty of Law developed a set of questions based on previous literature and interviews with numerous experts (see Figure 1 for instrument development and validation steps). We planned several question sessions for this investigation. The first session was used to collect respondents' demographic information, the second session was used to gain respondents' experiences with the vehicles they owned, and the third session was used to prepare questions about respondents' knowledge of ELV management (ELV causes, recycling techniques, recycling costs), and the final session was used to determine respondents' readiness to accept ELV. Cronbach's alpha for the total item is more than 0.05, which is excellent. The values for the scales of experience, understanding of ELV causes, recycling processes, and recycling prices are 0.83, 0.87, 0.79, and 0.82, respectively, and 0.87 for the scale of community readiness.

3.3. Criteria for model evaluation

Fit models in structural equation modeling (SEM) are evaluated using a variety of goodness-of-fit indicators. Because chi-squared tests are susceptible to sample size, many descriptive models of fit indexes have been created over time. A double match index was used in this work to examine the model fit between hypothetical models and sample data. In addition, some match indexes are taken into account when compared to the basic model. Approximate benchmarks for good model fit are values of 0.95 or higher for the Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) and values of 0.08 or less for Root Mean Square Error Approximation (RMSEA) and Standardized Root Mean Residual (SRMR). Suppose the null hypothesis of no difference is not rejected at each stage of the invariant test. This implies that the parameter limitation does not result in a worse solution than the base model, and the invariant hypothesis is empirically confirmed.

4. Results

The characteristics of the survey respondents are shown in Table 1. A total of 448 responses were received from 14 Malaysian states, with men accounting for 54.02% ($n = 242$) and women accounting for 45.98% ($n = 206$). The age range of respondents in this survey ranged from 26 to 35 years old (31.70%) to 56 years and older (7.81%). The bulk of respondents in this survey was Malay (72.10%), followed by respondents with an undergraduate degree education level of 34.82% ($n = 156$), and there were as many as 0.67% ($n = 3$) respondents who did not attend formal institutions. Respondents in this study also owned vehicles ($n = 369$), which was in agreement with the researcher's goals, as researchers would examine the experiences of respondents who had vehicles with their readiness to adopt the requirements of the ELV policy.

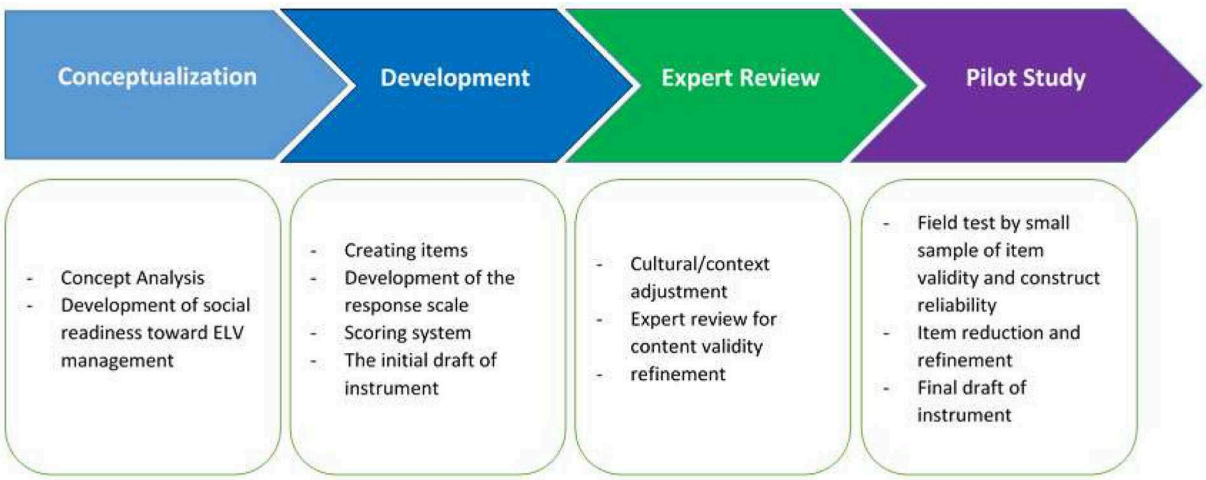

FIGURE 1
Instrument development and validation procedure.

TABLE 1 Sample characteristics and key frequencies.

Total $N = 448$					
Gender	Total	%	State of residence	Total	%
Male	242	54.02	Pahang	6	1.34
Female	206	45.98	Selangor	79	17.63
	448		Melaka	12	2.68
Age			Perlis	34	7.59
25 years and under	82	18.30	Pulau Pinang	4	0.89
26–35 years old	142	31.70	Johor	22	4.91
36–45 years old	139	31.03	Kedah	5	1.12
46–55 years old	50	11.16	Negeri Sembilan	6	1.34
56 years and older	35	7.81	Terengganu	2	0.45
	448		Perak	90	20.09
Race	Total	%	Kelantan	43	9.60
Malay	323	72.10	Sabah	34	7.59
Chinese	41	9.15	Sarawak	82	18.30
Indian	26	5.80	Wilayah Persekutuan	29	6.47
Bumiputera Sabah	19	4.24		448	
Bumiputera Sarawak	39	8.71	Occupation	Total	%
	448		Private sector	109	24.33
Educational level	Total	%	Government sector	226	50.45
No formal education	3	0.67	Self-employed	46	10.27
Primary school	4	0.89	Student	38	8.48
Secondary school	102	22.77	Unemployed	22	4.91
College/ STPM/ diploma	122	27.23	Retiree	7	1.56
Undergraduate degree	156	34.82		448	
Postgraduate masters	52	11.61	Vehicles ownership	Total	%
Doctor of philosophy	9	2.01	Yes	369	82.37
	448		No	79	17.63

4.1. Validity

The validity test results show the loadings value of each indicator and cross-loading to determine the validity of the instruments used in the study. The table shows the results of validity testing where it can be seen that the load factor > 0.5 and $p < 0.001$, then the variables tested in this study meet the convergent validity (see Table 2).

Table 3 illustrates that the AVE root on the major diagonal has a bigger value than the correlation to the variable under consideration. The variable Z_1 AVE root value of 0.737, for example, is bigger than 0.272, 0.061, 0.151, and 0.392. These findings indicate that the variable Z_1 satisfies the discriminant's validity. Similarly, the root value of the AVE is bigger than the correlation to other factors for other variables.

4.2. Reliability

Furthermore, the composite reliability value is used to determine the reliability test. If the composite reliability coefficient exceeds 0.7, the measuring instrument is declared to meet the composite reliability. Figure 2 presents the composite reliability coefficient values of all > 0.7 and Cronbach's alpha > 0.5, indicating that it meets the reliability standard.

TABLE 2 Combination of loadings and cross-loadings.

	*Z*1	*Z*2	*Z*3	*X*	*Y*	Type	SE	*P*-value
*Z*1-1	0.763	0.018	0.057	0.000	0.074	Reflective	0.043	<0.001
*Z*1-2	0.730	0.010	−0.068	−0.011	−0.100	Reflective	0.043	<0.001
*Z*1-3	0.785	−0.007	0.027	−0.017	0.070	Reflective	0.043	<0.001
*Z*1-4	0.666	−0.024	−0.022	0.032	−0.057	Reflective	0.043	<0.001
*Z*2-1	0.005	0.804	−0.037	−0.031	0.062	Reflective	0.043	<0.001
*Z*2-2	0.072	0.801	−0.051	0.025	0.031	Reflective	0.043	<0.001
*Z*2-3	0.037	0.744	0.047	−0.019	−0.116	Reflective	0.043	<0.001
*Z*2-4	0.047	0.733	0.049	0.026	0.016	Reflective	0.043	<0.001
*Z*3-1	0.052	0.111	0.695	−0.027	0.063	Reflective	0.043	<0.001
Z3-2	0.009	0.165	0.709	0.008	0.054	Reflective	0.043	<0.001
Z3-3	−0.061	0.130	0.722	−0.012	−0.015	Reflective	0.043	<0.001
Z3-4	−0.037	−0.177	0.649	0.013	−0.057	Reflective	0.043	<0.001
Z3-5	0.035	−0.026	0.731	0.017	−0.047	Reflective	0.043	<0.001
X-1	−0.116	0.124	−0.157	0.614	0.268	Reflective	0.044	<0.001
X-2	−0.053	0.010	−0.015	0.774	0.049	Reflective	0.043	<0.001
X-3	−0.100	0.056	0.028	0.762	0.041	Reflective	0.043	<0.001
X-4	−0.120	0.110	−0.097	0.657	−0.051	Reflective	0.043	<0.001
X-5	0.149	−0.102	0.048	0.721	−0.099	Reflective	0.043	<0.001
X-6	0.108	−0.035	0.024	0.660	−0.042	Reflective	0.043	<0.001
X-7	0.124	−0.141	0.139	0.722	−0.141	Reflective	0.043	<0.001
Y-1	0.058	0.048	0.058	0.104	0.770	Reflective	0.043	<0.001
Y-2	0.057	−0.076	0.070	0.005	0.858	Reflective	0.042	<0.001
Y-3	0.047	−0.087	0.076	0.029	0.803	Reflective	0.043	<0.001
Y-4	−0.033	−0.012	−0.039	−0.038	0.833	Reflective	0.042	<0.001
Y-5	−0.058	0.113	−0.091	−0.045	0.809	Reflective	0.043	<0.001
Y-6	−0.036	0.078	−0.122	−0.065	0.822	Reflective	0.043	<0.001
Y-7	−0.035	−0.060	0.051	0.017	0.805	Reflective	0.043	<0.001

X, Personal experience; Z1, Knowledge ELV causes; Z2, Knowledge recycling techniques; Z3, Knowledge recycling cost; Y, Social readiness.

4.3. Descriptive and bivariate analysis

We categorize respondents' responses into three groups: opponents, neutrals, and supporters. Bivariate analysis is utilized to illustrate the significant variations between each element. The majority of respondents rejected the ELV policy, as demonstrated by these results. Here from the results of the analysis, it was also determined that household income has a significant influence on a person's acceptance or rejection of the ELV policy (*p*-value 0.043) and that the duration of stay has the most significant influence on a person's acceptance of the ELV policy (*p*-value 0.005) (see Table 4).

4.4. General measurement model

To test the relationship between the direct and indirect variables of ELV management acceptance designed by the researchers in this study, several variables have been chosen to create an acceptance model based on individual experience, knowledge as a mediator, and readiness as the final output. We employ the SEM technique to answer our research questions. We also utilized this method to determine how our model influenced Malaysians' adoption of the ELV policy. The WarPLS 8.0 application aids in the analysis of research data.

Figure 3 illustrates the relationship between the variables that influence one another. Personal experience was found to be

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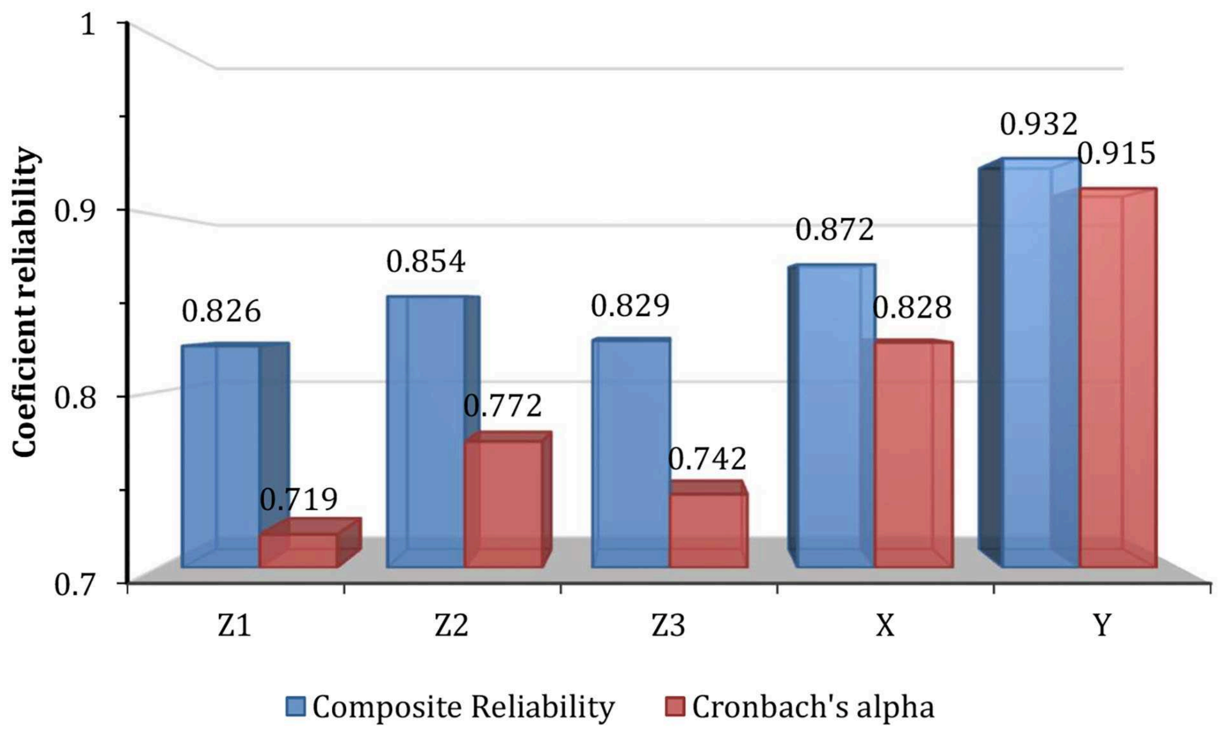

FIGURE 2
Composite reliability and Cronbach's alpha values. *X*, Personal experience; *Z1*, Knowledge ELV causes; *Z2*, Knowledge recycling techniques; *Z3*, Knowledge recycling cost; *Y*, Social readiness.

TABLE 3 AVE root and correlation coefficient.

	Z1	*Z2*	*Z3*	*X*	*Y*
Z1	0.737	0.272	0.061	0.151	0.392
Z2	0.272	0.771	0.516	0.322	0.598
Z3	0.061	0.516	0.702	0.321	0.497
X	0.151	0.322	0.321	0.703	0.295
Y	0.392	0.598	0.497	0.295	0.815

X, Personal experience; Z1, Knowledge ELV causes; Z2, Knowledge recycling techniques; Z3, Knowledge recycling cost; Y, Social readiness.

significantly correlated with social readiness with indigo = 0.06; *P* 0.001, and the knowledge related to the cause of ELV vehicles were found to be the mediator that strengthened the relationship between personal experience and social readiness, with a total effect of total = 0.44; *P* 0.001. With a discernible influence of = 0.63 and a significance level of *P* 0.001, knowledge regarding recycling costs was also found to be a good mediator. Thus, it can be concluded that knowledge regarding ELV management costs is the strongest mediation variable that can predict public acceptance. Finally, it was discovered that knowledge regarding recycling techniques could not be a good mediator because its significance level is more significant than 0.05 (*P* = 0.100). Overall, the regression model has an excellent fit; all outcomes satisfy the fir model's requirements and quality indexes (see Table 5). Therefore, it can be stated that the constructed model adequately describes social acceptability.

5. Discussion

Increasing ELV management knowledge, ELV management costs, and individual experience affect readiness, as shown by the findings of this study. A lack of awareness regarding ELV has fueled the public's opposition to implementing an ELV policy in Malaysia. This study has therefore explained why the government must increase its knowledge regarding the causes of ELV and the expense of maintaining ELV-containing vehicles, as knowledge has been shown to have a significant impact in this study.

This study's findings are consistent with prior research conducted in Indonesia, which indicates that a society's acceptance or rejection of ELV management norms can be predicted primarily by its level of knowledge (67). Other studies have demonstrated that an individual's acceptance of the norms governing ELV management is influenced by his or her experience and understanding of the effects and dangers posed by ELV (84–86). Government measures, such as increasing

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TABLE 4 Comparison between respondents supporting and opposing ELV management.

Demography factors	Opponents	Neutral	Supporters	*P*-value	
Gender	Male	229 (98%)	4 (2%)	-	0.493
	Female	211 (98%)	4 (2%)	-	
Education	No formal education	1 (100%)	-	-	0.598
	Primary school	4 (100%)	-	-	
	Secondary school	104 (100%)	-	-	
	College/ STPM/ diploma	109 (97%)	3 (3%)	-	
	Undergraduate degree	154 (97%)	5 (3%)	-	
	Postgraduate masters	58 (100%)	-	-	
	Doctor of philosophy	10 (100%)	-	-	
Age	25 years and under	73 (97%)	2 (3%)	-	0.321
	26–35 years old	141 (99%)	1 (1%)	-	
	36–45 years old	139 (99%)	2 (1%)	-	
	46–55 years old	60 (99%)	1 (1%)	-	
	56 years and older	27 (93%)	2 (7%)	-	
Household income	Below RM2,500	138 (99%)	1 (1%)	-	0.043
	RM2,501–RM5,000	124 (99%)	2 (1%)	-	
	RM5,001–RM8,000	78 (99%)	1 (1%)	-	
	RM8,001–RM11,000	56 (99%)	1 (1%)	-	
	RM11,000 and above	44 (94%)	3 (6%)	-	
Tenure of stay	<1 year	32 (100%)	-	-	0.005
	1–10 years	214 (99%)	1 (1%)	-	
	11–20 years	100 (99%)	1 (1%)	-	
	21–30 years	63 (94%)	4 (6%)	-	
	31–40 years	20 (91%)	2 (9%)	-	
	41 years and above	11 (100%)	-	-	
Vehicle ownership	Yes	366 (99%)	5 (1%)	-	0.124
	No	74 (99%)	3 (1%)	-	

negative effect campaigns from ELV vehicles, must continue to be developed and presented to the public as one explanation. Many government efforts, including the ELV management program, have not directly impacted various social circles (87, 88). The availability of platforms for continually disseminating information is crucial to facilitate information access for the entire community.

In this study, those who disagreed with and rejected ELV management policies imposed in Malaysia had a very high presentation, which showed that people's willingness to accept ELV's activities and knowledge are linked positively. This fits with research that shows rejection is higher when people do not know much about something (89). In the same way, researchers in Indonesia found that insufficient individual knowledge is linked to rejection (90). Concerning knowledge and rejection, a study about the barriers to implementing ELV management in developing countries shows that one of the biggest reasons for rejection is that the government does not educate the public about the policies they will implement (4).

Several factors, such as environmental knowledge upgrading programs, can be implemented at the individual, community, and societal levels to elevate social values (91, 92). Social media can increase knowledge at the individual level by delivering broadcasts or adverts directly to each user. Community-level interventions are implemented to enable communities in more prominent groups to develop a shared environmental consciousness (93). For instance, environmental awareness programs that the government can implement in homes or

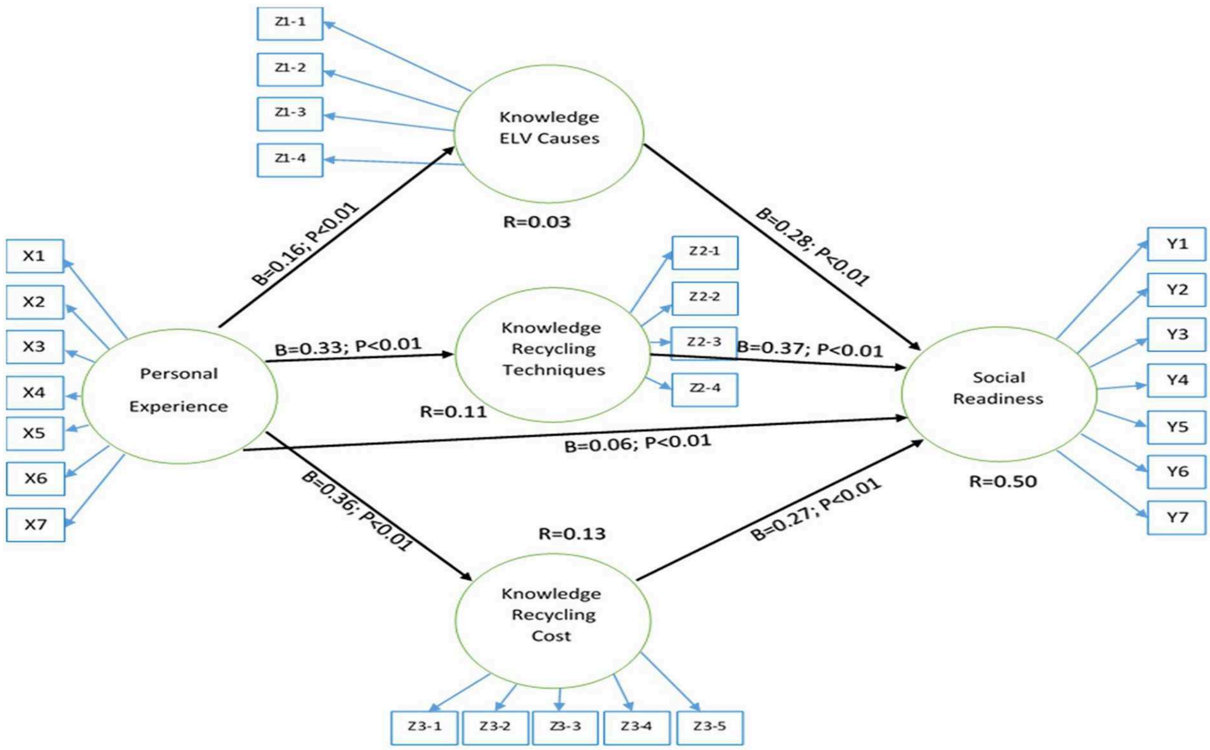

FIGURE 3
The final path model with standardized regression coefficients.

TABLE 5 Model fit and quality indices result.

Model fit and quality indices	Cut of value	Analysis result	Model
Average path coefficient (APC)	Accepted if $p < 0.005$	0.001	Fit
Average R-squared (ARS)	Accepted if $p < 0.005$	0.001	Fit
Average adjusted R-squared	Accepted if $p < 0.005$	0.001	Fit
Average blok VIF (AVIF)	Accepted if ≤ 5	1.292	Fit
Average full collinearity VIF	Accepted if ≤ 5	1.534	Fit
Tenenhaus GoF (GoF)	Small > 0.1 Medium > 0.25 Large > 0.36	0.38	Medium
Simpson's paradox ratio	Accepted if ≥ 0.7	1	Fit
R squared contribution ratio	Accepted if ≥ 0.9	1	Fit
Statistical supprenssion ratio	Accepted if ≥ 0.7	1	Fit
Non-linear bivariate causality direction ratio (NLBCDR)	Accepted if ≥ 0.7	1	Fit

villages to foster a sense of social trust can serve as a conduit for public acceptance of ELV regulations. In addition, its campaigns in broadcast media, the internet, etc., can be a readily accessible way of expanding public awareness. This demonstrates the need to enhance public awareness so that the community is more prepared and willing to adopt the ELV laws advocated by this study.

6. Managerial recommendations

According to the rapidly increasing number of ELVs in Malaysia, where no specific regulation in dealing with ELV exists, the government and researchers continue to seek the best solution to promote and implement ELV policies in Malaysia. Therefore, this research aims to ascertain how well-received the proposed ELV policy implementation will be in Malaysia. The study's findings show that the general public still needs to gain a greater understanding of ELV policies, mainly due to a lack of information about ELV vehicles, their management, and the potential harm they can cause. People's sentiment toward recycling their old cars is primarily influenced by the memories they have made behind the wheel.

Based on the findings, this study suggests different ways for the government to make rules about EVL that are acceptable to the public. Most importantly, this study shows that the government should work to improve the public's knowledge of ELV management, especially about why vehicles become ELVs, how to recycle them, and the costs of maintaining ELVs that will be paid for by owners who still want to use them. The government must also develop good ways to educate the public, such as through ads, flyers, ELV-related campaigns, and learning about the benefits of implementing ELV management. The government also needs to be able to fix problems with how people think about ELV recycling to help and encourage people to use a standard, environmentally friendly way to recycle ELV.

In addition, it was discovered that there are still a limited number of operators in Malaysia who can manage ELV following the established standards. Therefore, the Malaysian government must construct an ELV-related integrated management platform. In addition, the government must comprehend the costs associated with the ELV recycling process and the benefits realized if the ELV policy is successfully implemented so that economic barriers, which are one of the social barriers, can be eliminated. Malaysia should also advance recycling and reproduction technologies for ELV waste management.

7. Research implications

- In terms of limitations, this study tried to develop a model of community readiness for ELV management policies. However, in its development, researchers should have paid more attention to the acceptance model related to policies that had previously been made. Therefore, it is crucial to consider the policy acceptance model for future studies.
- In addition, with the development of the automotive sector in Malaysia, researchers must also explore in depth the competition between used car dealers and new car dealers to get richer results in seeing the problems that occur from an industry perspective.
- In this study, the offered acceptance model has limitations related to factors that describe community acceptance/readiness in the implementation of ELV, so we advise researchers to expand by adding various factors that can predict social acceptance of policies to get more comprehensive results in looking at community acceptance.
- We recommend employing a variety of research methodologies to delve deeper; e.g., qualitative methods or the use of mixed methods to produce more relevant results in the future.

8. Conclusions

Environmental sustainability is the ultimate aim of ELV policy. The results of this study provide numerous stakeholders with the information they need to establish suitable intervention programs to raise the understanding of all Malaysians, as has been done in several nations that have effectively implemented ELV-related legislation. Overall, the findings of this study indicate the need to increase public knowledge about ELV management, particularly at the community level, among all stakeholders, to achieve a solid understanding of the causes of ELV, the cost of ELV treatment, and the effects of ELV on health and the environment. According to the findings of this study, the public is more concerned about the cost of ELV treatment than the effects on health and the environment. In this study, it is also possible to demonstrate to stakeholders that the high level of community rejection is due to the absence of community-specific regulations. The results of the study also indicate that, even though individuals have positive recollections of their automobiles, they are more likely to comply with ELV management regulations if they are aware of the harmful effects of ELVs on environmental and social sustainability. Some techniques, such as advertising and ELV-targeted campaigns, can provide possibilities for widespread knowledge expansion. In addition, community members can organize meetings to discuss ELV-related concerns.

This study's advantages include the availability of representative samples, allowing for comparable and generalizable conclusions to larger communities throughout Malaysia. The report also contains extensive information regarding Malaysian society. Nonetheless, this study has limitations that must be overcome. This included the absence of ethnic additions in this study, as well as the absence of any consideration of naming criteria connected to prior ELV treatment. Moreover, to obtain better findings, future research could include other elements that predict acceptance, such as attitude, trust, etc. the restrictions of the discoverable are also flaws of this study.

Data availability statement

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

Author contributions

HA and CS: conceptualization, investigation, writing—review and editing, supervision, project administration, and funding acquisition. MM and JH: conceptualization, project administration, review, and editing. RI, CS, and VS: finalization. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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

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Ruoyu Wang,
University of Edinburgh,
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REVIEWED BY
Aiwei Wang,
Yangzhou University, China
Antonio Sanchez-Bayon,
Rey Juan Carlos University, Spain

*CORRESPONDENCE
Michela Bersia
✉ michela.bersia@unito.it

†These authors have contributed equally to this work and share first authorship

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The wellbeing of adolescents and the role of greenness: A cross-sectional study among Italian students

Giacomo Scaioli[1†], Giulia Squillacioti[1†], Michela Bersia[1,2*], Valeria Bellisario[1,2], Alberto Borraccino[1], Roberto Bono[1], Paola Dalmasso[1] and Patrizia Lemma[1]

[1]Department of Public Health and Pediatrics, University of Torino, Torino, Italy, [2]Post Graduate School of Medical Statistics, University of Torino, Torino, Italy

Introduction: Adolescence is a critical period of life, and the level of wellbeing acquired during this stage might have an influence on health status in adulthood. The wellbeing of adolescents is associated with both biological and environmental determinants. To date, few studies have evaluated the effect of exposure to urban green spaces (i.e., greenness) on adolescents' wellbeing. Therefore, the aim of this study is to assess the association between exposure to greenness and the wellbeing of adolescents, accounting for the level of urbanization surrounding schools.

Methods: In the frame of the 2018 Italian Health Behaviour in School-aged Children (HBSC), we analyzed cross-sectional data from the Piedmont Region. Exposure to greenness was quantified by the Normalized Difference Vegetation Index (NDVI). Schools were geocoded, and a fixed buffer (radius 1,500 m) centered on each school was then built to enable average NDVI calculations. Adolescents' wellbeing was assessed by self-reported psychological, somatic, and psychosomatic health complaints as follows. Respondents were asked how often, in the last 6 months, they had experienced: (a) headache, (b) stomachache, (c) backache, (d) dizziness, (e) feeling low, (f) irritability or bad temper, (g) feeling nervous, and (h) difficulties getting to sleep using the HBSC Symptom Checklist (HBSC-SCL), an eight-item tool. Multivariable, multilevel logistic regression models tested the association between exposure to NDVI and psychosomatic, somatic, and psychological health complaints, one at a time, using schools as a random intercept.

Results: In total, 2065 subjects (47.6% girls) aged 11 (48.4%) and 13 (51.6%) years were involved. Greenness was found to be inversely associated with reported psychosomatic (OR 0.72, 95% CI: 0.53–0.98) and psychological health complaints (OR 0.67, 95% CI: 0.49–0.92) in boys only, adjusting for age, urbanization level, and socioeconomic status, and stratifying by gender.

Discussion: Our results support the implementation of future policies for urban environmental design supporting the increase of green spaces, as suggested by the United Nations Sustainable Development Goals. Further studies are needed to confirm our findings.

KEYWORDS

greenness, wellbeing, adolescents, urbanization, psychosomatic health complaints

1. Introduction

Adolescence is a critical period of life, and the level of wellbeing acquired during this stage might have an influence on health status in adulthood (1, 2). Specifically, low levels of wellbeing in adolescents might be linked with an increased risk of the onset of cardiovascular diseases, elevated blood pressure, obesity, and smoking habits among teenagers, all conditions that persist later in life with age (1, 2). Given these premises, it is of utmost importance to investigate the wellbeing of young people and the factors potentially associated with higher or lower wellbeing levels.

Wellbeing is a multifaceted concept that can be described and measured in different ways (3–9). According to the Centers for Diseases Control and Prevention (CDCs), wellbeing "includes the presence of positive emotions and moods (e.g., contentment, happiness), and the absence of negative emotions (e.g., depression, anxiety), satisfaction with life, fulfillment, and positive functioning" (10). Wellbeing is further defined as a balance between psychological, social, and physical resources and challenges: if the former predominates, wellbeing levels are impaired (11).

An appropriate, indirect measure of the wellbeing of adolescents could be self-reported scales exploring a wide symptomatology, both psychological and somatic (4, 12, 13), previously investigated among adolescents (4, 14, 15). Self-reported measures are needed and highly recommended for this category of people because adolescents are usually in good health, and therefore, objective and instrument-measured health data are usually not available (4). In this regard, a recent worldwide meta-analysis showed a stable trend of psychosomatic health complaints since 2010 among adolescents (15). At the country level, Bersia et al. report an increasing trend of psychosomatic health complaints among adolescents in the last decade in Italy, especially for psychological complaints and among 13- to 15-year-old girls (4).

Regarding the potential determinants influencing the level of wellbeing of adolescents, previous studies have investigated the relationships between academic stress, social support (i.e., family, peers), violence exposure, socioeconomic status, and physical activity (4, 13, 16).

Recently, wellbeing was found to be related to contact with public green space, also known as "greenness." Greenness, which has been defined as "green schoolyards" (17), is the availability of parks (green space) (18) and tree density (19), and the accessibility of and distance of residential areas from urban green spaces (20). Regardless of the adopted methodology, higher exposure to greenness has been associated with positive health outcomes, both mental and physical: improved mental health and reduced stress, lower body weight, reduced blood pressure, stronger immune system, decreased incidence of diabetes, overall lower mortality, and faster hospital recovery (21–23).

To the best of our knowledge, few studies have evaluated the effect of exposure to greenness on the mood, perceived stress, and resilience of adolescents (18, 24). These studies demonstrate that the percentage of park area within cities could be used to predict perceived stress levels (18) and that students in green schoolyards build competence and cooperative social relationships (17), which have positive protective effects on wellbeing. From a wider point of view, exposure to greenness could be significantly associated with improved adolescent mood (24). As the concept is relatively new, the current literature indicates the need for further evidence to better understand the relationship between greenness and wellbeing among adolescents.

Strictly related to greenness, the concept of urbanization as "a process that leads to the growth of cities due to industrialization and economic development and that leads to urban-specific changes in specialization, labor division, and human behaviors" (25) has increased worldwide in recent decades. According to World Bank data, from 1990 to 2020, the percentage of the world population living in urban areas increased from 43 to 56% (26), and it has been estimated that more than 80% of the global population will live in urban areas in 2050 (26). Although urbanization has been proven to have some positive effects on health, mainly due to easier access to healthcare services and higher education and career opportunities (27), this phenomenon might also impact levels of wellbeing. Previous studies investigating how the increased level of urbanization could modulate the level of wellbeing in adults and adolescents (28, 29) have found that urbanization significantly affects the subjective wellbeing of the general population only in some regions and areas (29). These results might have been due to the complex relationship between urbanization and wellbeing, which might also depend on factors such as the proximity of rural areas to large cities, economic factors, and the level of innovation in the area (28). Urbanization is also related to greenness; urban sprawl and/or increased population density have led to a reduction in green spaces (30) and citizens' access to green spaces and natural vegetation (31).

The present study aims to assess the potential relationship between greenness exposure and wellbeing in adolescents living in Piedmont, a northwestern region of Italy, taking into account the level of urbanization in the area surrounding their schools. The main hypothesis of this study is that higher exposure to greenness is associated with improved wellbeing in adolescents.

2. Methods

Data were collected as part of the Italian 2018 Health Behavior in School-aged Children (HBSC) study. The study is a World Health Organization (WHO) collaborative international project aiming to describe health-related attitudes and behaviors in the adolescent population (32). A detailed description of the international and Italian HBSC study protocol can be found elsewhere (33, 34).

As the primary sampling unit, schools were selected by systematic cluster sampling from a list of all public and private schools obtained from the Italian Ministry of Education, University, and Research. A representative sample of adolescents aged 11, 13, and 15 years (corresponding to the 6th, 8th, and 10th grades, respectively) for each of the Italian regions was invited to participate in the study. Data on the students' social background, health indicators, and health-related behaviors were collected in classroom settings using a standardized, anonymous, self-administered questionnaire.

According to the international protocol, Italian study procedures, methods, and questionnaires were formally approved by the Ethics Committee of the Italian National Institute of Health. Participation was voluntary and opt-out consent was obtained from the parents/caregivers of the students involved. The anonymity and confidentiality of all participants were ensured (32, 33).

The present study relies on data from Piedmont, a northwestern Italian region, the second largest region in Italy, with a population of more than four million inhabitants, nearly 550,000 of whom are of school age (Italian national statistical institute 2020) (35). For the present study, only data related to students aged 11 and 13 years were considered. Since greenness measures were collected at the school level, and since students aged 11 and 13 years attend school widely distributed within the whole Italian territory, unlike high schools, which are often far from the students' homes, the measurement of greenness in the surroundings of the schools attended by the students is a more reliable measure for those aged 11–13 years than for those aged 15 years.

2.1. Outcome variables

2.1.1. Psychological and somatic health complaints

The HBSC Symptom Checklist (HBSC-SCL) is a measure composed of eight items (36, 37). The checklist shows adequate test-retest reliability and psychometric properties and has been extensively used to study adolescent mental wellbeing (36, 37). Respondents were asked to indicate how often in the last 6 months they had experienced: (a) headache, (b) stomachache, (c) backache, (d) dizziness, (e) feeling low, (f) irritability or bad temper, (g) feeling nervous, and (h) difficulties getting to sleep. Response options ranged from "about every day" to "rarely or never" for each symptom. These eight items, which are referred to as psychosomatic health complaints (PHC), can be further grouped into somatic (SOMHC: headache, stomachache, backache, and dizziness) and psychological health complaints (PSYHC: feeling low, irritability, feeling nervous, and sleeping difficulties).

According to the international report (38), a binary cut-off of the presentation of "at least two health complaints more than once a week" was used for somatic, psychological, and overall health complaints (39).

2.2. Potential determinants of the outcome variables

2.2.1. Exposure to greenness

Exposure to greenness was evaluated through the Normalized Difference Vegetation Index (NDVI). All sampled schools were initially geolocalized, and a fixed buffer (radius 1,500 m) around each school was then built to allow for NDVI calculations. Schools were considered proxies of students' home addresses, given that adolescents of 11 and 13 years old usually attend schools near their homes and do not have independent mobility (40).

NDVI is a metric used to quantify vegetated biomass from satellite images, calculated by measuring the ratio of the difference between the near-infrared (NIR) and red light to their sum. This measure ranges from −1 to +1: higher positive values indicate the presence of active photosynthetic vegetation (healthy green vegetation). NDVI was assessed from cloud-free satellite images (Landsat 5), referring to the same year of sampling of the HBSC study (2018), during summer to capture the maximum vegetated canopy cover (41). A radius of 1,500 m was decided upon in order to consider all the green spaces that could be accessed by the students attending the school in question. Shorter radii could have led to an underestimation of the greenness around the schools included in the study (22).

2.3. Control variables and confounding factors

Control variables and potential confounding factors, namely urbanization, gender, age, and socioeconomic status (SES), were included.

2.3.1. Urbanization

Urbanization is included in the model based on the Italian Institute of Statistics (ISTAT) classification (42). Since 2011, Eurostat (and therefore ISTAT) has classified municipalities into three different classes of urbanization (high, medium, low) using a tool based on population density and the number of inhabitants evaluated within regular grids with cells of one square kilometer (43).

2.3.2. Socioeconomic status (SES)

SES was measured using the Family Affluence Scale (FAS), a six-item scale developed and validated within the HBSC study (44, 45). FAS is composed of six indicators of the SES of the family:

- Whether the family has a car, van, or truck;
- Whether the adolescent has their own bedroom;
- How many times the adolescent has traveled away on holiday with the family;
- How many computers the family owns;
- Ownership of a dishwasher; and
- The number of bathrooms in the adolescent's house.

The score ranges from 0 to 13. According to scientific literature, the scores of the responses to the four questions were summed up and divided into three groups: 0–6 (low), 7–9 (medium), and 10–13 (high) SES (45).

2.4. Statistical analysis

Categorical variables were described with percentages and absolute numbers, and continuous variables were described with means and standard deviations. Fisher's exact test or the Mann–Whitney test were used to compare boys and girls, as appropriate. Multivariable, multilevel logistic regression models were performed using "school" as the higher level and students as the lower level for the following outcome variables: (1) psychosomatic; (2) somatic; and (3) psychological health complaints. As independent variables, the NDVI (1,500 m) was considered a continuous variable showing the estimates as one-IQR increase. Moreover, given the interaction between gender and the health outcomes, all models were stratified for gender and adjusted for age group, SES, and urbanization. A two-tailed statistical significance level of 5% was set up. All analyses were performed using STATA v16.1 (StataCorp LLC: College Station, TX, USA).

3. Results

The overall regional sample included 2,065 subjects aged 11 (48.4%) and 13 (51.6%) years, of which 47.6% were girls. Within the sample, 48.3% of the adolescents declared at least two psychosomatic health complaints (PHC) more than once a week, while 18% (11.5% of boys and 25.3% of girls) and 38.3% (32.4% of boys and 44.6% of girls) presented at least two somatic (SOMHC) and psychological health complaints (PSYHC) more than once a week, respectively (Table 1).

3.1. Univariable and multivariable, multilevel logistic regression analyses—Association between greenness and psychosomatic health complaints

Univariable models assessing the association between greenness and PHC (outcome variable) showed that, in boys, a one-IQR increase in greenness levels was associated with lower odds of presenting at least two psychosomatic health complaints more than once a week (OR 0.78, 95% CI: 0.63–0.98). After adjusting for age group, urbanization, and SES, the association was confirmed (OR 0.72, 95% CI: 0.53–0.98). The same association, although not statistically significant, was found in girls (OR 0.92, 95% CI 0.63–1.35) (Figure 1 and Supplementary material 1).

Considering PSYHC and SOMHC as separate outcomes, the results of the univariable, multilevel logistic regression models show that a one-IQR increase in greenness level was significantly associated with lower odds of presenting psychological health complaints in boys (OR 0.76, 95% CI: 0.60–0.95). After adjusting for age group, urbanization, and SES, the opposite association was confirmed among boys (OR 0.67, 95% CI: 0.50–0.92), while for girls, the association was not statistically significant (OR 0.91, 95% CI: 0.66–1.26). Somatic health complaints did not appear to be associated with the levels of greenness in the areas surrounding the schools (Figure 1 and Supplementary materials 2, 3).

4. Discussion

The present study aimed to assess whether the environment, specifically green spaces, could be associated with wellbeing in a sample of 11- and 13-year-old students living in Piedmont, a northwestern region of Italy. The study hypothesis was that higher exposure to greenness could be associated with improved wellbeing, measured as reported psychosomatic, psychological, and somatic health complaints. Our findings partially confirm our hypothesis: a higher exposure to greenness was associated with a lower occurrence of psychosomatic and psychological health complaints in boys but not with SOMHC. Previous studies on this topic have shown encouraging results (46): Ward et al. showed that higher green space exposure was related to greater emotional wellbeing among adolescents (47), and Feng et al. found that greenness, measured as the percentage of land use within each statistical area of residence covered by green space, was associated with parent-reported levels of mental wellbeing in 12- to 13-year-old students (48). Moreover, Wang et al. demonstrated that greenness, measured as the NDVI, was associated with a decreased risk of serious psychological distress in teenagers when considering the 350 m radius (49).

TABLE 1 Description of the sample.

		Boys ($n = 1{,}082$)	Girls ($n = 983$)	Total ($n = 2{,}065$)	p-value
Age category	11th year	522 (48.2%)	478 (48.6%)	1,000 (48.4%)	0.895
	13th year	560 (51.8%)	505 (51.4%)	1,065 (51.6%)	
At Least two somatic health complaints more than once a week (SOMHC)		124 (11.5%)	245 (25.3%)	369 (18.0%)	<0.001
At least two psychological health complaints more than once a week (PSYHC)		348 (32.4%)	437 (44.6%)	785 (38.3%)	<0.001
At least two psychosomatic health complaints more than once a week (PHC)		437 (40.8%)	554 (56.7%)	991 (48.3%)	<0.001
Normalized Difference Vegetation Index (NDVI) 1,500 meters		0.52 (±0.15)	0.52 (±0.15)	0.52 (±0.15)	0.670
Urbanization density	Low	260 (24.1%)	219 (22.3%)	479 (23.2%)	0.640
	Medium	589 (54.4%)	546 (55.5%)	1,135 (54.9%)	
	High	233 (21.5%)	218 (22.2%)	451 (21.9%)	
Family affluence scale (FAS)	Low	241 (22.7%)	256 (26.4%)	497 (24.5%)	0.085
	Medium	514 (48.4%)	465 (48.0%)	979 (48.2%)	
	High	307 (28.9%)	248 (25.6%)	555 (27.3%)	

Results are expressed as percentages and absolute numbers, and NDVI 1,500 with means and standard deviations. *P*-values are calculated with Fisher's exact test or the Mann–Whitney test.

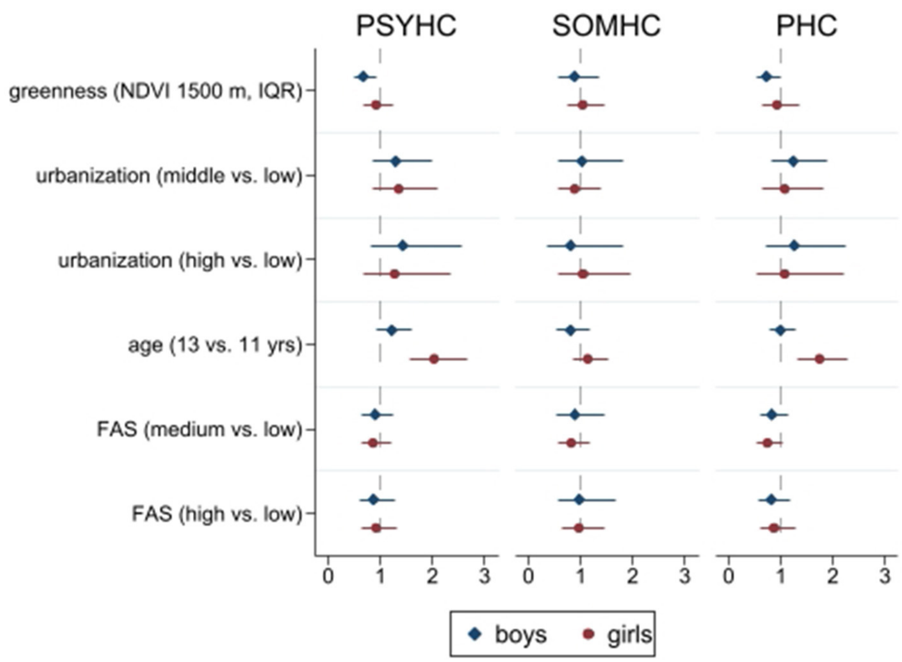

FIGURE 1
Multivariable multilevel regression models. Outcomes: PSYHC, Psychological Health Complaints; SOMHC, Somatic Health Complaints; PHC, Psychosomatic Health Complaints; NDVI, Normalized Difference Vegetation Index; IQR, Interquartile Range; FAS, Family Affluence Scale. Source: Own elaboration.

The association between exposure to greenness and lower psychosomatic and psychological health complaints might be linked to: (1) Higher chances of being engaged in outdoor physical activities among adolescents living closer to green areas. Physical activity has been shown to increase psychological wellbeing in adulthood as well as in children and adolescents (50). The relationship between physical activity and greenness has also been assessed by studies that demonstrate how the urban environment could influence the level of physical activity of citizens (51), showing a positive effect of living in a neighborhood with a high number of parks (52). (2) Green spaces in residential areas could offer meeting places to develop and maintain social bonds within the neighborhood, thus increasing social capital, defined as "features of social organizations, such as networks, norms, and trust that facilitate action and cooperation for mutual benefit" (53). In this regard, a recent systematic review demonstrated a strong link between green spaces and prosocial behavior among children and adolescents (54). (3) More green spaces can also lead to better air quality, which can have positive effects on health (55). This hypothesis was confirmed by Outdin et al.: air pollution [in terms of nitric oxide (NO_2)] was associated with an increased risk of antipsychotic or sedative compound prescriptions in children and adolescents (56), and Bakolis et al. showed that long-term exposure to air pollutants (NO_2, NOx, and PM2.5) is associated with mental disorders and physical health complaints indicative of mental distress (57).

The present study found a significant association between greenness and psychological health complaints in boys but not in girls. For females, the same association did not appear significant. Previous studies on this topic have shown mixed results (58, 59). Specifically, studies have noted that women frequent public parks less than men, which could further exemplify the differences between men and women in the association between greenness and psychological health complaints (59).

4.1. Strengths and limitations

The main strength of the study is the standardized, international protocol of the HBSC survey, which facilitates a high standard of data collection (32, 33). Another strength is the representativeness of the students of the Piedmont region. The novelty of the topic should also be mentioned, i.e., the association of wellbeing, measured as subjective somatic and psychological complaints, and greenness, measured using the NDVI, a validated instrument that "accurately reflects the amount of neighborhood greenness that can be observed directly by humans from the ground" (60). The measurement of greenness by the NDVI also reduces the potential bias of a self-reported perception of the amount of greenness by study participants, thus representing an objective measure of greenness.

The main limitation of the study is the self-reported nature of the survey. This could have led to the misinterpretation of some of the questions by the study participants, thus lowering the quality of the data. However, the HBSC survey is an international survey with a validated protocol and a high standard of data retrieval methods. Moreover, self-reported health complaints are reliable instruments for assessing the outcome of the present study (wellbeing) (4). Another limit is represented by NDVI calculated in a buffer radius of 1,500 m surrounding the schools attended by the students. This may reflect the presence of green spaces in the area surrounding the schools but not the neighborhood where the students reside. However, Italian secondary schools are usually widely and uniformly distributed within the whole territory and can therefore be assumed to be very close to their students' residences. Therefore, the NDVI of the 1,500-m radius could be considered a proxy of the greenness around the students' homes. This does not apply to Italian third-grade schools; thus, students aged 15 years (first year of third-grade school) were excluded from the overall sample.

4.2. Conclusions

In conclusion, the study points out that greenness could be associated with lower psychosomatic, especially psychological, health complaints in male adolescents. These results might be of interest to decision-makers with regard to promoting local policies aimed at building public parks and, more broadly, greener cities, through the implementation of policies that redesign the urban environment to increase green spaces, as suggested by the United Nations Sustainable Development Goals (target 11.7) (61). The results of the study also underline the need for interventions to detect and reduce the underlying factors that lead to gender differences in the relationship between greenness and the wellbeing of adolescents. Further studies are needed to confirm the findings of this paper.

Data availability statement

The datasets presented in this article are not readily available because the data presented in this study are not publicly available according to the Italian HBSC data access policy. Requests to access the datasets should be directed to paola.dalmasso@unito.it.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Italian National Institute of Health (Ref. PROT-PRE 876/17). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

PL, PD, RB, and AB conceived of the presented project. VB, GSq, RB, PL, PD, and AB retrieved the data. GSc, GSq, VB, MB, PL, and PD analyzed the data. GSc, GSq, VB, MB, and AB wrote the paper. PL, PD, and RB critically revised the paper for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1050533/full#supplementary-material

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EDITED BY
Yunquan Zhang,
Wuhan University of Science and Technology, China

REVIEWED BY
Shazia Rehman,
Pak-Austria Fachhochschule Institute of Applied Sciences and Technology, Pakistan
Worradorn Phairuang,
Kanazawa University, Japan

*CORRESPONDENCE
Yanchao Feng
✉ m15002182995@163.com

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How does the air pollution prevention and control action plan affect sulfur dioxide intensity in China?

Shuhai Niu, Yidong Chen, Ruiwen Zhang and Yanchao Feng*

Business School, Zhengzhou University, Zhengzhou, China

As a part of China's efforts to mitigate and control air pollution in key areas, the Air Pollution Prevention and Control Action Plan was implemented in 2013, and several regulatory measures were introduced. Based on the data from 271 prefecture-level cities between 2008 and 2018, the difference-in-differences model is used to explore the effect of it on sulfur dioxide intensity in our study, and several significant results are as follows: (1) The baseline results suggest a 23% reduction in sulfur dioxide intensity in pilot cities compared to non-pilot cities. (2) The total factor productivity fails to play a partial mediating role in reducing the sulfur dioxide intensity under the implementation of the policy. (3) The results of the triple differences model suggest that the policy still exerts significant adverse effects on sulfur dioxide intensity in the pilot areas of the carbon emission trading scheme.

KEYWORDS

sulfur dioxide intensity, air pollution control policy, total factor productivity, quasi-natural experiment, China

1. Introduction

Taking advantage of China's reform and openness, China has made remarkable economic progress and improved people's living conditions. However, it also leads to some problematic environmental issues. Air pollution, represented by sulfur dioxide pollution, is a serious problem that many developing countries, such as China, pay close attention to Arceo et al. (1). On the one hand, sulfur dioxide pollution causes very high environmental costs due to its contribution to fog-haze episodes (2). However, sulfur dioxide pollution can adversely affect human health and ecological environment (3). China's air pollution is severe as the world's largest energy consumer (4). For example, the 2007 World Development Indicators data show that some cities exceed the maximum air pollution index (above 500), while more than 60% of the world's most polluted cities are located on the Chinese mainland. According to the 2018 Environmental Performance Index (EPI), China's environmental performance index ranked fourth from the bottom in 2018. Although the Chinese government has implemented a series of policies since the 1980's to control sulfur dioxide emissions and improve air quality, sulfur dioxide pollution remains high due to large amounts of sulfur dioxide emissions into the atmosphere in some regions of China (5). From the comparison presented in Figure 1, areas polluted with sulfur dioxide are still primarily concentrated in the central and eastern regions. However, sulfur dioxide emissions in 2018 have decreased, compared to sulfur dioxide pollution in 2008.

To improve air quality, China has been doing its best to control air pollution, as evidenced by the 148 policy documents issued by the central government from 1973 to 2016 (6). For instance, the first national conference on environmental protection was held in 1973, marking

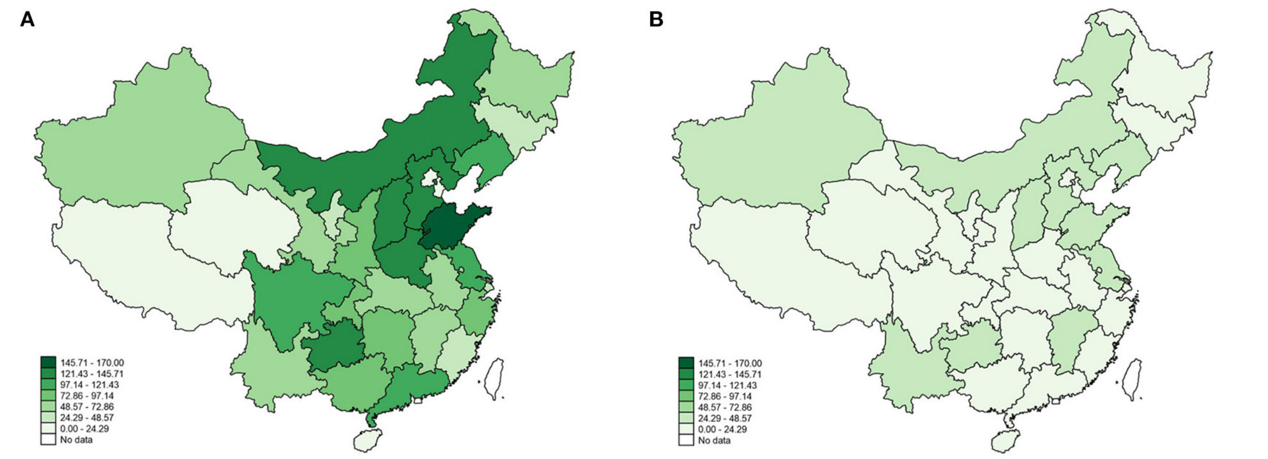

FIGURE 1
Sulfur dioxide emission in **(A)** 2008 and **(B)** 2018.

the beginning of China's air pollution control efforts. In addition, the Tentative Standards for Industrial Wastes Emission was promulgated in 1973, which set industrial emission standards. In 1995, China tried to achieve coordinated development of the regional economy, society and atmospheric environment by issuing air pollution regulatory standards, formulating planning opinions, issuing action plans, and implementing policies and measures. In 2000, the Chinese government promulgated the Law on the Prevention and Control of Air Pollution, aiming to establish "two control areas" throughout the country, namely acid rain prevention and control areas and sulfur dioxide prevention and control areas. However, implementing this policy can only curb the trend of acid rain and sulfur dioxide pollution. It cannot reverse the problem of acid rain and sulfur dioxide pollution. In particular, since General Secretary Xi Jinping took office, the country has paid more attention to controlling air pollution. In 2013, the State Council issued the "Action Plan for Prevention and Control of Air Pollution," which contains 10 provisions requiring that by 2017, the PM_{10} concentration at the prefecture level and above cities will drop by more than 10% compared to 2012, and the number of days with air quality standards will increase year by year. $PM_{2.5}$ concentrations in the Beijing-Tianjin Hebei region, the Yangtze River Delta, and the Pearl River Delta should fall by about 25, 20, and 15%, respectively (7). In addition, the APPCAP policy has been called the strictest air pollution control system in human history. From the data in Figures 2, 3, we can see that in the second year after the implementation of the APPCAP policy, sulfur dioxide emissions decreased significantly in 2015. At the same time, the sulfur dioxide intensity also maintained a downward trend year by year, but it remains to be explored whether this benefit from implementing the APPCAP policy is worth further exploration.

Although there is growing evidence of the correlation between environmental protection policy and environmental pollution (7–9), there is a massive scarcity of empirical effort regarding China's APPCAP policy on air pollution intensity, especially sulfur dioxide intensity. We regard the implementation of the APPCAP policy in China as a quasi-natural experiment and study the impact of the implementation of the APPCAP policy on sulfur dioxide intensity. In 2013, the Chinese government established the APPCAP pilot region in 47 cities. The APPCAP policy not only strictly constrains the total amount of pollutants discharged, but also emphasizes the comprehensive treatment of sulfur dioxide, NO compounds, volatile organic compounds and micro-particulate matter. The APPCAP policy can guide more social capital in the field of air control and restrict the production activities of the heavily polluting industry to a certain extent, thus benefiting air pollution control. In this context, concerns are raised: Can the APPCAP policy reduce the intensity of sulfur dioxide? If so, through which channels? Also, is there heterogeneity in the APPCAP policy effects on sulfur dioxide intensity among different regions? Answering these issues provides helpful insights for China and other developing countries to formulate similar environmental governance policies.

The contributions of our paper are primarily manifested in four aspects. First, our research differs from previous literature on the effect of air pollution control. We focus on pollution on the intensity level, which provides a novel perspective for analyzing the air pollution control effect of APPCAP. Secondly, in this paper, various models are applied, such as, DID model, PSM-DID model, IV test, DDD model, etc., which effectively solve the problems of model selection bias, endogenous problem, and sample selection bias and obtain sound research conclusions. Third, to clarify the impact mechanism and mediating influence, we select total factor productivity (TFP) as the mediating variable in this paper. Last but not least, exploring the sulfur dioxide intensity reduction effect of the APPCAP policy can provide strong evidence for further expansion of this plan in China and benefit other developing countries seeking to reduce air pollution.

The remainder of our paper is structured as follows: Section 2 presents the literature review, and the empirical strategy is described in Section 3. Section 4 shows the empirical results and a series of analyses. Section 5 draws conclusions and policy recommendations.

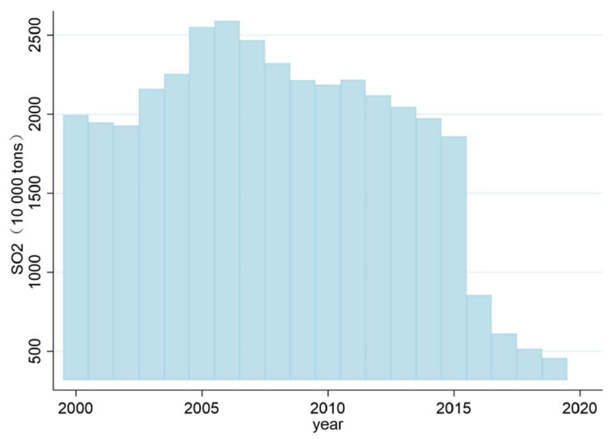

FIGURE 2
National sulfur dioxide emission changes from 2000 to 2020.

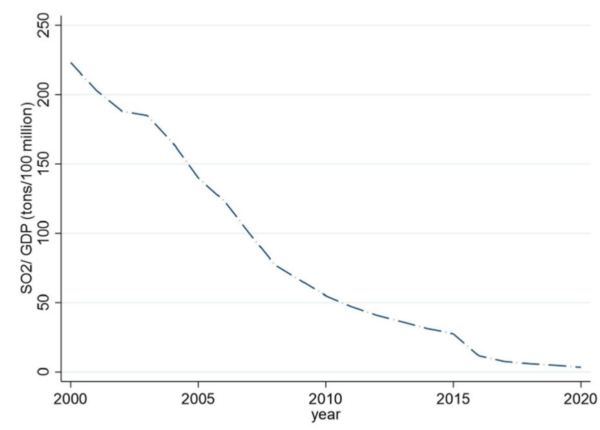

FIGURE 3
National sulfur dioxide intensity changes from 2000 to 2020.

2. Literature review

Our paper is mainly related to three types of literature. The first type of literature is on research on energy efficiency and air pollution. Energy efficiency is divided into single-factor energy efficiency and total-factor energy efficiency. Although single-factor energy efficiency can be measured in terms of energy consumption per capita of GDP, total-factor energy efficiency considers the impact of multiple input-output variables on energy factors. Gu and Yan (10) used data from all A-share listed companies from 2008 to 2018 to find that the promulgation of ambient air quality standards can significantly reduce $PM_{2.5}$ concentrations, and its implementation has remarkably improved the total factor productivity of listed enterprises in pilot cities. Wang et al. (11) found that regulating the atmospheric environment can significantly inhibit the growth of industrial total factor productivity by selecting panel data from 37 industrial sectors in China from 2003 to 2016 as the research object. Using the panel vector auto-regressive method (PVAR) and panel data from 30 provinces in China between 2005 and 2018, Li et al. (12) found that improving agricultural green total factor productivity by significantly reducing air pollution, in line with the work of Ahmed et al. (13), who used the PMG method and panel data of 50 states of America from 2005 to 2019. Based on the data from 30 provinces on the China from 2004 to 2017, Liu et al. (14) use the difference-in-differences (DID) method to find that the APPCAP policy has promoted the improvement of provincial energy efficiency. However, the impact on energy efficiency in different provinces is heterogeneous. Referring to the research ideas and methods of the above paper, it is necessary to consider the total factor productivity in our study and explore the role of the total factor productivity in the control of air pollution by the APPCAP policy.

The second type of literature describes and estimates the temporal and spatial changes in air pollutants after implementing the APPCAP policy. Based on panel data from 271 prefecture-level cities from 2008 to 2018 and using difference-in-differences (DID) and propensity score matching difference-in-differences (PSM DID) methods, Yu et al. (7) found that APPCAP significantly reduced $PM_{2.5}$ concentration and SO_2 emissions in the pilot areas. Based on the panel data of $PM_{2.5}$ concentration in 197 cities at the prefecture level and above in China from 2006 to 2016, Zhao et al. (15) found that the APPCAP policy has a significant smog control effect on the Beijing-Tianjin-Hebei region, but do not have noticeable policy effects on the Yangtze River Delta and Pearl River Delta regions. Zhang et al. (16) found that APPCAP effectively reduced China's per capita carbon emissions at the national level without considering spatial spillover effects. Using the empirical data of 109 resource-based cities from 2004 to 2018, Wu et al. (17) find that air pollution prevention and control actions significantly affect the air quality of growing, mature, and declining cities. However, the policy effect on regenerative resource-based cities is not apparent. However, Huang et al. (18) estimated the health impact of APPCAP on 74 critical cities from 2013 to 2017, suggesting that the effect of APPCAP on ozone and nitrogen dioxide emission control was not noticeable.

The third type of literature is the impact on human physical and mental health and disease risk after implementing the APPCAP policy. For example, Maji et al. (19) used air pollution data from 35 points in Beijing from 2014 to 2018 and found that Beijing's air quality improved significantly over the past 5 years, while $PM_{2.5}$ and O_3 mortality rates dropped remarkably. Yue et al. (20) combine chemical transport models with remote sensing and monitoring data and find a reduction in disease and mortality associated with exposure to lower concentrations of $PM_{2.5}$ after implementing APPCAP. Zhao and Kim (21) use nationally representative CFPS survey data conducted in 2012, 2014, and 2016 and find that APPCAP significantly reduces physician-diagnosed chronic diseases of the respiratory and circulatory systems. However, Yue et al. (20) found that the policy implementation effect of APPCAP is limited. More ambitious policies are needed if DAPP (deaths attributable to $PM_{2.5}$ pollution) is to be further significantly reduced.

In summary, although the existing literature has done much affluent research on the implementation effect of the APPCAP policy from different perspectives, there is still a lack of analysis of the national distribution data of APPCAP pilot cities (7), as well as little if any empirical work has been done to investigate the APPCAP policy effect on sulfur dioxide intensity.

3. Empirical strategy

3.1. Empirical framework

Taking China's APPCAP policy as a quasi-natural examination, we conduct a DID model to explore such policy's impact on sulfur dioxide intensity. As a magnificent tool for policy assessment, the DID estimation can principally avoid endogeneity problems. Explicitly, our DID estimation can contrast sulfur dioxide intensity in APPCAP cities (treatment group) and non-APPCAP cities (control group) in the pre-and post-implementation of the APPCAP policy, and the estimated equation is as follows:

$$ISO_{it} = \alpha_0 + \alpha_1 Time_i \times Treat_t + \gamma_i\, Control_{it} + \mu_i + \theta_i + \varepsilon_{it} \quad (1)$$

Where i denotes city, t indexes year, respectively. ISO_{it} is the independent variable and refers to sulfur dioxide intensity. If city i implements the APPCAP policy, the value of $Time_i$ is 1, and 0 otherwise. $Treat_i$ is the dummy variable. $Treat_i$ =1 denotes the APPCAP policy has been implemented and $Treat_i = 0$ represents the APPCAP policy has not been implemented. $Control_{it}$ is a series of control variables. The city fixed effects (μ_i), and the year fixed effects (θ_t) are also included in our equation. ε_{it} indicates the random error term.

The coefficient of $Time \times Treat$, α_1, captures the net impact of China's APPCAP policy on sulfur dioxide intensity. Explicitly, a negative and significant indicates that the APPCAP policy effectively reduces sulfur dioxide intensity and approves the pollution-reduction effect of the APPCAP policy. Instead, a positive and significant indicates that the APPCAP policy aggravates sulfur dioxide intensity. Furthermore, the insignificant suggests that the APPCAP policy fails to influence pollutant emissions. In addition, $Control_{it}$ implies the control variables selected in this study, including per capita GDP, industrial structure, industrialization level, population density, FDI, temperature, and rainfall.

According to the method of Wen et al. (22), in order to figure out the mediating effect of the mechanism, we choose the total factor productivity (TFP) as our mediating variable to investigate the extent of the influence of the explanatory variable on the explained variable through the mediating variable. Furthermore, the explicit test model is as follows:

$$ISO_{it} = \beta_1 + \omega_1 Time_i \times Treat_t + \rho_1 \quad (2)$$

$$TFP_{it} = \beta_2 + \omega_2 Time_i \times Treat_t + \rho_2 \quad (3)$$

$$ISO_{it} = \beta_3 + \omega_3 Time_i \times Treat_t + \omega_4 TFP_{it} + \rho_3 \quad (4)$$

Where β represents a constant and ω represents a coefficient Matrix, ρ represents the error term, and TFP_{it}represents the total factor productivity. In addition to using the OLS estimation method, the Bootstrap test is also used to verify whether TFP played an intermediary role in the APPCAP policy's effect on sulfur dioxide intensity in our study. Among them, the Bootstrap method is a non-parametric estimation method. When the final Bootstrap confidence interval does not contain a value of 0, the mediating effect is significantly not equal to 0. Through the Bootstrap test, the robustness of the mediation effect can be further judged.

The test step is as follows: In step (1), we test the total effect; if the coefficient ω_1 is significant, step (2) is performed; otherwise, the test ends. In step (2), we test the coefficients ω_2 and ω_4, and when both are significant, the indirect effect is significant, and we go directly to step (4) for further testing. If at least one of the two is not significant, the test for step (3) will be performed. In step (3), we perform a bootstrap check. When the results are significant, indicating significant indirect effects and the procedure progresses to step (4); Otherwise, the mediating effect is insignificant, and the test stops. In step (4), we test the coefficient ω_3; if the result is significant, it indicates that the direct effect is significant, and the process enters step (5); if it is not significant, then the direct effect is not significant, we only find an intermediate effect, and the effect is wholly mediated. In step (5), we compare whether $\omega_2 \times \omega_4$ and ω_3 are the same, if they are the same, indicating a partial mediating effect, if different, indicating the presence of a masking effect. The above process can determine whether the APPCAP policy is associated with sulfur dioxide intensity by influencing the mediating variable, total factor productivity (TFP).

3.1.1. Measures of sulfur dioxide intensity

Sulfur dioxide emission and GDP are selected to measure the magnitude of sulfur dioxide intensity in our work, and we use sulfur dioxide emissions to GDP to express sulfur dioxide intensity. In particular, our empirical analysis below is dominated by Log (sulfur dioxide intensity) and supplemented by sulfur dioxide intensity.

3.1.2. Measures of the APPCAP policy

Time × *Treat*, our core explanatory variable, represents a proxy measure for the APPCAP policy shock. Specifically, if a city is an APPCAP city, then the key explanatory variable is 1 in the ongoing and subsequent years and 0 in all others. There are 47 cities in the "three districts and ten groups" that belong to the vital air pollution areas in APPCAP policy, such as Beijing–Tianjin–Hebei, Yangtze River Delta, Pearl River Delta, central Liaoning, Shandong, Wuhan, and its surrounding areas, Chang-Zhu-Tan, Chengdu, Chongqing, the economic zone on the west side of the straits, central and northern Shanxi, Shaanxi, Guanzhong, Ganning and Urumqi, accounting for 17.34% of all-city sample (271 cities) during sample period. These 47 cities are treated as the pilot cities (i.e., treated groups), and the rest 224 cities are treated as the non-pilot cities (i.e., control groups). The mean values of the critical variables in the pilot and non-pilot cities are provided in Table 1.

3.1.3. Measures of TFP

Malmquist was first proposed by the Swedish economist Sten Malmquist in 1953 and has been widely recognized by the academic community. Therefore, this paper uses Malmquist to measure TFP, and its calculation formula is as follows:

$$Malmquist_t = \frac{D^t\left(x^{t+1}, y^{t+1}\right)}{D^t\left(x^t, y^t\right)} \quad (5)$$

3.1.4. Source of data

APPCAP has been implemented since 2013, and therefore, this study selects 2008–2018 as the regression period. The data of the explained and explanatory variables and control variables in our study are obtained from the "China City Statistical Yearbook," "China

TABLE 1 The main values of key variables in the pilot and non-pilot cities.

Variables	Non-pilot period		Pilot period	
	Non-pilot samples	Pilot samples	Non-pilot samples	Pilot samples
Sulfur dioxide intensity	109.748	46.728	51.687	16.192
Urbanization level	51.812	52.952	52.760	52.559
Proportion of secondary industry	51.155	51.735	46.496	45.980
Proportion of tertiary industry	34.355	41.183	40.783	48.939
Industrialization level	44.646	44.665	41.424	41.710
Per capita gdp (yuan)	63,626.530	109,657.200	57,801.030	114,894.700
Proportion of energy saving expenditure	3.098	2.781	55,862.660	24,312.610
Population density (10,000 people/km^2)	386.577	803.607	390.729	769.853
Energy consumption (10,000 tons of coal)	1,298.165	3,120.640	970.167	2,347.052
FDI (10,000 yuan)	45,117.020	281,775.100	57,811.600	320,500.500
Rainfall (mm)	959.056	1,082.276	3,740.900	4,717.751

Statistical Yearbook on the Environment from 2008 to 2018," and "The local Statistical Yearbook." The per capita GDP is deflated using the per capita GDP index based on 1978. Foreign direct investment (FDI) is initially converted using the exchange rate and then deflated using the fixed asset investment price index in 1990 as the base year. The descriptive statistics of the variables are listed in Table 2.

4. Empirical findings

4.1. Baseline results

Table 3 reveals the baseline regression results of the effect of China's APPCAP policy on sulfur dioxide intensity. The logarithm of sulfur dioxide intensity is taken as the outcome variable. Both columns (1) and (2) control for the city-fixed effects, whereas the difference is that column (2) also adds six city-level control variables. Furthermore, we include year-fixed effects; the results are in columns (3) and (4). Whether control variables are included or not, the coefficients of $Time \times Treat$ are significantly negative at the level of 1%, indicating that the APPCAP policy can reduce the sulfur dioxide intensity in pilot cities.

Through the analysis of column (4) in Table 3, we can find that the estimated coefficient of the core explanatory variable is reduced by 0.230 due to the implementation of the APPCAP policy. In other words, sulfur dioxide intensity in pilot cities dropped by an average of 23% compared to non-pilot cities. Furthermore, the APPCAP policy was first implemented in 2013; hence, the DID estimate captures a 6-year average treatment effect. This means the APPCAP cities reduce the intensity of SO2by 3.83% per year (23%/6). In sum, China's APPCAP policy effect is statistically and economically significant.

Considering the control variables, we primarily figure out the estimation results in column (4) of Table 3. The coefficient of GDP per capita is statistically and significantly negative, implying that the increase in GDP per capita comes at the cost of more air pollution. The positive effect of GDP per capita on sulfur dioxide intensity outweighs the negative effects. The annual average rainfall is significantly and negatively associated with sulfur dioxide intensity, illustrating that cities with higher rainfall can effectively remove SO_2, in line with the findings of Dong et al. (23). As presented in Table 3, other control variables, such as industrialization level and population density, do not remarkably affect sulfur dioxide intensity.

4.2. Dynamic DID

The DID model requires no systematic differences in the trend of sulfur dioxide intensity before implementing the APPCAP policy, and even if there are differences, these differences are fixed. The horizontal axis in Figure 4 implies the years before and after the APPCAP policy, e.g., pre_3 suggests the third year prior to the APPCAP policy and time_3 presents the third year after the APPCAP policy. The results of the parallel trend test shown in Figure 5 show that the coefficient estimates for the APPCAP pilot cities in the periods leading up to policy implementation are insignificant. In the second year after the implementation of the policy, the estimation coefficient gradually becomes significant and negative, which indicates that the implementation of the policy has a specific lagging effect and cannot have significant results in the current period of policy issuance. In summary, there was no significant difference between the pilot and non-pilot cities before the policy implementation, and the effect began to be produced in the second year after the policy implementation, so we consider that our study sample passed the parallel trend test.

4.3. Robustness checks

4.3.1. PSM-DID estimates

In order to solve systematic differences, we further combine propensity score matching with DID (PSM-DID). Namely, we cannot guarantee that APPCAP and non-APPCAP cities have similar characteristics before implementing the APPCAP policy. There may be a considerable variation in the 271 cities we have chosen as samples before, so we use the PSM-DID approach to mitigate systematically. Table 4 shows the PSM-DID test results, indicating that the APPCAP can reduce the sulfur dioxide intensity because the four cross-term

TABLE 2 Descriptive statistics.

Variables	Unit	Obs	Mean	Std. dev.	Min	Max
Sulfur dioxide intensity	Tons/100 million yuan	2,663	69.82	98.069	0.078	1,117.189
Per capita GDP	Yuan	2,758	69,588.108	44,479.502	11,282.535	704,725.910
Industrial structure	Secondary/tertiary	2,758	1.358	0.597	0.234	5.714
Industrialization level		2,393	42.957	12.015	3.91	87.252
Population density	Person/km^2	2,733	457.602	390.154	1.499	3,822.741
Foreign investment	10,000 yuan	2,621	98,399.062	202,774.81	17	3,175,038.7
Rainfall	Annual average rainfall	2,763	2,595.635	3,860.889	29.3	20,855.373

TABLE 3 DID regression results.

Variables	(1) Sulfur dioxide intensity (ln)	(2) Sulfur dioxide intensity (ln)	(3) Sulfur dioxide intensity (ln)	(4) Sulfur dioxide intensity (ln)
Time*treat	−1.273***	−0.630***	−0.243***	−0.230***
	(−15.860)	(−11.343)	(−5.261)	(−4.928)
Per capita GDP (ln)		0.211***		0.328***
		(3.361)		(6.744)
Industrial structure		0.471***		−0.032
		(10.319)		(−0.820)
Industrialization level (%)		0.133		0.010
		(0.519)		(0.050)
Population density (ln)		−0.011		0.018
		(−0.163)		(0.345)
FDI (ln)		−0.102***		−0.011
		(−5.060)		(−0.676)
Rainfall (ln)		−0.559***		−0.084***
		(−34.086)		(−3.358)
City fixed effect	√	√	√	√
Year fixed effect			√	√
Constant term	3.664***	5.714***	4.372***	1.341**
	(199.354)	(7.096)	(149.657)	(2.087)
N	2,663	2,209	2,663	2,209
R^2	0.095	0.544	0.754	0.731

t statistics in parentheses,*p < 0.1, **p < 0.05, ***p < 0.01.

coefficients are significant at the significant level of 1%. The PSM-DID approach is the same as the results of the DID approach, and there is no significant difference in the estimated coefficients of the interaction, implying that the APPCAP policy still effectively reduces sulfur dioxide intensity, lending further support to the robustness of the results.

4.3.2. Placebo test

To check whether omitted variables influence the DID estimates, we designed a placebo test by randomly assigning APPCAP status to cities so that we can figure out whether our findings are the result of APPCAP policy. Because 47 cities are treated as pilot cities, we decided to randomly select the same number of cities as the treatment group, constituting a pseudo-interaction term. Then, we perform the regression with the setting of Equation (1). Based on our assumptions, and the results should not be remarkable unless the random cities are the same as the actual cities. To make the results more convincing, we ran the random procedure 500 and 1000 times, respectively.

Figures 4A, B show the distribution of the *p*-value obtained from 500 and 1,000 simulations randomly assigning the APPCAP status to cities and the curve is the kernel density distribution of the estimation coefficient. Furthermore, the horizontal dashed line is a significance level of 0.1, and most of the estimates' *p*-value is more prominent than 0.1, implying that passing the great test is a small probability event.

These observations suggest that unobserved factors do not drive the adverse and significant effects of APPCAP on sulfur dioxide intensity.

4.3.3. Substitute dependent variable

To further eliminate the possibility of primary regression results being influenced by other factors, we conduct a robustness test on the DID model result by substituting the dependent variable because we consider that the impact of the APPCAP is not limited to sulfur dioxide intensity. Therefore, we choose carbon dioxide emissions and carbon intensity as the dependent variable. We can assume that the result is robust if the cross-term coefficients between the time and treat dummy variable are remarkable. The result in Table 5 shows that the core conclusions of this study still stand.

4.3.4. DDD estimates

To further demonstrate that our results are robust, this study expands the DID model to a DDD model by introducing the dummy variable of the carbon emission trading scheme, and the areas covered by the carbon emission trading scheme include Chongqing, Beijing, Tianjin, Shanghai, Guangdong, and Hubei. The triple cross-term can be understood as a change in sulfur dioxide intensity of the pilot area after the implementation of the carbon emission trading scheme and the APPCAP simultaneously. The coefficient of triple cross-term can be understood as the net effect of APPCAP on sulfur dioxide intensity in pilot areas after taking into account initial differences in policy effect caused by various external factors, the influence of different explanatory variables, differences between pilot and non-pilot areas, and the implementation of carbon market construction policies. As we can see in Table 6, both columns (1) and (2) control for the city-fixed effects, whereas the difference is that column (2) also adds six city-level control variables. Furthermore, we include year-fixed effects; the results are given in columns (3) and (4). In column (4) of Table 6, the coefficients are significantly negative at the 5% level, indicating that the implementation of the APPCAP has significantly reduced the sulfur dioxide intensity in the pilot areas when the carbon emission trading scheme is implemented.

4.4. IV estimates

Various potential factors can affect the selection of APPCAP cities, which will further lead to the estimation bias of the DID model. Furthermore, our DID estimates would inevitably suffer from endogeneity problems if these factors simultaneously influence $Time \times Treat$ and sulfur dioxide intensity. Therefore, our study takes an IV test as an additional robustness test by using the ventilation coefficient as an instrumental variable based on Hering and Poncet (24).

An IV should satisfy both relevance and exogenous. First, does the ventilation coefficient satisfy the relevance requirement? According to the study by Box (25), wind speed influences horizontal pollution dispersion, and the mixed layer height can affect vertical pollution dispersion. Therefore, we define the ventilation coefficient as the product of wind speed and mixed layer height. The higher the value, the faster the pollution spreads; this means that there is a negative relevance between the ventilation coefficient and the

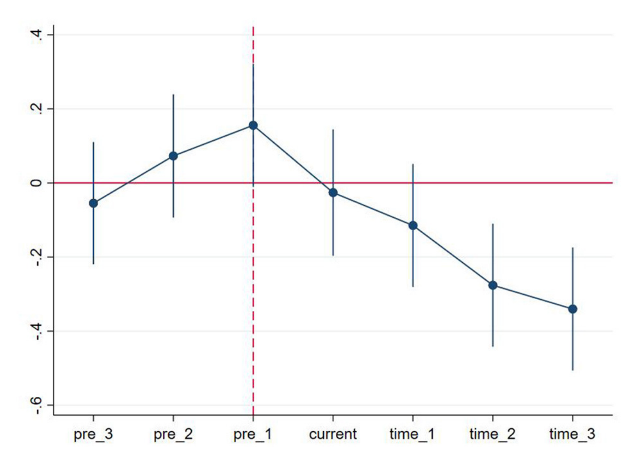

FIGURE 5
Parallel trend test of sulfur dioxide intensity in the experimental and control groups.

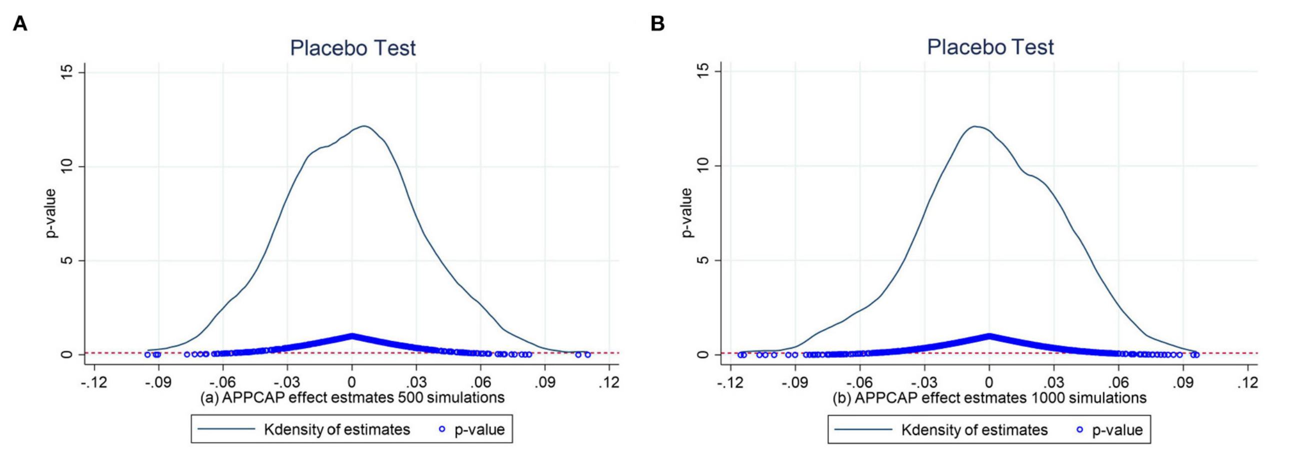

FIGURE 4
Placebo test. **(A)** 500 times. **(B)** 1,000 times.

sulfur dioxide intensity, in line with the relevance requirement. Second, does the ventilation coefficient satisfy the exogenous requirement? According to the method of Yu et al. (7), we collect wind speed information for 10 m height and boundary layer height (used to measure mixed layer height for 75 × 75 grids) in the ERA data. This data is from the European Center for Medium Weather Forecasting (ECMWF), which means that the ventilation coefficient has no direct relationship with sulfur dioxide intensity. Therefore, the ventilation coefficient fulfills the exogenous requirement.

Table 7 represents the estimated results of our IV test, and the estimated coefficients of *Time* ventilation coefficient* from column (1) to column (4) are significantly negative at the 1% level. Therefore, our results are still robust. To sum up, even considering the potential selection bias problem in pilot cities, APPCAP policy still contributes to reducing sulfur dioxide intensity, which highlights the robustness of the core finding of this study.

4.5. Heterogeneity analysis

The pilot areas differ in many ways, for instance, in the climate, human factors, economic conditions, and natural environment. Therefore, to test whether regional differences will lead to bias in the regression results, in other words, we need to figure out if the APPCAP policy affects the pilot areas in different conditions, so we perform a heterogeneity analysis. We further divide the 47 pilot cities into three dimensions for DID regression, respectively, and the three dimensions are east and mid-west, heating and non-heating, and coastal and inland. Finally, we can consider our conclusion of this study to be robust if the cross-term coefficient is remarkable. Table 8 shows that all the cross-term coefficients are significantly negative at the 1% level, which means that the APPCAP policy has significantly reduced the sulfur dioxide intensity in the east or mid-west, heating or non-heating, and coastal and inland pilot areas.

4.6. Impact mechanism test

Table 9 reports the regression results for Equation (2), (3), and (4). Column (1) is the result of regression to Equation (1); the test results in column (1) show that the influence coefficient of the core explanatory variables on sulfur dioxide intensity is −0.299, which is significantly negative at the 1% level. Furthermore, it means that the implementation of the APPCAP policy can reduce the sulfur dioxide

TABLE 4 PSM-DID estimates.

Variables	(1) Sulfur dioxide intensity (ln)	(2) Sulfur dioxide intensity (ln)	(3) Sulfur dioxide intensity (ln)	(4) Sulfur dioxide intensity (ln)
Time*treat	−1.273***	−0.630***	−0.243***	−0.230***
	(−15.860)	(−11.343)	(−5.261)	(−4.928)
Control variables		√		√
City fixed effect	√	√	√	√
Year fixed effect			√	√
Constant term	3.664***	5.714***	4.372***	1.341**
	(199.354)	(7.096)	(149.657)	(2.087)
N	2,663	2,209	2,663	2,209
R^2	0.095	0.544	0.754	0.731

t statistics in parentheses, *p < 0.1, **p < 0.05, ***p < 0.01.

TABLE 5 Substitute dependent variable estimates.

Variables	(1) Carbon dioxide (ln)	(2) Carbon dioxide (ln)	(3) Carbon intensity (ln)	(4) Carbon intensity (ln)
Time*treat	−0.053***	−0.051***	−0.003**	−0.001*
	(−7.253)	(−7.159)	(−2.423)	(−1.671)
Control variables		√		√
City fixed effect	√	√	√	√
Year fixed effect	√	√	√	√
Constant term	2.955***	2.474***	0.026***	0.057***
	(635.583)	(25.897)	(30.957)	(5.477)
N	2,723	2,241	2,722	2,241
R^2	0.697	0.732	0.269	0.406

t statistics in parentheses, *p < 0.1, **p < 0.05, ***p < 0.01.

TABLE 6 DDD test estimates.

Variables	(1) Sulfur dioxide intensity (ln)	(2) Sulfur dioxide intensity (ln)	(3) Sulfur dioxide intensity (ln)	(4) Sulfur dioxide intensity (ln)
Time*treat*market	0.814***	0.218	−0.238**	−0.234**
	(3.855)	(1.498)	(−2.081)	(−2.020)
Treat*carbon market	0.425	0.622**	0.892***	0.697***
	(1.029)	(2.288)	(4.048)	(3.281)
Time*carbon market	−1.106***	−0.556***	−0.078	−0.009
	(−10.556)	(−7.635)	(−1.311)	(−0.150)
Time*treat	−1.206***	−0.576***	−0.196***	−0.194***
	(−13.104)	(−9.179)	(−3.681)	(−3.649)
Control variables		√		√
City fixed effect	√	√	√	√
Year fixed effect			√	√
Constant	3.699***	5.926***	4.331***	1.464**
	(141.209)	(7.464)	(141.067)	(2.276)
N	2,663	2,209	2,663	2,209
R^2	0.136	0.559	0.756	0.733

t statistics in parentheses, *p < 0.1, **p < 0.05, ***p < 0.01.

TABLE 7 IV estimates.

Variables	(1) Sulfur dioxide intensity (ln)	(2) Sulfur dioxide intensity (ln)	(3) Sulfur dioxide intensity (ln)	(4) Sulfur dioxide intensity (ln)
Time*ventilation coefficient	−3.060***	−1.464***	−4.133***	−2.687***
	(−4.594)	(−2.950)	(−10.893)	(−7.733)
Control variables		√		√
Year fixed effect	√	√		
City fixed effect			√	√
Constant term	4.355***	1.168	3.931***	3.587***
	(35.164)	(1.507)	(94.768)	(3.232)
N	2,653	2,200	2,653	2,200

z-statistics in parentheses, *p < 0.1, **p < 0.05, ***p < 0.01.

intensity. Column (2) is the result of regression to Equation (2), showing that the coefficient is insignificant. Column (3) is the result of regression to Equation (3). The test results in column (3) show that after controlling TFP, the impact coefficient of the core explanatory variables on sulfur dioxide intensity is −0.289, which is significantly negative at the 1% level. So we cannot directly conclude whether TFP has a mediating effect, so we further perform a Bootstrap test to find out whether the mediating effect of TFP exists. Based on the above results, we further perform a Bootstrap test, as shown in Table 10, the revised confidence interval does not contain 0, so we can conclude that implementing the APPCAP policy can reduce the sulfur dioxide intensity, and TFP failed to play a mediating role in it.

5. Conclusions and policy implications

It is generally believed that implementing environmental regulatory policies is an effective tool for air pollution governance. To improve air quality, China has piloted the APPCAP policy since 2013. Evaluating the influence of the APPCAP policy on sulfur dioxide intensity is of great significance for environmental regulatory policy formulation and economic development in China and other developing countries. Based on a panel data covering 271 prefecture-level cities between 2008 and 2018, our paper isolates the effect of the APPCAP policy on sulfur dioxide intensity with the employment of DID method and PSM-DID approach. We draw several main findings: (1) The baseline results suggest a 23% reduction in sulfur

TABLE 8 Heterogeneity analysis.

Variables	(1) Sulfur dioxide intensity (ln)	(2) Sulfur dioxide intensity (ln)	(3) Sulfur dioxide intensity (ln)	(4) Sulfur dioxide intensity (ln)	(5) Sulfur dioxide intensity (ln)	(6) Sulfur dioxide intensity (ln)
Time*treat	−0.200***	−0.416***	−0.176***	−0.255***	−0.285***	−0.240***
	(−3.294)	(−4.805)	(−2.621)	(−3.859)	(−3.202)	(−4.193)
Control variables	√	√	√	√	√	√
City fixed effect	√	√	√	√	√	√
Year fixed effect	√	√	√	√	√	√
Constant term	3.043***	−1.754*	1.123	1.117	1.270	0.620
	(3.325)	(−1.865)	(1.139)	(1.255)	(0.959)	(0.815)
N	1,031	1,178	1,083	1,126	514	1,695
R^2	0.732	0.749	0.742	0.731	0.726	0.741

t statistics in parentheses; *p < 0.1, **p < 0.05, ***p < 0.01.

TABLE 9 Impact mechanism estimates.

Variables	(1) Sulfur dioxide intensity (ln)	(2) TFP	(3) Sulfur dioxide intensity (ln)
Time*treat	−0.299***	0.068	−0.289***
	(−4.576)	(0.947)	(−4.456)
TFP			−0.113***
			(−5.969)
Control variables	√	√	√
City fixed effect	√	√	√
Year fixed effect	√	√	√
N	2,164	2,204	2,164
R^2	0.325	0.001	0.336

Standard errors in parentheses, *p < 0.1, **p < 0.05, ***p < 0.01.

TABLE 10 Bootstrap test: Total factor productivity.

Trails	Effect	ω-value	S	Z-value	*P*-value	95% confidence interval	
						Lower limit	Upper bound
ω_3	Direct effect	−0.235	0.035	−6.66	0.000	−0.304	−0.180
$\omega_2 * \omega_4$	Intermediary effect	0.001	0.001	0.99	0.321	0.001	0.003

dioxide intensity in APPCAP cities compared to non-APPCAP cities. (2) An IV test deals with potential endogeneity problems, corroborating the baseline results. (3) The results of the DDD model suggest that China's APPCAP still exerts significant adverse effects on sulfur dioxide intensity in the pilot areas of the carbon emission trading scheme. (4) Our mechanism analysis indicates that total factor productivity (TFP) fails to play a partial mediating role in reducing the sulfur dioxide intensity under the implementation of the APPCAP policy. (5) The APPCAP policy significantly adversely affects the sulfur dioxide intensity in the heterogeneous analysis.

We derive three policy recommendations from our results. First, the Chinese government should further expand the scale of its APPCAP policy. Our main finding is that the APPCAP policy has a powerful sulfur dioxide intensity reduction effect. Further expansion of the APPCAP policy can improve air quality while ensuring rapid economic development. Moreover, non-APPCAP regions can learn from APPCAP regions' successful experiences. Because of the regional difference, the APPCAP policy should be formulated with sufficient consideration of local air pollution and economic development. It is vital to combine policies tailored to local conditions. In addition, if we properly combine the APPCAP policy with other local policies in different cities, it will likely have an excellent synergistic effect.

Second, the government should further improve the APPCAP policy to cover as many air pollutants as possible and specify specific emission control targets, such as adding long-term specific emission control indicators for air pollutants such as SO_2, NO_2, CO, and O_3, in order to achieve the vision of gradually upgrading air quality standards and catching up with national air quality standards as soon as possible. At the same time, the specific formulation of policy formulation should also depend on improving air quality and cannot be rigid, blind, and "one-size-fits-all."

Third, as a potential intermediary factor, total factor productivity is vital in reducing sulfur dioxide intensity under the APPCAP policy, while the effectiveness of it is poor in this study. Therefore, China's local government departments should pay more attention to the energy efficiency of enterprises and how to improve the energy efficiency of enterprises in the first place, which not only has a positive impact on air governance but also helps to improve the level of local economic development. In addition, government departments should establish the concept of green development and innovative development, increase investment in R&D subsidies for local enterprises, and encourage enterprises to develop new technologies and improve energy efficiency to improve air quality.

Data availability statement

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

Author contributions

SN and YF: conceptualization and visualization. SN: methodology and software. RZ: validation and funding acquisition. YF: formal analysis. YC and YF: data curation, writing–review and editing, and supervision. YC: writing–original draft preparation. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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

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EDITED BY
Yunquan Zhang,
Wuhan University of Science and Technology, China

REVIEWED BY
Giulia Squillacioti,
University of Turin, Italy
Feifei Feng,
Zhengzhou University, China

*CORRESPONDENCE
Zhongjie Fan
✉ fanzhongjie@pumch.cn
Cheng Huang
✉ eedc2003@sina.com

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Association between the temperature difference and acute exacerbations of chronic obstructive pulmonary disease: A time-series analysis with 143,318 hospital admissions in Beijing, China

Jia Fu[1], Yanbo Liu[2], Yakun Zhao[1], Yuxiong Chen[1], Zhenge Chang[1], Kai-Feng Xu[3], Cheng Huang[4]* and Zhongjie Fan[1]*

[1]Department of Cardiology, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China, [2]Department of International Medical Services, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China, [3]Department of Respiratory Medicine, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China, [4]Department of Thoracic Surgery, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing, China

Purpose: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) has the adverse influence on quality of life and creates significant healthcare costs. However, there were sparse studies investigating the correlation between AECOPD hospital admissions and temperature change. Therefore, it is noteworthy to investigate the impact of various temperature differences and recognize the susceptible population. The purpose of this study was to investigate the impact of temperature differences on AECOPD hospital admissions, and to give potentially helpful material for disease preventative efforts.

Methods: The distributed lag non-linear model was adopted to characterize the exposure-response relationship and to assess the impact of temperature difference. The stratified analysis and sensitivity analysis were also conducted to determine the susceptible populations and examine the robustness of the results.

Results: There were 143,318 AECOPD hospital admissions overall during the study period. The AECOPD hospital admissions had significant association with the daily mean temperature difference (DTDmean) such as the extreme-cold temperature difference (1st DTDmean), the ultra-cold temperature difference (5th DTDmean), the ultra-hot temperature difference (95th DTDmean) and the extreme-hot temperature difference (99th DTDmean). Besides, there was the "*U*-shaped" association between DTDmean and 21 days cumulative relative risk of AECOPD.

Conclusion: The AECOPD hospital admissions was correlated with the DTDmean temperature differences, especially the extreme-cold and extreme-hot temperature difference. Moreover, people older than 65 years were more susceptible to the extreme-hot and extreme-cold temperature difference.

KEYWORDS

AECOPD, temperature change, temperature, temperature difference, distributed lag non-linear model

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a general disease characterized by ongoing airflow restriction and respiratory symptoms (1). Globally, COPD is a leading cause of morbidity and mortality (2). Statistics show that COPD is now one of the three leading causes of death worldwide, with 90% of deaths taking place in low- and middle-income nations (3). A thorough investigation found that COPD contributed 2.6% of the world's disability-adjusted life years in 2015 (4). Because of the ongoing exposure to relevant risk factors and an aging population, it is anticipated that the burden of COPD will rise globally in the future decades (5). Acute worsening of the initial respiratory symptoms that necessitates a change in treatment is known as the acute exacerbation of COPD (AECOPD) (6). According to estimates, COPD patients experience 1–4 exacerbations annually (7). AECOPD might hasten the deterioration of lung function (8), which lead to less physical activity and an increased risk of death (9, 10). AECOPD also has significant association with damaged quality of life (11), which are the major culprits of hospitalizations (12). Research has shown that AECOPD is to blame for 10% of all medical hospitalizations (13). In brief, AECOPD can generate huge healthcare burdens.

Previously reported works have demonstrated that ambient temperature have significant association with COPD hospitalization, emergency visits and so forth. For example, a Spanish study found that hospital admissions and mortality for COPD exacerbation were more frequent in autumn and winter (14). A case-crossover study in Taiwan demonstrated the exacerbation rate of COPD on event days increased by 0.8% for every 1°C decrease in air temperature (95% C.I. 1.015–1.138) (15). A study from 2004 to 2011 discovered that during periods of extreme weather, adults over 60 years old had an increased risk of admission for pneumonia and COPD (16). However, the impacts of ambient temperature have received more research attention. Studies on the relationship between AECOPD hospital admissions and temperature changes were scarce, particularly in Beijing, China. Additionally, the indicator of temperature change was relatively 1-fold. Hence, it is important to investigate the impact of various temperature differences and recognize the susceptible population. The purpose of this study was to investigate the impact of temperature differences on AECOPD hospital admissions, and to give potentially helpful material for disease preventative efforts.

2. Materials and methods

2.1. Data gathering

The hospital admissions data of the AECOPD were obtained from the Beijing Municipal Health Commission Information Center and this study was set as the period from January 1, 2013 to December 31, 2016. The data included the anonymous personal information (age, gender, discharge diagnosis, date of birth), hospital admission data (hospitalization date and hospital name), and address information (birthplace and present address). International Classification of Diseases 10th revision was used to define AECOPD (ICD-10: J41-J44). To rule out the effect of the floating population on the study's findings, the Beijing resident population were filtrated according to the address information of patients. The daily hospital admissions of different gender subgroups (male and female), different age subgroups (age < 65, age ≥ 65) and total population were calculated by using the IBM SPSS 26 and R (version 4.1.1). The Peking Union Medical College Hospital (PUMCH) Institutional Review Board approved the study's conduct.

The China Meteorological Administration provided the daily meteorological data. It contained both the temperature data [daily maximum temperature (Tmax), mean temperature (Tmean), and minimum temperature (Tmin)], and other meteorological factors [Wind Speed (WS), Relative Humidity (RH), and Air Pressure (AP)]. As for meteorological data, four kinds of temperature differences were calculated respectively to represent the temperature change. It contained overall temperature range (TR, Tmax today minus Tmin today), daily mean temperature difference (DTDmean, Tmean today minus Tmean yesterday), daily maximum temperature difference (DTDmax, Tmax today minus Tmax yesterday), and daily minimum temperature difference (DTDmin, Tmin today minus Tmin yesterday). The level of air pollution was regarded as one of the confounding factors and adjusted in our study because prior research indicated that air pollution had an adverse influence on multiple respiratory disorders (17–19). Our study adjusted the Air Quality Index (AQI), which represented the main effects of the level of air pollution because there were numerous types of air pollutants and the daily major pollutant concentration levels fluctuated. The Beijing Environmental Protection Bureau provided the AQI data for the same period.

The influenza viruses can trigger exacerbations of respiratory diseases (20–22), the public holiday (PH) and day of the week (DOW) might have an influence on the behavioral patterns, so the influenza epidemic (IF), PH, and DOW were also regarded as confounding factors and adjusted in our statistical model. When the positive rate of influenza virus isolation in any given week exceeded 20% of the highest weekly positive rate in the observation season in the north of China, it was defined as the influenza endemic according to the method used in prior study (23). The Chinese National Influenza Center provided the influenza data (https://ivdc.chinacdc.cn/cnic/zyzx/lgzb).

2.2. Statistical analysis

Since temperature typically has a lag effect and prior research disclosed that correlation between COPD and temperature was non-linear (24, 25). The distributed lag non-linear model (DLNM) was constructed to concurrently match the effect and lag effect of independent variables (26). The distributed lag non-linear model was adopted to characterize the exposure-response relationship and to assess the impact of meteorological parameters (27). Because hospital admissions for respiratory disorders are small probability events that occur independently, the daily counts of AECOPD admissions were viewed as a quasi-Poisson distribution in this model to control the overdispersion in the number of hospitalizations (28). To eliminate the seasonal and long-term trends in AECOPD admission, the natural cubic spline function for time was applied. To eliminate the effects of other meteorological conditions and air pollution, the natural cubic spline functions for RH, WS, AP, and AQI were also included. As previously stated, the DOW, PH, and IF were also regarded as confounding factors and adjusted in model in the meantime. The main model is shown in detail below:

$$\begin{aligned} \log\left[E\left(Y_t\right)\right] = {} & \alpha + cb\left(Temp_t,\ lag, df = 4\right) \\ & + ns\left(Time,\ df = 7\ per\ year\right) + ns\left(WS,\ df = 3\right) \\ & + ns\left(AP, df = 3\right) + \ ns\left(RH, df = 3\right) \\ & + \ ns\left(AQI, df = 3\right) + \beta_1 * DOW + \beta_2 * IF + \beta_3 * PH \end{aligned}$$

$E\left(Y_t\right)$ represent the number of AECOPD hospital admissions on day t. α and β were the model intercept and regression coefficient, respectively. cb meant the cross-basis function and ns indicates the natural cubic spline function. Tmp refer to the temperature difference. *Time* refers to the time to control the season and long-term trends. WS, AP, RH, and AQI represent the daily mean wind speed, air pressure, relative humidity, and air quality index on day t, respectively. *DOW*, *IF*, *and PH* are the indicator for day of the week, influenza epidemic status and public holiday. *df* represent the degree of freedom. All statistical analyses were performed using R (version 4.1.1) software, and the two-sided p-value of 0.05 was conducted to assess statistical significance.

The single day lag effect was examined using a 3D map that included lag days (Lag), relative risk (RR), and temperature differences. The maximum lag of 37 days was chosen to fully detect the influence of temperature differences and the probable harvesting effects. The figure of association between the specific percentile temperature difference (1st: extreme-cold temperature difference; 5th: ultra-cold temperature difference; 95th: ultra-hot temperature difference; 99th: extreme-hot temperature difference) and relative risk in various lag days were also charted. The extreme-cold, ultra-cold, ultra-hot and extreme-hot temperature difference means first, fifth, ninety-fifth and ninety-ninth percentile temperature difference. The cumulative relative risk of AECOPD hospital admission (CRR) was set to 21 days to fully detect the influence of temperature differences and avoid excessive accumulation. In addition, the stratified analysis was also conducted to determine the susceptible populations and examine the robustness of the results. In various subgroups, the most moderate temperature difference (MMTD) in the total population was taken as the standard. To assess the reliability of findings and the robustness of statistical model, we also conducted sensitivity analyses. We changed the degrees of freedom to 6 per year for *Time* and 4 for *RH*, *WS*, *AP*, and *AQI,* or 8 per year for *Time* and 5 for *RH*, *WS*, *AP*, and *AQI* in the statistical model to recalculate the CRR of temperature differences. R (version 4.1.1) was used for all statistical analysis along with the packages of "dlnm" and "mgcv."

TABLE 1 AECOPD daily hospital admissions of the total population and subgroups in Beijing from January 1, 2013 to December 31, 2016.

	Sum	Max	Min	Average	SD
Total	143,318 (100%)	226	17	98.1	39.421
Male	95,555 (66.7%)	158	12	65.4	25.627
Female	47,763 (33.3%)	110	2	32.69	15.948
<65	24,938 (17.4%)	47	0	17.07	8.231
≥65	118,380 (82.6%)	189	13	81.03	32.678
IF	-	1 (N = 523)	0 (N = 938)	-	-
PH	-	1 (N = 462)	0 (N = 999)	-	-

SD, standard deviation; <65, people under the age of 65; ≥65, people at the age of 65 and above; IF, influenza epidemic (one represents the presence of influenza epidemic on the observation day); PH, public holiday (one represents the presence of public holiday on the observation day).

TABLE 2 Baseline information for different temperatures and meteorological data from January 1, 2013 to December 31, 2016.

	Min	Max	Average	SD
AQI	23	485	123.65	75.173
RH (%)	8	97	53.43	19.858
WS (m/s)	3	34	9.29	4.754
AP (hPa)	994	1,044	1,016.56	10.166
Tmean (°C)	−16	32	12.88	11.169
Tmax (°C)	−13	42	18.95	11.392
Tmin (°C)	−17	27	7.13	11.338
TR (°C)	1	26	11.82	4.31
DTDmean (°C)	−7	7	0	2.263
DTDmin (°C)	−9	11	0	2.778
DTDmax (°C)	−14	16	0	3.574

SD, standard deviation; AQI, air quality index; RH, relative humidity; WS, wind speed; AP, air pressure; Tmean/max/min, daily mean/max/min temperature; TR, temperature range; DTDmean/max/min, daily mean/max/min temperature difference.

3. Results

3.1. Descriptive analysis

Tables 1, 2 summarized daily hospital admissions of AECOPD and meteorological data. The total population and subgroups' daily hospital admissions for AECOPD were shown in Table 1. There were 143,318 AECOPD hospital admissions overall between January 1, 2013, and December 31, 2016. While 24,938 of them were under 65 and 95,555 of them were men. There were 523 days of the influenza epidemic and 462 days of public holidays throughout the research period. The meteorological information is displayed in Table 2. The average values of Tmax, Tmean, Tmin, WS, RH, and AP were 18.95, 12.88°C, and 7.13°C, 9.29 m/s, 53.43% and 1,016.56 hPa respectively during the period of study. The average

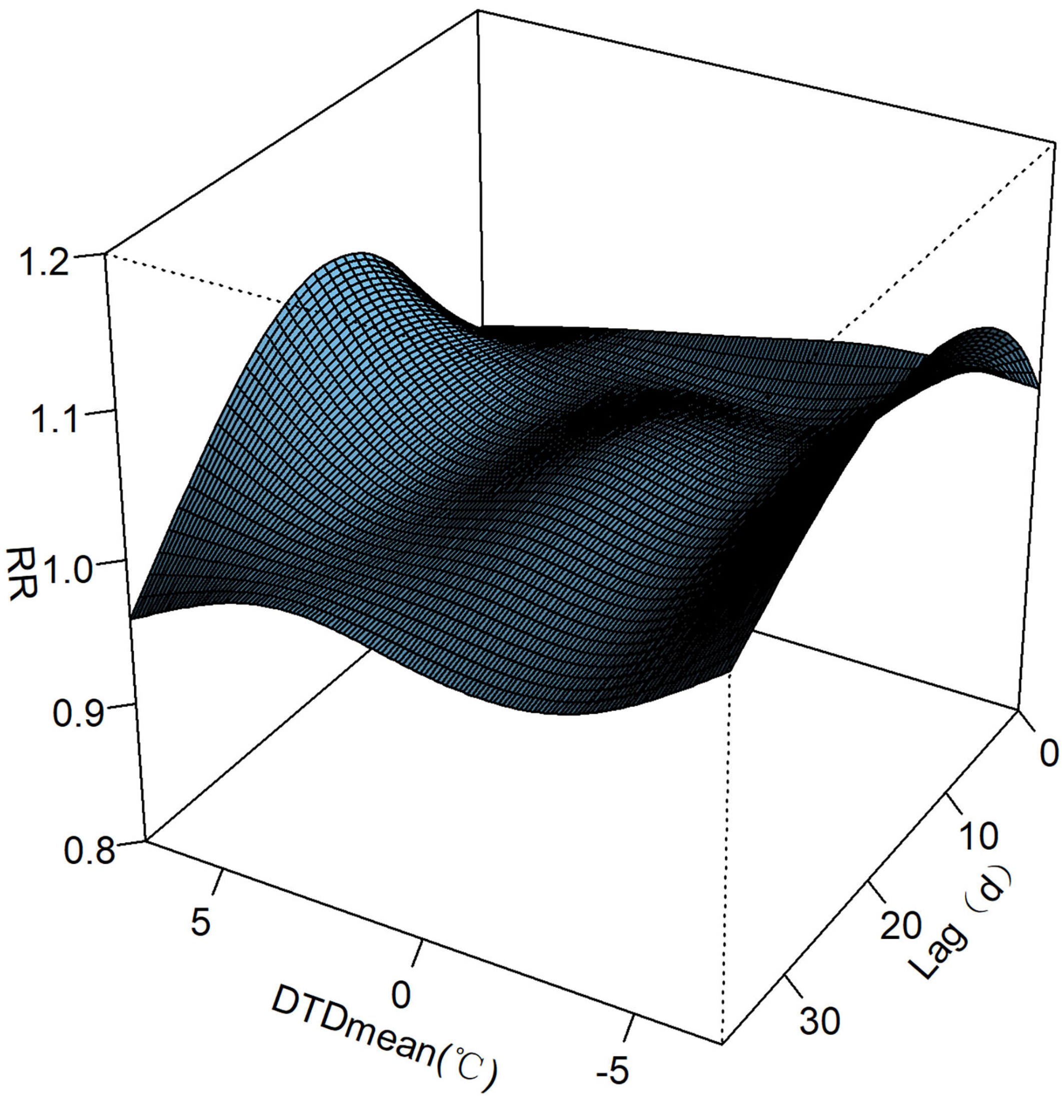

FIGURE 1
Association among the DTDmean, lag days and the relative risk of AECOPD hospital admissions in Beijing.

value of temperature range was 11.82°C and the average value of daily maximum/ mean/minimum temperature differences were all 0°C.

3.2. Single day relative risk

Figure 1 depicted the overall trend of the association among the DTDmean, lag days and the relative risk of AECOPD hospital admissions. In general, the RR became larger and larger with the increase of the absolute value of DTDmean in the mid-term of lag days.

Figure 2 depicted the result that the AECOPD hospital admissions had significant association with the extreme-cold temperature difference (1st DTDmean), the ultra-cold temperature difference (5th DTDmean), the ultra-hot temperature difference (95th DTDmean) and the extreme-hot temperature difference (99th DTDmean). As for the extreme-cold temperature difference, the AECOPD hospital admissions had significant association from lag 1 to lag 36 days and the maximum of RR was in lag 15 days. As for the ultra-cold temperature difference, the AECOPD hospital admissions had significant association from lag 0 to lag 2 days and the maximum of RR was in lag 0 days. As for the ultra-hot temperature difference, the AECOPD hospital admissions had significant association from lag 10 to lag 25 days and the maximum of RR was in lag 17 days. As for the extreme-hot temperature difference, AECOPD hospital admissions had significant association from lag 8 to lag 29 days and the maximum of RR was in lag 17 days.

3.3. Cumulated relative risk

Figure 3 showed the *U*-shaped curve association between the DTDmean and the 21 days CRR (95% C.I.) of AECOPD hospital

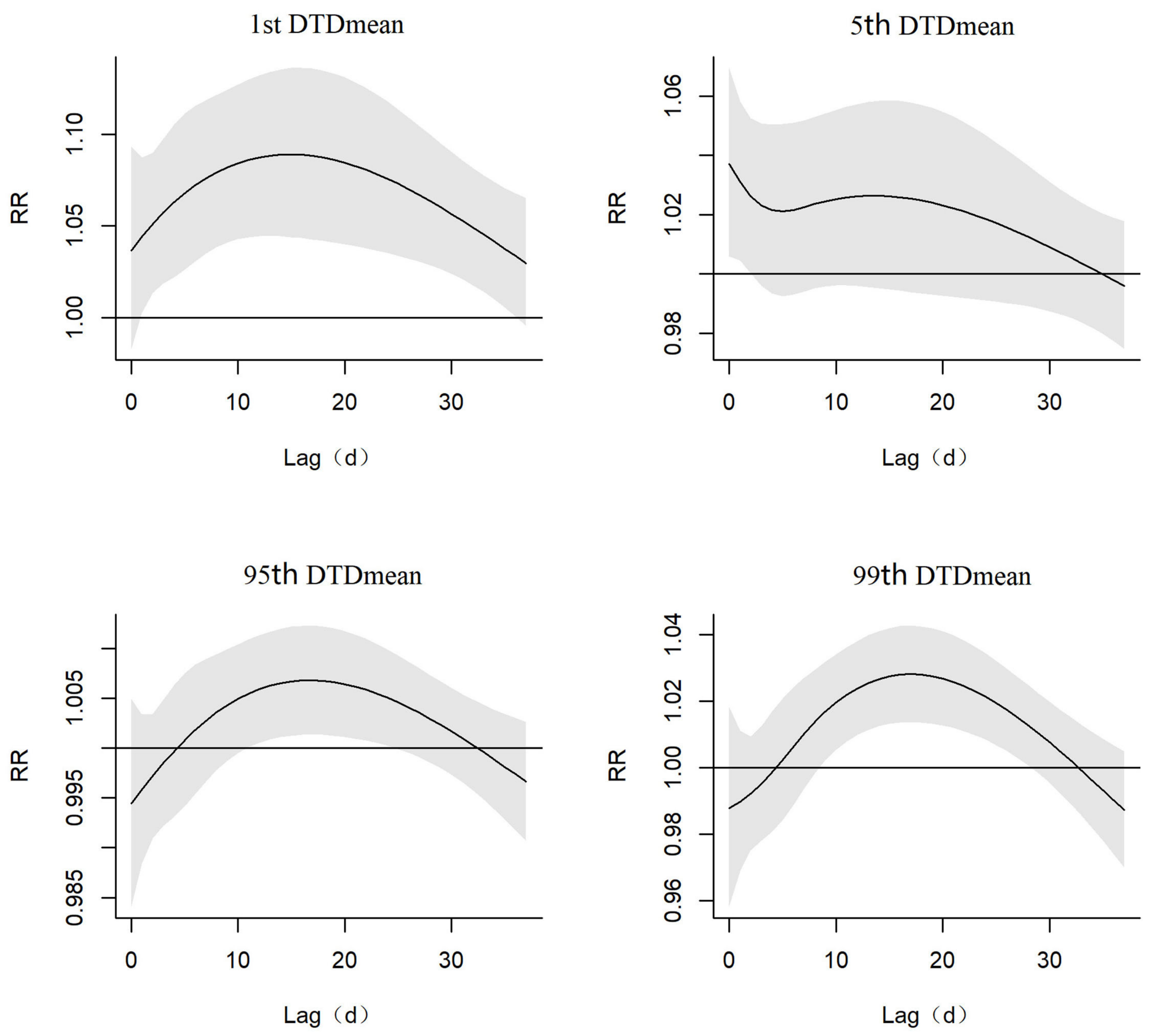

FIGURE 2
Relative risk (include 95% C.I.) of the extreme-cold, ultra-cold, ultra-hot, and extreme-hot of DTDmean temperature difference in AECOPD hospital admissions in different lag days.

admissions. From Table 3, we found that the 21 days CRR of AECOPD was significant when it was in the extreme-cold temperature difference (1st DTDmean), the ultra-hot temperature difference (95th DTDmean) and the extreme-hot temperature difference (99th DTDmean). When the DTDmean was −6°C, the 21 days cumulated relative risk was 1.79 (95% C.I. 1.08–2.96) and when the DTDmean was 5°C, the 21 days cumulated relative risk was 1.46 (95% C.I. 1.11–1.93).

3.4. Stratification effect

Figure 4 and Table 4 depicted the results for the association between the DTDmean and the 21 days CRR of AECOPD hospital admissions in different gender groups in Beijing. It showed that the effect of DTDmean was similar in male and female population. For example, when the DTDmean was −6°C (1st DTDmean), the 21 days CRR for male and female subgroups were 1.70 (95% C.I. 0.96–3.00) and 1.89 (95% C.I. 0.91–3.92), respectively.

Figure 5 and Table 5 depicted the results for the association between the DTDmean and the 21 days CRR of AECOPD hospital admissions among different age groups in Beijing. It showed that people older than 65 years were more susceptible to the extreme-hot and extreme-cold temperature difference. For example, when the DTDmean was −6°C (1st DTDmean), the 21 days CRR for younger and older subgroups were 1.41 (95% C.I. 0.53–3.37) and 1.87 (95% C.I. 1.11–3.14), respectively.

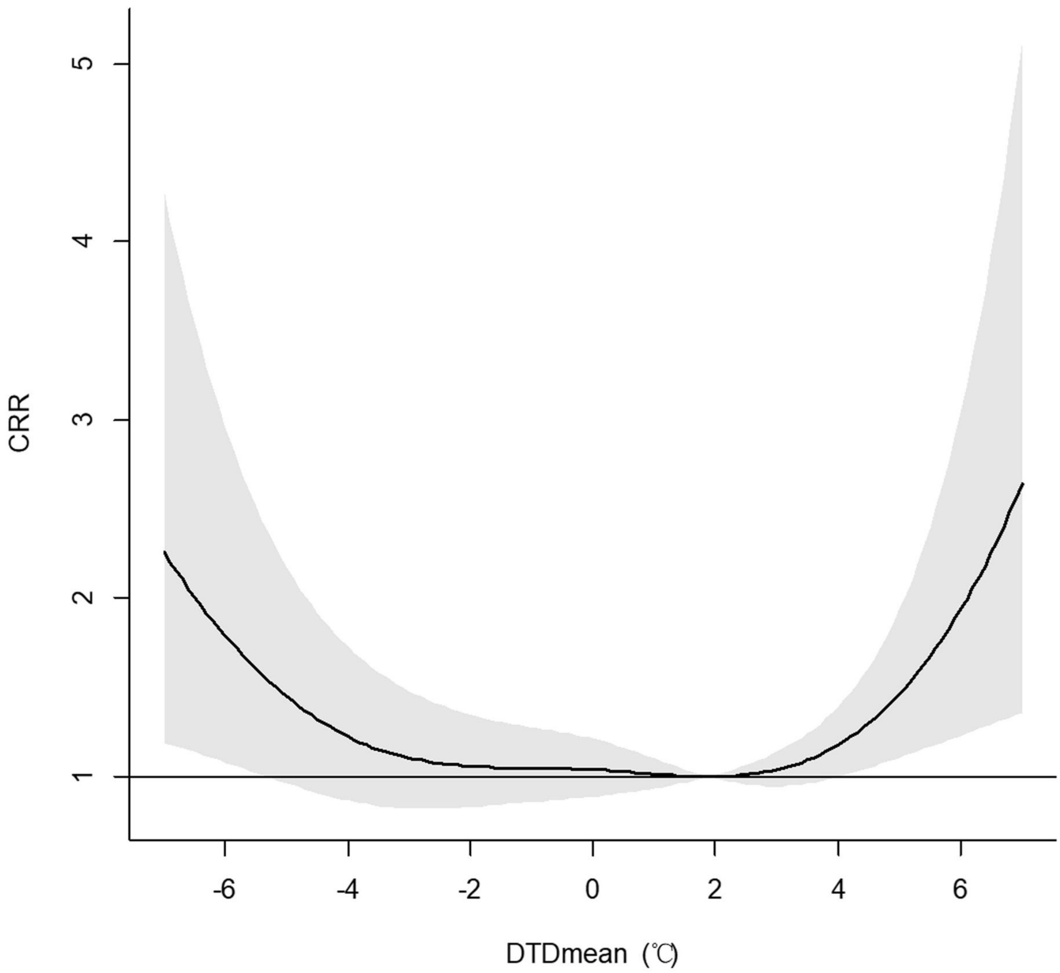

FIGURE 3
Association between the DTDmean and the 21 days cumulated relative risk (include 95% C.I.) of AECOPD hospital admissions among the total population in Beijing.

3.5. Other temperature differences

Additionally, we tried to look for the correlation between other temperature changes and AECOPD hospital admissions. However, most of them had no significance. Check out the Supplementary material for further information.

TABLE 3 The 21 days CRR and 95% C.I. of AECOPD in the total population in Beijing at the different DTDmean percentiles during the period from 2013 to 2016.

Percentiles	CRR	95% C.I. low	95% C.I. upp
P1 (−6°C)	1.79	1.08	2.96
P5 (−4°C)	1.22	0.87	1.73
P95 (4°C)	1.18	1.00	1.39
P99 (5°C)	1.46	1.11	1.93

CRR, cumulated relative risk; C.I., confidence interval.

3.6. Sensitivity analysis

To examine how robust our results were, the degrees of freedom were modified. As shown in Supplementary Figures 7, 8, the results were in line with the original statistical model substantially. It showed that the primary models generated reliable findings.

4. Discussion

Utilizing a distributed lag non-linear model, our study discovered that there were significant correlations between the hospital admissions of AECOPD and the temperature difference. Overall, a large change in temperature could lead to a rise in AECOPD hospital admissions both when temperature raised and declined extremely.

Although different studies have different indicators of temperature change, most of the results were similar from different geological areas. For example, wintertime temperature variability was linked to a higher occurrence of incident respiratory disorders, according to a Chinese cohort of 66,820 older individuals in Hong Kong (≥65 years) with 10–13 years of follow-up. The HR per 1°C change in temperature variability (TV) was 1.20 (1.08–1.32)

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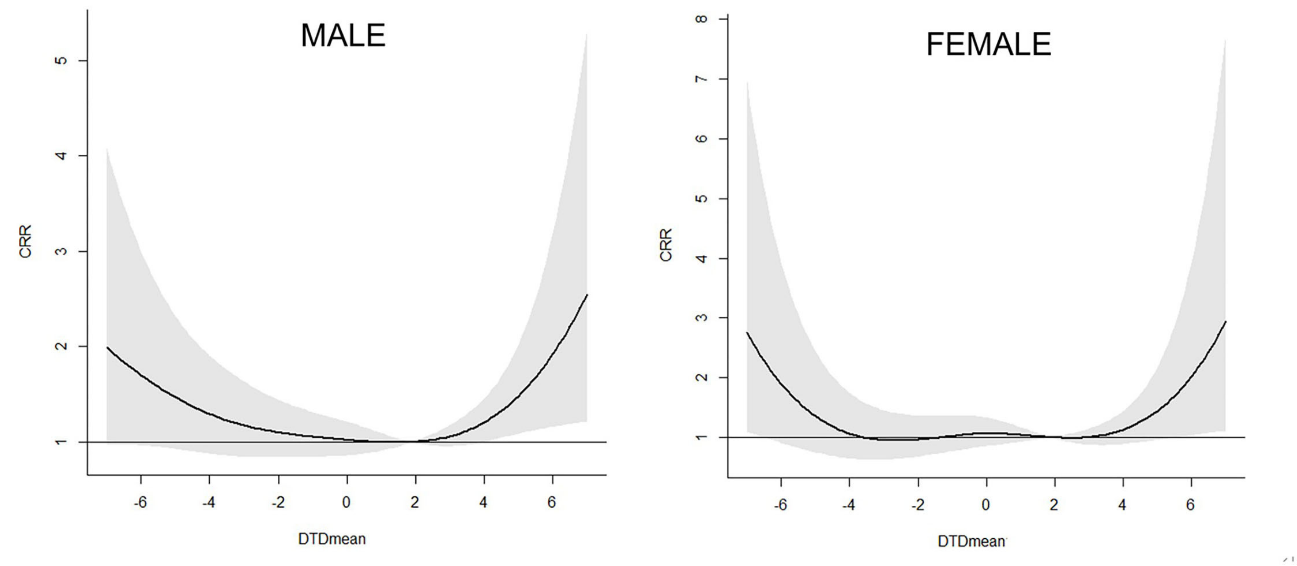

FIGURE 4
Association between the DTDmean and the 21 days cumulated relative risk (include 95% C.I.) of AECOPD hospital admissions in different gender subgroups in Beijing.

TABLE 4 The 21 days CRR and 95% C.I. of AECOPD in the different sex groups in Beijing at the different DTDmean percentiles during the period from 2013 to 2016.

Percentiles	Male (N = 95,555)			Female (N = 47,763)		
	CRR	95% C.I. low	95% C.I. upp	CRR	95% C.I. low	95% C.I. upp
P1 (−6°C)	1.70	0.96	3.00	1.89	0.91	3.92
P5 (−4°C)	1.30	0.88	1.91	1.06	0.65	1.75
P95 (4°C)	1.21	1.00	1.45	1.13	0.89	1.44
P99 (5°C)	1.49	1.09	2.03	1.44	0.96	2.18

CRR, cumulated relative risk; C.I., confidence interval.

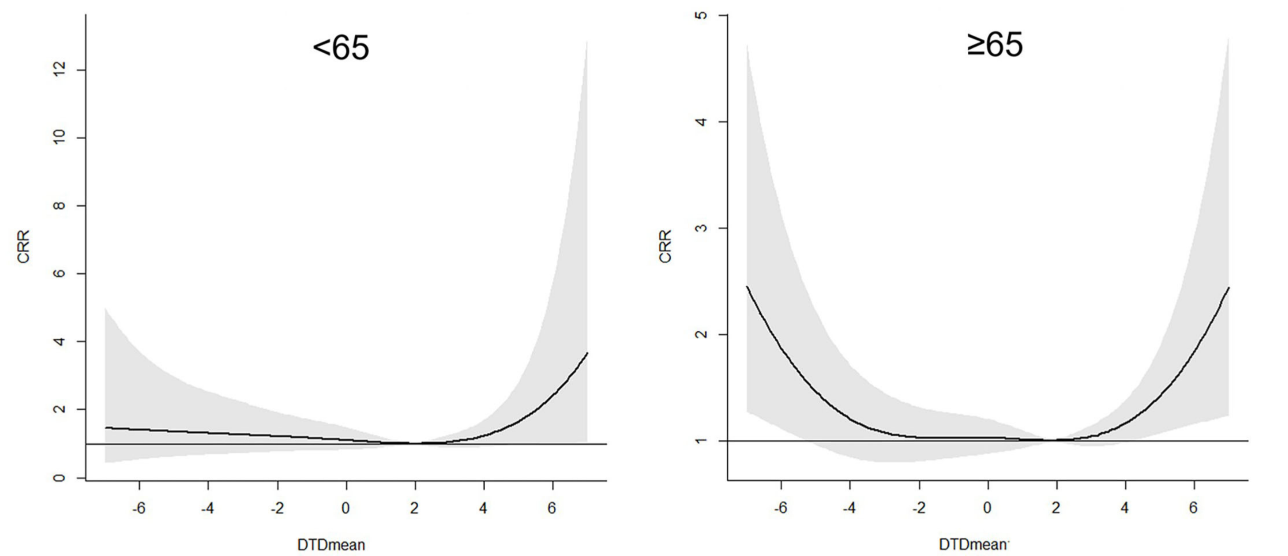

FIGURE 5
Association between the DTDmean and the 21 days cumulated relative risk (include 95% C.I.) of AECOPD hospital admissions in different age subgroups in Beijing.

TABLE 5 The 21 days CRR and 95% C.I. of AECOPD in the different age groups in Beijing at the different DTDmean percentiles during the period from 2013 to 2016.

Percentiles	<65 (*N* = 24,938)			≥65 (*N* = 118,380)		
	CRR	95% C.I. low	95% C.I. upp	CRR	95% C.I. low	95% C.I. upp
P1 (−6°C)	1.41	0.53	3.37	1.87	1.11	3.14
P5 (−4°C)	1.31	0.67	2.54	1.20	0.84	1.72
P95 (4°C)	1.24	0.90	1.70	1.16	0.98	1.38
P99 (5°C)	1.66	0.97	2.83	1.42	1.07	1.89

CRR, cumulated relative risk; C.I., confidence interval; <65, people under the age of 65; ≥65, people at the age of 65 and above.

for all incident respiratory disorders and 1.41 (1.15–1.71) for COPD in wintertime (29). A Taiwan study showed that when the diurnal temperature range exceeded 9.6°C, COPD admissions to the emergency room rose by 14% (30). A Korean study found that daily temperature fluctuation was typically linked to emergency hospitalization for pneumonia, COPD and total respiratory. (31). Extreme temperature changes between adjacent days were linked to increased mortality for diseases like pneumonia, and COPD, according to a nationwide study that adopted mortality data from more than 100 cities in the USA (32). The study across 135 US cities found that the standard deviation of temperature was related to increases in the incidence of COPD mortality in yearly summer from 1985 to 2006 (33).

Several hypotheses can be made with care, even if the precise physiological processes of the temperature change effect on AECOPD are yet not completely understood. People's capacity to adjust to local climates was hampered by temperature variations, which could raise the chance of unfavorable health consequences like respiratory disorders (34, 35). Temperature changes have been proven to alter the physiological changes in the circulatory system, lower the immune system's response to respiratory infections, and create an inflammatory nasal response in people with persistent allergic rhinitis (36–39). All of these may trigger respiratory events. The effect also could be explained by the influence of extreme ambient temperatures in some way. The effects of temperature on the respiratory system were as follows: Patients with COPD may experience bronchoconstriction and inflammation due to the direct impacts of cold air, which became more pronounced as the temperature dropped (40). Cold temperature can also aggravate respiratory diseases by a rise in airway bacterial and viral infections, inflammatory factor infiltration, and mucus secretion that follows (41, 42). Cold temperature can affect mucin secretion through a variety of mechanisms, while abnormal airway mucin secretion can lead to obstruction of mucin clearance, increase the chance of infection, and contribute to the development of COPD (43). While cytokines may be released in response to a heated environment, this could lead to the inflammatory response and respiratory distress (44, 45).

In addition, our findings showed people older than 65 years were more sensitive to the extreme-cold or extreme-hot temperature difference. It was agreed with the results in previous studies. A nationwide study suggested that people over 75 and those with respiratory conditions were shown to be particularly vulnerable to temperature changes between days (32). Aging decreased thermoregulation ability and immune system responses to environmental factors (36, 46).

The study contains some solid points. First, the study collected information of over 143,000 AECOPD hospital admissions between January 1, 2013, and December 31, 2016. And the data covered all secondary and tertiary hospitals in Beijing. Longer study periods and larger sample sizes may yield more trustworthy and precise research findings. Furthermore, this is the first research on the association between temperature differences and hospital admissions for AECOPD in Beijing as far as we are aware. At the same time, we analyzed the various temperature differences to find the better indicators of temperature change. Lastly, a number of confounding variables were taken into account in the research, including the impact of the influenza, AQI, and statutory holiday. There are still some limitations to this study. Our research was limited to Beijing, thus results may not generalize to other locales. Besides, as the lack of individualized exposure data, many potential risk factors that could affect the AECOPD hospital admissions such as complication and medication situation were not included.

5. Conclusion

The AECOPD hospital admissions was correlated with the DTDmean temperature differences, especially the extreme-cold and extreme-hot temperature difference. Moreover, people older than 65 years were more susceptible to the extreme-hot and extreme-cold temperature difference.

Data availability statement

The datasets presented in this article are not readily available because this dataset is now confidential. Requests to access these datasets should be directed to fanzhongjie@pumch.cn.

Ethics statement

The studies involving human participants were reviewed and approved by Peking Union Medical College Hospital (PUMCH) Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

The conception and design in the study were contributed by JF, CH, and ZF. The database was organized by YC, JF, and YL.

The methodology was provided by ZF. The statistical analysis was done by ZC and YZ. The software was operated by K-FX and CH. The first draft of the manuscript was written by JF. The submitted version of the work was reviewed, revised, and approved by all authors.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1112926/full#supplementary-material

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EDITED BY
Ang Li,
Chinese Academy of Medical Sciences and Peking Union Medical College, China

REVIEWED BY
Yibing Yang,
Chinese Center for Disease Control and Prevention, China
Mostafa Yuness Abdelfatah Mostafa,
Minia University, Egypt

*CORRESPONDENCE
Xiaoqing Jin
✉ redjin@whu.edu.cn

†These authors have contributed equally to this work and share first authorship

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Short-term effects of ambient air pollution on emergency department visits for urolithiasis: A time-series study in Wuhan, China

Haoyue Xu[1,2†], Yaqi Liu[2†], Jianing Wang[2] and Xiaoqing Jin[1*]

[1]The Emergency Center, Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China, [2]The Second Clinical School, Wuhan University, Wuhan, Hubei, China

Background: Previous studies have explored the correlation between short-term exposure to air pollution and urinary system diseases, but lack of evidence on the correlation between air pollution and urolithiasis.

Methods: Daily data of emergency department visits (EDVs), concentrations of six air pollutants (SO_2, NO_2, $PM_{2.5}$, PM_{10}, CO, and O_3) and meteorological variables were collected in Wuhan, China, from 2016 to 2018. And a time-series study was conducted to investigate short-term effects of air pollutants on urolithiasis EDVs. In addition, stratified analyses by season, age and gender were also conducted.

Results: A total of 7,483 urolithiasis EDVs were included during the study period. A 10-$\mu g/m^3$ increase of SO_2, NO_2, $PM_{2.5}$, CO, PM_{10}, and O_3 corresponded to 15.02% (95% confidence interval [CI]: 1.69%, 30.11%), 1.96% (95% CI: 0.19%, 3.76%), 1.09% (95% CI:−0.24%, 2.43%), 0.14% (95% CI: 0.02%, 0.26%), 0.72% (95% CI: 0.02%, 1.43%), and 1.17% (95% CI: 0.40%, 1.94%) increases in daily urolithiasis EDVs. Significant positive correlations were observed between SO_2, NO_2, CO, and O_3 and urolithiasis EDVs. The correlations were mainly among females (especially $PM_{2.5}$ and CO) and younger people (especially SO_2, NO_2, and PM_{10}) but the effect of CO was more obvious in elders. Furthermore, the effects of SO_2 and CO were stronger in warm seasons, while the effects of NO_2 were stronger in cool seasons.

Conclusion: Our time-series study indicates that short-term exposure to air pollution (especially SO_2, NO_2, CO, and O_3) was positively correlated with EDVs for urolithiasis in Wuhan, China, and the effects varied by season, age and gender.

KEYWORDS
air pollution, urolithiasis, emergency department visits, time-series study, public health

1. Introduction

Urolithiasis, a common urinary system disease, including stone in kidney, ureter, bladder, and urethra. Although rarely life-threatening, urolithiasis can often cause intense pain and is associated with increased risks of urinary tract infection, hydronephrosis, and renal function decline (1). In recent decades, urolithiasis's incidence rate and prevalence have continued to rise worldwide and its burden mainly concentrated in Asia and Eastern Europe (41). In the analysis of geographical differences, the prevalence rates of kidney stones were higher in the hot south and southwest regions of China (3). A present study indicated that currently kidney stones affect about one in 17 adults (the adjusted prevalence rate was 5.8%; 6.5% in men and 5.1% in women) in China (3). Renal colic caused by urolithiasis is a common complaint in the emergency department and a significant burden for healthcare systems and emergency departments (4), and it is estimated that this burden is likely to increase over time (39). Therefore, an improved understanding of the risk factors of urolithiasis is of great significance to public health. Some studies have explored the correlation between urolithiasis and diet habits, obesity, diabetes, metabolic syndrome, fluid intake, and environmental factors, such as geographical and meteorological factors (5–7). Among them, the correlations between seasonal changes, ambient temperature and urolithiasis have been extensively studied (7). However, the correlation between air pollutants, the important components of the exposed air environment, and urolithiasis has rarely been explored.

In recent years, air pollution has been considered as one of the crucial factors threatening human health. Exposure to ambient air pollution is associated with an increased risk of global mortality and incidence rate from various diseases, especially in developing countries (8, 9). Several studies have also reported that air pollutants may affect renal function through oxidative stress, inflammatory responses, and other mechanisms, leading to the development of a range of urological diseases, such as chronic kidney disease and renal failure (10, 11, 40). Oxidative stress and inflammation have been suggested as the potential mechanistic pathways affecting stone formation (12, 13). Therefore, we hypothesized that exposure to air pollution might also be correlated with an increased risk of urolithiasis. Our study will be beneficial for hospitals to understand the potential risk of urolithiasis from exposure to ambient air pollution to take precautions and maintain order on particularly heavily polluted days.

Given the above contents, we conducted a time-series study on the correlations between six ambient air pollutants (SO_2, NO_2, $PM_{2.5}$, PM_{10}, CO, and O_3) and emergency department visits (EDVs) for urolithiasis in Zhongnan Hospital of Wuhan University from January 1, 2016 to December 31, 2018. Season, gender and age differences were considered to examine the adverse health effects of air pollution on different groups. Furthermore, we also drew exposure-response relationship curves between EDVs for urolithiasis and air pollutants and explored the co-effects among six air pollutants.

2. Materials and methods

Wuhan, the capital of Hubei province, is located in central China (latitude 30°35'N and longitude 114°17'E) and consists of seven central districts and six suburban and rural districts (Figure 1). At the end of 2018, Wuhan had a land area of 8,494.41 square kilometers and a population of 11.1 million (http://www.wuhan.gov.cn). As the core city of the Yangtze River Economic Belt, Wuhan is an essential industrial base and transportation hub in China. Vehicle exhaust and industrial emissions are the primary sources of air pollution. Wuhan has a typical subtropical monsoon climate, with hot and humid summers and cold and dry winters. The average temperature is 4.4°C in January and 30.3°C in July.

2.1. Emergency department visits data

The majority of the EDVs of Zhongnan Hospital are from the Wuchang District of Wuhan, where the hospital is located. It is a district that contains 19% of the population of the whole urban area and 12% of the population of Wuhan overall (http://www.wuhan.gov.cn). The daily number of EDVs from January 1, 2016 to December 31, 2018 were obtained from Zhongnan Hospital of Wuhan University in Wuhan, China. The EDV data followed a quasi-Poisson distribution. Outpatient visits diagnosed with urolithiasis (mainly kidney stones) ($N = 7{,}483$) were selected as our study population. To ensure the accuracy of the study results, we removed duplicate records and non-Wuhan permanent residents and re-matched the tenth version of the International Classification of Diseases, with codes N20-N23. The study protocol was approved by the Medical Ethics Committee of Zhongnan Hospital (IRB number: 20211018K).

2.2. Air pollution and meteorological data

Daily ambient air pollution data (SO_2, NO_2, $PM_{2.5}$, PM_{10}, CO, and O_3) from January 2016 to December 2018 was obtained from the Wuhan Ecological Environment Bureau website (http://hbj.wuhan.gov.cn/). The daily average concentrations of air pollutants were measured from the fixed-site monitoring stations. Average daily air pollutant concentrations at the monitoring stations were used as a proxy for the overall exposure of all populations. The maximum 8-h average of O_3 and the daily 24-h average of the remaining pollutants were calculated.

The data of two meteorological parameters (daily average temperature [°C] and relative humidity [%]) during the study period were obtained from the Meteorological Data Sharing Service System of the China Meteorological Administration (Beijing, China). Environmental and meteorological data were missing for 32 days (2.92%). Therefore, dates with missing data were excluded from our study.

2.3. Statistical analysis

Generalized additive model (GAM) was used to conduct this time-series study. Because daily emergency visits followed an over-dispersed Poisson distribution, quasi-Poisson regression was used in the GAM. Several covariates were introduced to control for their potential confounding effects. First was a natural cubic smooth function for calendar time, with 7 degrees of freedom (df) per year to exclude long-term and seasonal trends over 2 months (14). Second, natural smooth functions of the two variables were incorporated into the model: mean temperature (6 df) and relative humidity (3 df), to control for the confounding effect of meteorological factors on the correlation between air pollution and urolithiasis EDVs (15). Third, indicators such as public holidays (Holiday) and "day of the week" (*DOW*) were adjusted as dummy variables in the GAM (15).

The model was as follows:

$$\log E(Yt) = \beta Z_t + DOW + ns(time, df) + ns(temperature, 6) \\ + ns(humidity, 3) + int\,erecept$$

where $E(Yt)$ is the estimated daily EDVs for kidney stones at day t; β indicates the log-relative rate of urolithiasis correlated with increased air pollutant units; Z_t represents the pollutant concentrations at day t; *DOW* is a dummy variable for the day of the week; *ns* refers to the natural cubic regression smooth function. The exposure-response (E-R) relationship was drawn between air pollutants and urolithiasis EDVs by adding a 3 df natural spline function to the above model.

To test the stability of the model, three sensitivity analyses were performed. First, due to the uncertainty of the optimal lag days, we further introduced a single-day lag, including lag0, lag1, lag2, lag3, lag4, lag5, lag6, and lag7, and a multi-day moving average exposure, including lag0-1, 0-2, 0-3, 0-4, 0-5, 0-6, and 0-7. To determine the optimal lag structure, model fits were calculated based on three statistics: Akaike Information Criterion (AIC), Generalized Cross Validation (GCV), and Partial Autocorrelation Function (PACF). Second, for the smoothness of the temporal trend, we chose alternative df with 4–10 per year. Third, two-pollutant models were built to assess the stability of the effect estimates after adjusting for co-pollutants and added co-pollutants with a correlation coefficient < 0.7 to the two-pollutant model. In addition, three stratified analyses were conducted respectively according to season (warm: April to September; cool: October to March), age (<45 years, 45–65 years, and ≥65 years), and gender (females, males). The statistical significance of the differences between the strata effect estimates were further tested by calculating 95% confidence intervals as $\hat{Q}_1 - \hat{Q}_2 \pm 1.96\sqrt{(S\hat{E}_1)^2 + (S\hat{E}_2)^2}$, where Q_1 and Q_2 are the estimates for two categories, and $S\hat{E}_1$ and $S\hat{E}_2$ are their respective standard errors. All statistical analyses were performed in R software (version 4.1.0) using the MGCV package. Results were two-sided and $p < 0.05$ were statistically significant. The results were expressed as the percentage change in urolithiasis EDVs per 10 $\mu g/m^3$ increase in each pollutant concentrations.

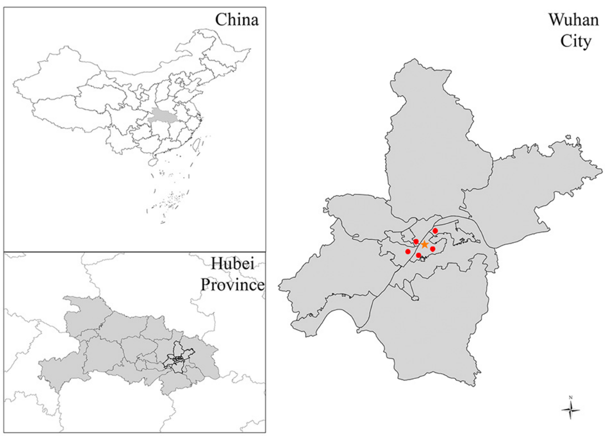

FIGURE 1
The location of Wuhan, the location of the hospital (the orange star), and monitoring stations (red dots).

3. Result

Table 1 summarizes the descriptive statistics of EDVs for urolithiasis, air pollutants, and weather data. We collected a total of 7483 cases of urolithiasis admitted to the emergency system of

TABLE 1 The summary of daily air pollutants, weather conditions, and daily emergency department visit for urolithiasis (*N* = 7,483) during our study period (January 1, 2016–December 31, 2018).

	Mean	SD	Min	P25	Median	P75	Max
Air pollutant concentration ($\mu g/m^3$)[a]							
SO_2	9.55	5.53	2.70	5.50	8.00	12.25	49.50
NO_2	47.87	19.36	14.00	32.76	45.12	60.96	125.00
$PM_{2.5}$	50.79	30.91	6.93	28.89	43.96	64.47	204.70
PM_{10}	83.55	47.49	8.60	48.70	76.50	108.00	561.50
CO	1,005.63	302.68	356	794.00	952.00	1,172.00	2,372.00
O_3	87.40	47.63	4.20	49.60	80.20	121.41	255.00
Meteorological measures							
Temperature (°C)	17.87	9.31	−4.00	10.00	18.89	25.98	35.42
Humidity (%)	74.99	13.38	36.00	65.25	75.75	85.50	100.00
Emergency department visit for kidney stones	7	4	0	4	6	9	25
Season (*N*)							
Warm[b]	8	4	0	4	7	11	25
Cool[c]	6	3	0	3	5	8	24
Gender (*N*)							
Male	5	3	0	2	4	7	19
Female	2	2	0	1	2	3	9
Age (*N*)							
<45	4	3	0	2	4	6	16
45–65	2	2	0	1	2	3	16
≥65	1	1	0	0	0	1	5

[a]24-h average for $PM_{2.5}$, PM_{10}, SO_2, and NO_2; maximal 8-h average for O_3.
[b]Warm season: from April to September.
[c]Cool season: from October to March.
SD, standard deviation; P25, 25th percentile; P75, 75th percentile; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; PM_{10}, particulate matter with an aerodynamic diameter less than or equal to 10 μm; O_3, ozone; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide.

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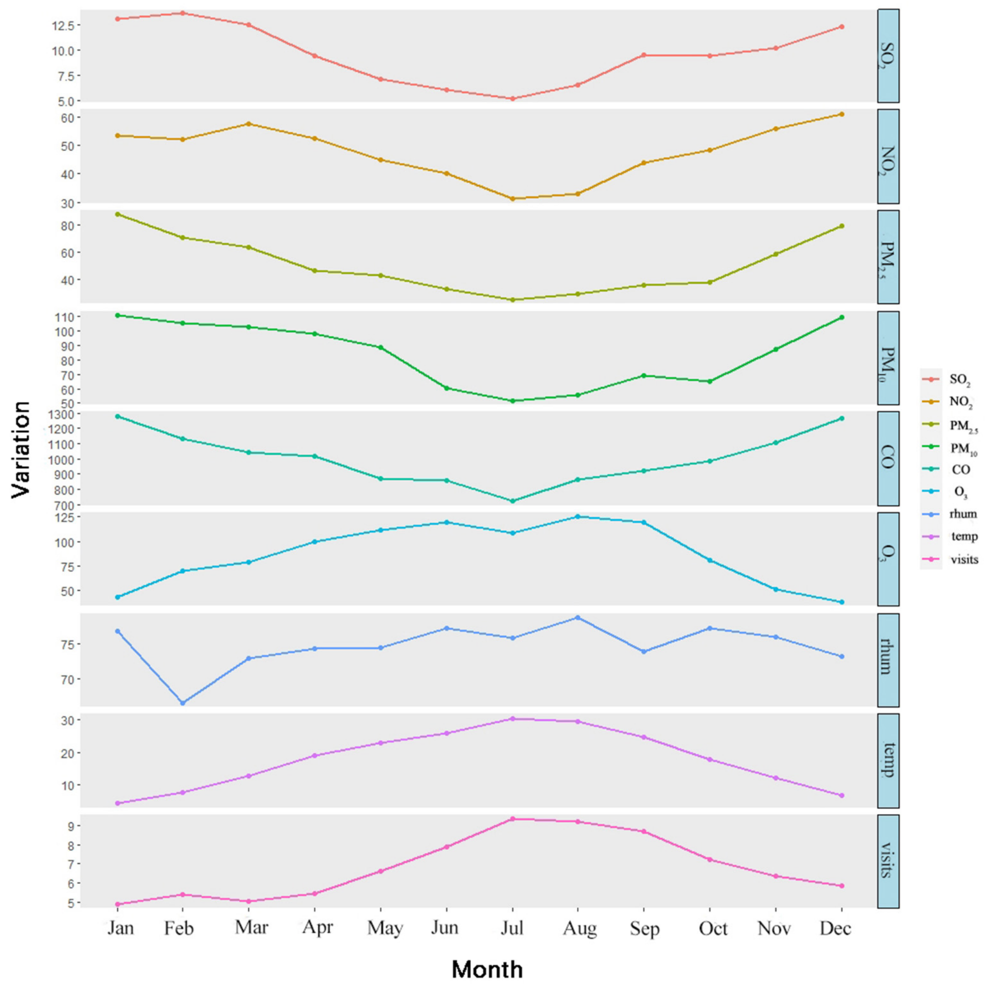

FIGURE 2
The monthly average variation of pollutants, temperature, relative humidity, and daily emergency department visits for urolithiasis.

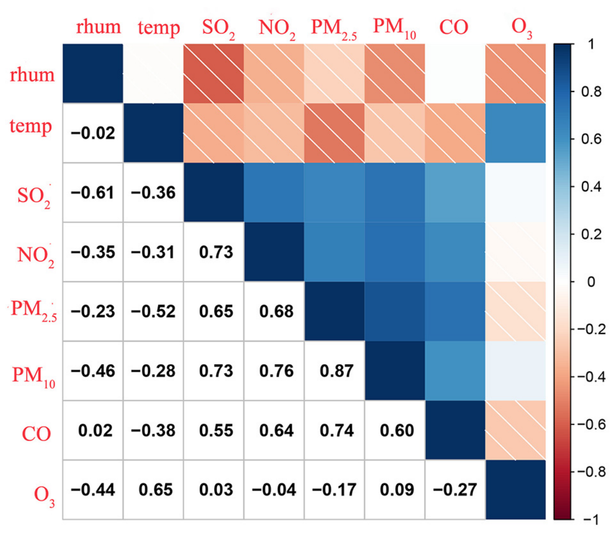

FIGURE 3
Spearman correlations among exposure variables in Wuhan, China (2016–2018). temp, Temperature; rhum, Relative Humidity.

Zhongnan Hospital of Wuhan University from January 1, 2016 to December 31, 2018. The annual mean temperature was 17.87°C and the annual mean humidity was 74.99%. During our study period, an average of seven people presented EDVs for urolithiasis daily. Among all patients, male, female, age <45 years, age 45–65 years, and age ≥65 years were 72.9, 27.1, 58.6, 33.1, and 8.3% respectively. The EDVs for urolithiasis in warm seasons (57.7%) were higher than those in cool seasons (42.3%). The annual average concentrations of air pollutants were 50.79 μg/m^3 for $PM_{2.5}$, 83.55 μg/m^3 for PM_{10}, 47.87 μg/m^3 for NO_2, 1,005.63 μg/m^3 for CO, 9.55 μg/m^3 for SO_2, and 87.40 μg/m^3 for O_3. During our study, there were 229 (20.9%) and 382 (24.8%) days respectively where NO_2 and $PM_{2.5}$ levels exceeded Chinese secondary ambient air quality standards. Other air pollutants were within the standard range most of the time. The monthly average variation of pollutants, temperature, relative humidity, and daily emergency department visits for urolithiasis are shown in Figure 2.

Generally, there were moderate to strong correlation coefficients among $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO (Spearman's correlation coefficient ranged from 0.55 to 0.87), and they all were weakly correlated with O_3 (−0.27 to 0.09). All pollutants were negatively correlated with temperature except for O_3 (0.65) and with relative humidity except for CO (0.02) (Figure 3).

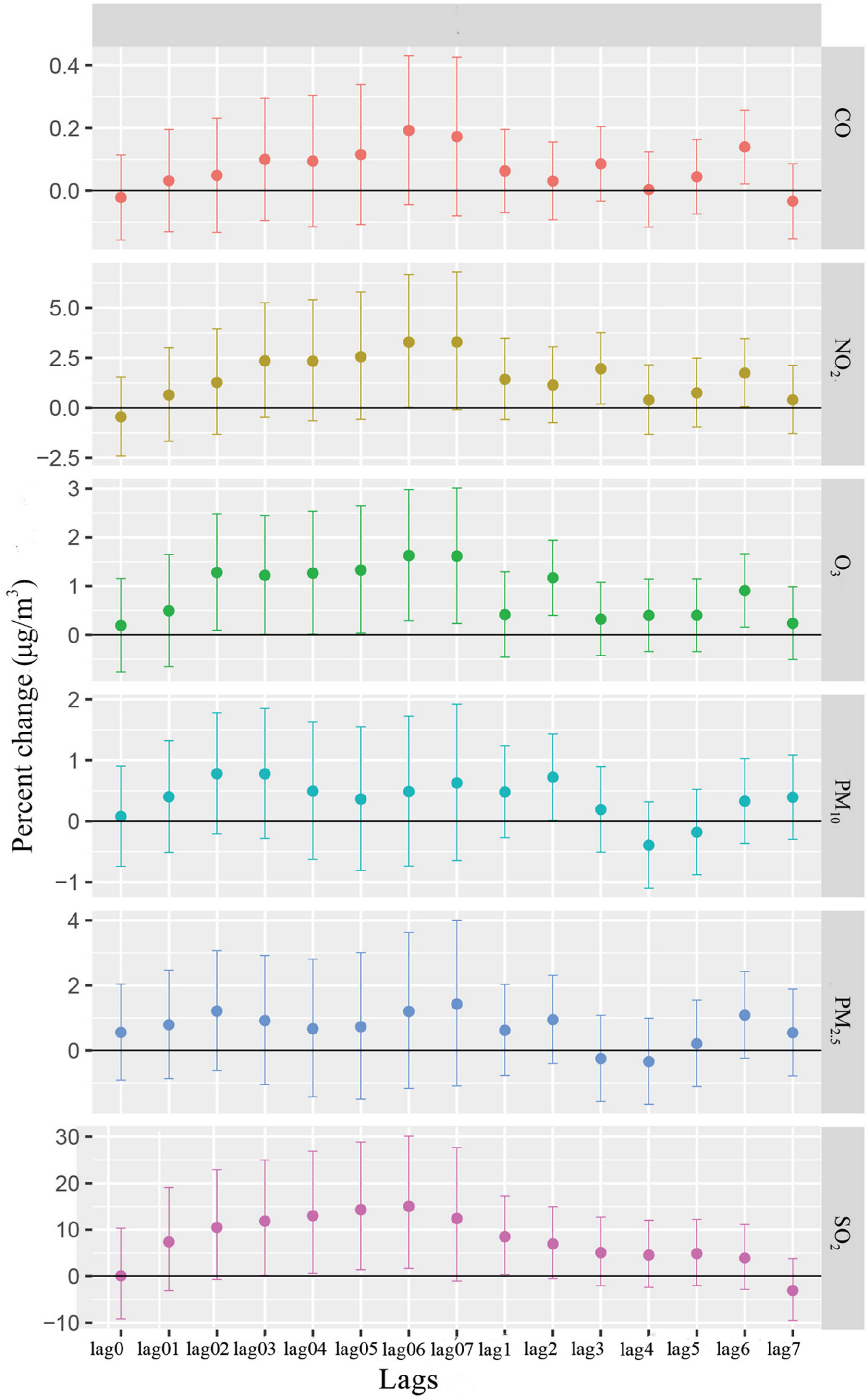

FIGURE 4
Percentage change (%) of EDVs for urolithiasis (mean and 95%CI) associated with a 10 $\mu g/m^3$ increase in various air pollutant concentrations using different lag structures.

Figure 4 exhibits the percentage change (mean and 95% CI) in urolithiasis EDVs associated with a 10 $\mu g/m^3$ increase in the concentration of six pollutants when using different lag structures—single lag day (lag1-lag7) and moving average lag models (lag01-lag07). Notably, we found statistically significant correlations between emergency hospital admissions for urolithiasis and SO_2, NO_2, CO, and O_3. According to the model fitting statistics, we selected lag06 for SO_2, lag3 for NO_2, lag6 for $PM_{2.5}$ and CO, and lag2 for PM_{10} and O_3 as the best lag structures because they can produce the smallest AIC/GCV/PACF values. A total of 10 $\mu g/m^3$ increases of SO_2, NO_2, $PM_{2.5}$, CO, PM_{10}, and O_3 respectively corresponded to increases in daily EDVs for urolithiasis of 15.02% (95% CI: 1.69%,

TABLE 2 Percent change (95% CI) in urolithiasis EDVs with a 10 μg/m^3 increase in air pollutant concentrations by season, gender and age in Wuhan, China.

Pollutants	Season		Gender		Age		
	Cool	Warm	Male	Female	Younger	Middle	Elder
SO_2^a	−0.45 (−2.41, 1.55)	40.29 (8.02, 82.21)*	12.44 (−2.61, 29.83)	22.43 (−0.54, 50.72)	21.75 (4.50, 41.84)*	6.13 (−12.53, 28.77)	0.17 (−32.08, 47.74)
NO_2^b	3.84 (1.30, 6.44)*	−0.46 (−3.18, 2.33)	1.83 (−0.22, 3.92)	2.31 (−0.71, 5.42)	3.05 (0.83, 5.32)*	0.33 (−2.37, 3.10)	0.20 (−5.19, 5.90)
$PM_{2.5}^c$	0.59 (−1.04, 2.24)	2.08 (−0.59, 4.83)	0.16 (−1.37, 1.70)	3.32 (1.14, 5.54)*	1.81 (0.19, 3.45)#	−0.99 (−3.02, 1.08)#	3.90 (−0.14, 8.11)#
PM_{10}^d	0.67 (−0.52, 1.88)#	0.79 (−0.13, 1.71)#	0.74 (−0.07, 1.55)	0.61 (−0.58, 1.82)	0.90 (0.04, 1.77)*	0.41 (−0.70, 1.52)	0.74 (−0.07, 1.55)
CO^c	0.09 (−0.07, 0.24)	0.21 (0.01, 0.41)*	0.04 (−0.10, 0.18)	0.34 (0.15, 0.54)*	0.15 (0.01, 0.30)*	0.00 (−0.18, 0.19)	0.40 (0.04, 0.76)*
O_3^d	2.47 (0.77, 4.21)*	2.47 (0.77, 4.21)*	1.30 (0.41, 2.19)	0.81 (−0.53, 2.18) *	1.22 (0.24, 2.21)*	1.34 (0.17, 2.52)*	0.06 (−2.26, 2.44)

*$p < 0.05$.
[a]Moving average of lag 06 was used for SO_2.
[b]Single average of lag 3 was used for NO_2.
[c]Single average of lag 6 was used for $PM_{2.5}$ and CO.
[d]Single average of lag 2 was used for PM_{10} and O_3.
#Statistically significant for between group difference.

30.11%), 1.96% (95% CI: 0.19%, 3.76%), 1.09% (95% CI: −0.24%, 2.43%), 0.14% (95% CI: 0.02%, 0.26%), 0.72% (95% CI: 0.02%, 1.43%), and 1.17% (95% CI: 0.40%, 1.94%) (Table 2). The associations of all pollutants with EDVs for urolithiasis were generally positive, but in all lag structures we examined, $PM_{2.5}$ and PM_{10} were statistically insignificant.

The exposure-response (E-R) curves of air pollutants and urolithiasis EDVs are shown in Figure 5. The E-R relationships of CO and O_3 were nearly linear, indicating no thresholds for their associations with EDVs for urolithiasis. The curve for NO_2 showed a steep slope at concentrations <40 μg/m^3 and became a J-shape at concentrations > 40μg/m^3. For the curve of $PM_{2.5}$, a steep slope was observed at concentrations < 50 μg/m^3, a relatively flat slope at concentrations between 50 μg/m^3 and 100 μg/m^3, and became steep again at concentrations > 100 μg/m^3. The E-R curves of PM_{10} and SO_2 rose sharply when the concentrations were < 75 μg/m^3 and < 10 μg/m^3 and gradually flattened after the concentrations were higher than the critical values.

Table 2 displays how different effect estimates of ambient air pollution on urolithiasis EDVs varied by season, gender, and age. In season-specific analysis, the results suggested that the correlations between urolithiasis EDVs and SO_2 and CO were generally stronger in warm seasons than in cool seasons, while correlations with NO_2 were stronger in cool seasons. In gender-specific analysis, stronger correlations between $PM_{2.5}$ and CO and urolithiasis EDVs were observed in females than in males. Among female patients, $PM_{2.5}$, CO, and O_3 were significantly correlated with urolithiasis EDVs, whereas the results were positive but not significant in male patients. In age-specific analysis, the effects of SO_2, NO_2, and PM_{10} tended to be greater for people aged < 45 years, while CO was more apparent in people aged ≥ 65 years, and the correlation of O_3 was more pronounced in people aged 465 years.

The estimated effects were not significantly affected by adjusting for temporal smoothness using an alternative df from 4 to 10 per year (Supplementary Figure 1). Table 3 shows the correlations between urolithiasis EDVs and air pollution after adding co-pollutants with spearman's correlation coefficients < 0.7 to the two-pollutants model for adjustment. When adjusting for all other pollutants, we found that the risk estimates of CO and O_3 on urolithiasis EDVs remained statistically significant. The correlations of PM_{10}, SO_2, and urolithiasis EDVs were statistically significant only when controlling for CO. For $PM_{2.5}$, the estimated effects were insignificant regardless of which pollutant was adjusted.

4. Discussion

According to statistics, the prevalence of urolithiasis is gradually rising (16). Due to the acute nature of presentation, urolithiasis generates a large number of emergency department visits and hospital admissions (17). In recent years, numerous epidemiological studies have reported the positive correlations between air pollution and the development of urological diseases. However, few studies have explored the correlations between air pollutants and urolithiasis. Our research demonstrated a significant correlation between short-term exposure to air pollutants, including SO_2, NO_2, CO, and O_3 and increased risks of urolithiasis. The correlations between CO, O_3 and urolithiasis EDVs were robust with co-pollutants adjustment. The correlations were found mainly in females (especially from $PM_{2.5}$ and CO) and in younger people (especially from SO_2, NO_2, and PM_{10}). In contrast, the correlation between O_3 and urolithiasis EDVs was more pronounced in males and middle-aged people, and the correlation of CO was more evident in elders. The effects of SO_2 and CO were stronger in warm seasons than in cool seasons, while the effect of NO_2 was more substantial in cool seasons. Our findings have added to the limited evidence that air pollution may be a potential risk factors for the incidence of urolithiasis.

During our study period, the annual average concentrations of NO_2 (58.89 μg/m^3) and $PM_{2.5}$ (47.87 μg/m^3), and PM_{10} (83.55 μg/m^3) in Wuhan exceeded China's National Ambient Air Quality standards (40 μg/m^3, 40 μg/m^3 and 15 μg/m^3). Since Wuhan is the largest city in central China, the expansion of cities, the development of industry, the increase of motor vehicles, and the growth of population may all be contributors to the severe air pollution.

Our study observed positive correlations between air pollutants (including SO_2, NO_2, $PM_{2.5}$, PM_{10}, CO, and O_3) and the EDVs

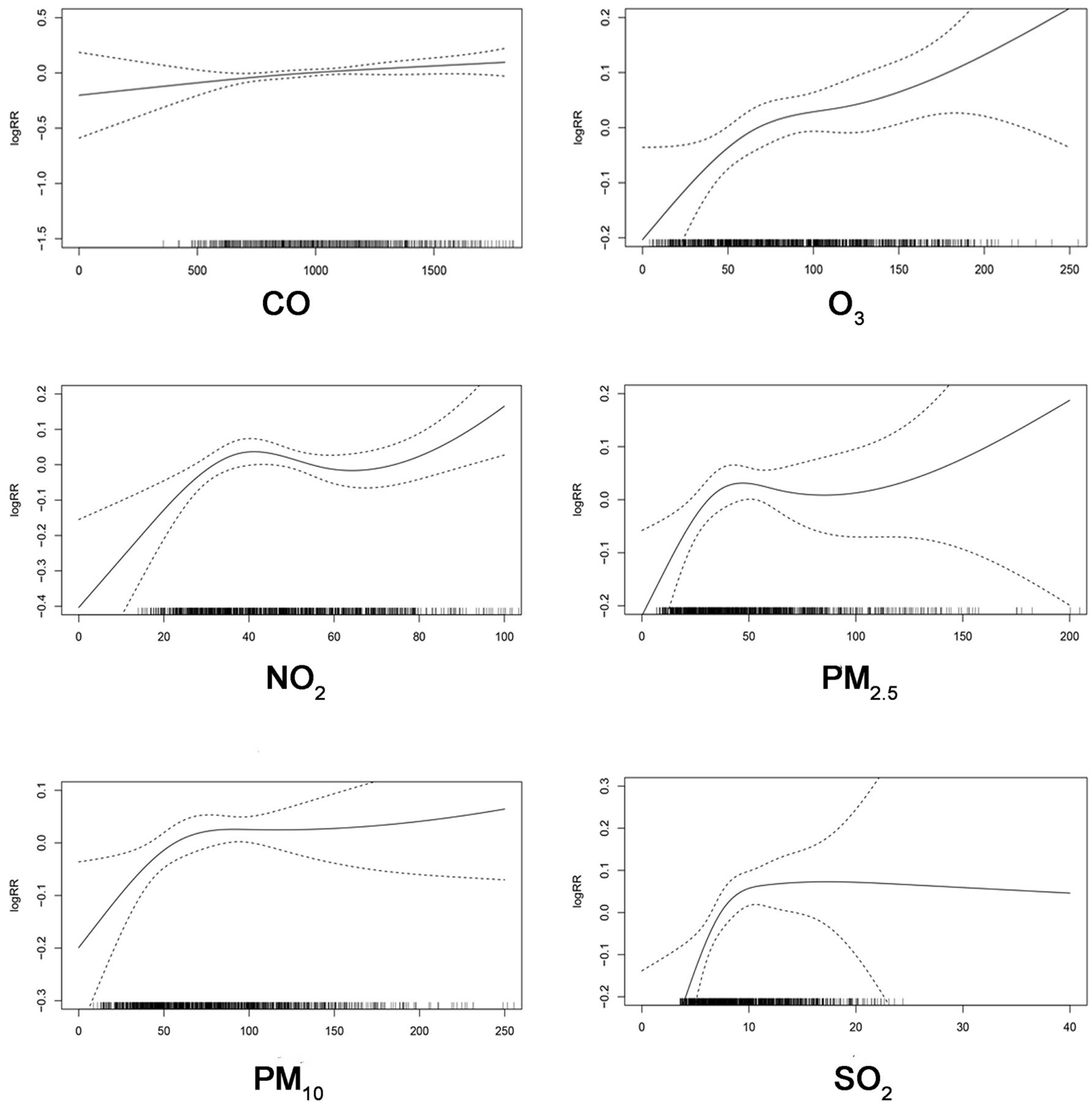

FIGURE 5
The exposure-response relationship curves of SO_2, NO_2, $PM_{2.5}$, PM_{10}, CO, and O_3.

for urolithiasis, especially SO_2, NO_2, CO and O_3, which is partially consistent with previous studies. Oxidative stress may be a primary mechanism of the positive correlations (18). Studies have shown that air pollutants, including O_3, SO_2, CO, NO_2, and PM, are sources of several ROS and other byproducts of oxidative stress (19). In kidneys, they can cause damage to renal tubular epithelial cells and participate in the modification of crystalloid regulators (13, 20, 21), further affecting the formation of calcium oxalate crystals and urinary stones (22–25). Another potential mechanism is that air pollutants can affect urinary tract metabolites (26, 38), and specific urinary tract metabolites such as dimethyl-L-arginine and 2-oxo-arginine are thought to be associated with the formation of kidney stones (27). In addition, immune damage caused by gaseous pollutants may also play an important role (28). Macrophage-associated immune damage is a major change in the immune response observed in renal stone disease (2) and may promote the formation of Randall's plaque (calcified spots appearing in the renal papillae before the formation of kidney stones) and calcium oxalate stones (29). However, the exact biological mechanism remains unknown and warrants further study.

Our findings are partially consistent with those of previous studies. For example, a time series study conducted in Korea mentioned that $PM_{2.5}$ and CO might be new potential risk factors for urolithiasis (18). A nationwide time-series study in China observed consistent associations between same-day $PM_{2.5}$ and several genitourinary diseases, including nephritis, nephrosis, and renal sclerosis; chronic renal failure; and calculus of urinary tract (30). However, $PM_{2.5}$ did not demonstrate a significant correlation with urolithiasis in our study, which may due to different study designs, study populations, confounding factors, such as outdoor activities and dietary habits on disease, and the characteristics of different urban air pollution mixtures (31).

Our study further demonstrated the association between short-term exposure to air pollutants and daily EDVs for urolithiasis varied according to season, age and gender. It is observed that

TABLE 3 Percent change (%, mean and 95% CI) in EDVs for urolithiasis in two-pollutant models.

Two-pollutants		Percent change
SO_2^a	–	**15.02 (1.69, 30.11)***
	$+PM_{2.5}$	13.35 (−0.01, 28.50)
	+CO	**14.33 (1.10, 29.29)***
	$+O_3$	9.51 (-3.72, 24.57)
NO_2^b	–	**1.96 (0.19, 3.76)***
	$+PM_{2.5}$	**1.99 (0.22, 3.79)***
	+CO	**2.30 (0.51, 4.11)***
	$+O_3$	1.37 (-0.44, 3.22)
$PM_{2.5}^c$	–	1.09 (-0.24, 2.43)
	$+SO_2$	0.83 (-0.52, 2.19)
	$+NO_2$	1.11 (-0.21, 2.45)
	$+O_3$	1.05 (-0.27, 2.38)
PM_{10}^d	–	0.72 (0.02, 1.43)
	+CO	**0.77 (0.07, 1.48)***
	$+O_3$	−0.30 (−0.36, 1.17)
CO^c	–	**0.14 (0.02, 0.26)***
	$+SO_2$	**0.13 (0.02, 0.25)***
	$+NO_2$	**0.16 (0.04, 0.28)***
	$+PM_{10}$	**0.15 (0.03, 0.27)***
	$+O_3$	**0.15 (0.03, 0.26)***
O_3^d	–	**1.17 (0.40, 1.94)***
	$+SO_2$	**0.99 (0.19, 1.81)***
	$+NO_2$	**1.02 (0.23, 1.82)***
	$+PM_{2.5}$	**1.16 (0.39, 1.93)***
	$+PM_{10}$	**1.02 (0.20, 1.84)***
	+CO	**1.20 (0.43, 1.97)***

*$p < 0.05$.
[a]Moving average of lag 06 was used for SO_2.
[b]Single average of lag 3 was used for NO_2.
[c]Single average of lag 6 was used for $PM_{2.5}$ and CO.
[d]Single average of lag 2 was used for PM_{10} and O_3.

the effects of SO_2 and CO on urolithiasis EDVs were stronger in warmer seasons. This may be attributed to the physiological impact of temperature itself. Mechanisms of this correlation include insufficient fluid intake, increased sweating, and water evaporation, which lead to concentrated urine and further promote calcium, oxalic acid, uric acid, phosphate crystallization, and stone formation (32, 33). It is supposed the difference that NO_2 showing higher effects in cool seasons might be related to varying concentrations, sources and composition of air pollution in different seasons (34).

In age stratification, our study indicates that SO_2, NO_2 and PM_{10} tended to have more significant effects in people aged <45 years, which is contrary to the epidemiological evidence of a high incidence rate of urolithiasis in the elderly (35). This may be because young people usually have more outdoor activities, increasing their exposure to air pollutants. However, O_3 and CO would significantly increase the risk of urolithiasis in middle-aged and older adults. In gender stratification, it is found that females are more vulnerable to $PM_{2.5}$ and CO, while males are more susceptible to O_3. We cannot find sufficient evidence in the literature for the phenomenon that different individual pollutants have a maximum impact on people of different ages and genders. Since individual pollutants are rarely produced in isolation, so sorting out the effects of individual pollutants is severely limited by potential confounding factors. Observational studies based on populations should consider correlations between them (36).

Interpreting trends in exposure-response relationships is critical to assessing public health. In the present research, threshold concentrations were not observed above which NO_2 and $PM_{2.5}$ were not correlated with urolithiasis EDVs. It is worth noting that the E-R curve for SO_2 flattens out at high concentrations. This may result from a "harvest effect", where sensitive populations might have already been affected and gone to the hospital before air pollutant concentrations reached significant levels (37). Multiple factors such as location, population sensitivity, air pollution mixtures, and climate characteristics may impact the E-R relationship (31). Therefore, more research is still needed in the future to explore the characteristics of the E-R relationship.

Our study has some noted limitations. First, average concentrations of air pollutants measured by stationary site monitoring were used to represent individual exposures, leading to misclassification of exposures and ignoring the spatial effect of air pollution on urolithiasis. Secondly, some factors were not taken into account that may affect the formation of urolithiasis and impair a person's tolerance to air pollutants, such as dietary habits, lifestyle, and metabolic syndrome. As a result, combined estimates may skew the effects of air pollutants in specific populations. Third, the data we collected was only from a highly polluted city; thus, the general study application of study may be limited. Therefore, further studies are needed to confirm our results, and molecular biology or animal experiments are necessary to explore the exact mechanisms between air pollutants and urinary stones formation.

5. Conclusion

Our time-series study found that ambient air pollution (especially SO_2, NO_2, CO, and O_3) positively correlated with the EDVs for urolithiasis in Wuhan, China. These effects were found to vary by season, gender, and age. Our study adds limited evidence to how air pollutants affect urolithiasis and we hope this study can support hospitals and clinical staff in taking effective preventive measures to maintain emergency department order, particularly on heavily polluted days.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of

Zhongnan Hospital (IRB number: 20211018K). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HX: methodology, software, visualization, and writing—original draft. YL: investigation, writing—reviewing, and editing. JW: illustration production. XJ: supervision, project administration, and funding acquisition. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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Conflict of interest

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

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1091672/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Percentage change (%) of EDVs for urolithiasis (mean and 95%CI) associated with a 10 $\mu g/m^3$ increase in various air pollutant concentrations at their peak lag day using different degrees of freedom per day.

SUPPLEMENTARY TABLE 1
Percent change (mean and 95% CI) in EDVs for urolithiasis associated with a 10 $\mu g/m^3$ increase in concentrations of six pollutants using different lag structures.

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EDITED BY
Ruoyu Wang,
University of Edinburgh, United Kingdom

REVIEWED BY
Sumona Mondal,
Clarkson University, United States
Guowen Song,
Iowa State University, United States

*CORRESPONDENCE
Akimasa Hirata
✉ ahirata@nitech.ac.jp

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Estimation of the number of heat illness patients in eight metropolitan prefectures of Japan: Correlation with ambient temperature and computed thermophysiological responses

Akito Takada[1], Sachiko Kodera[1], Koji Suzuki[2], Mio Nemoto[3], Ryusuke Egawa[4,5], Hiroyuki Takizawa[5] and Akimasa Hirata[1]*

[1]Department of Electrical and Mechanical Engineering, Nagoya Institute of Technology, Nagoya, Japan, [2]Architecture, Design, Civil Engineering, and Industrial Management Engineering, Nagoya Institute of Technology, Nagoya, Japan, [3]Department of Environment Systems, Graduate School of Frontier Sciences, The University of Tokyo, Chiba, Japan, [4]School of Engineering, Tokyo Denki University, Tokyo, Japan, [5]Cyberscience Center, Tohoku University, Sendai, Japan

The number of patients with heat illness transported by ambulance has been gradually increasing due to global warming. In intense heat waves, it is crucial to accurately estimate the number of cases with heat illness for management of medical resources. Ambient temperature is an essential factor with respect to the number of patients with heat illness, although thermophysiological response is a more relevant factor with respect to causing symptoms. In this study, we computed daily maximum core temperature increase and daily total amount of sweating in a test subject using a large-scale, integrated computational method considering the time course of actual ambient conditions as input. The correlation between the number of transported people and their thermophysiological temperature is evaluated in addition to conventional ambient temperature. With the exception of one prefecture, which features a different Köppen climate classification, the number of transported people in the remaining prefectures, with a Köppen climate classification of Cfa, are well estimated using either ambient temperature or computed core temperature increase and daily amount of sweating. For estimation using ambient temperature, an additional two parameters were needed to obtain comparable accuracy. Even using ambient temperature, the number of transported people can be estimated if the parameters are carefully chosen. This finding is practically useful for the management of ambulance allocation on hot days as well as public enlightenment.

KEYWORDS

ambient heat, ambulance dispatch, heat adaptation, heat illness, global warming

1. Introduction

Global warming is making heat waves more intensive, longer-lasting, and more common worldwide (1–3). The mortality and mobility of heat-related illness caused by heat waves have been extensively studied (4–7). To assess the impact of further global warming, different climate models have been proposed at the overall warming temperatures of 1.5°C, 2°C, and 3°C (8, 9). According to Song et al. (10), the risk factors for heat-related mortality are different at the global, intermediate, and local scales.

In aging societies, heat-related morbidity and mortality are expected to increase (11). Japan has the highest proportion of the elderly in the world (12). The yearly number of cases of heat-related illness transported by ambulance over the entirety of Japan, with its total population of 125 million, has been increasing gradually, from a range of 40,000 to 60,000 from 2010 to 2017 and then reaching a record high of 95,137 in 2018. Since then, it has remained high, at 60,000–70,000 (13). The number of cases registered with the use of an ambulance is closer to the actual number of cases than is the case in other countries, as ambulance transportation is free in Japan.

A positive correlation has been reported between ambient temperature and the number of heat illness patients (14–16). The surge of transported patients on hot summer days results in a greater ambulance use, causing temporary shortages. Thus, estimating the number of heat illness patients is essential for ambulance allocation management and dynamic systems operation on hot summer days (17).

Heat-related illnesses are broadly classified according to two symptoms, namely, dehydration and collapse of heat balance (18). The thermophysiological parameters for these are water loss and core temperature, respectively, although the two are related. The time course response of thermoregulation is significantly affected by age, lifestyle, and environment, making the epidemiology and pathology of heat stroke difficult to ascertain.

Several methods of estimating numbers of cases of heat-related illness have been proposed using analysis (19, 20) and machine learning taking weather data (21, 22). In Nishimura et al. (20), we demonstrated that estimation using regression models has comparable accuracy to that produced by a machine learning architecture. Our regression model identifies that the weather condition is associated with adverse heat illness events not only on the day of the event but also on preceding days (∼3days). This is particularly obvious for non-external heat-related illness in the elderly. Thus, additional efforts are needed to identify external heat-related illness or estimate total number of patients. In particular, the association between population-level estimated core temperature and water loss with the number of transported people is worth evaluating in different regions.

In this study, we developed an estimation model for the number of heat illness patients in eight metropolitan prefectures in Japan. In particular, an integrated computational technique was used that took into account multiphysics and thermophysiology to derive the thermophysiological response of a standard test subject for different weather condition. Heat adaptation at different prefectures is also considered.

2. Methods

2.1. Data sources

Eight prefectures with different climatic conditions were selected for this study, as shown in Figure 1. The northernmost, Hokkaido, is at 43°03'51" N and 141°20'49" E, and the southernmost, Fukuoka, is located at 33°36'23" N and 130°25'05"E. The climates are classified as Df and Cfa within the Köppen scheme (23).

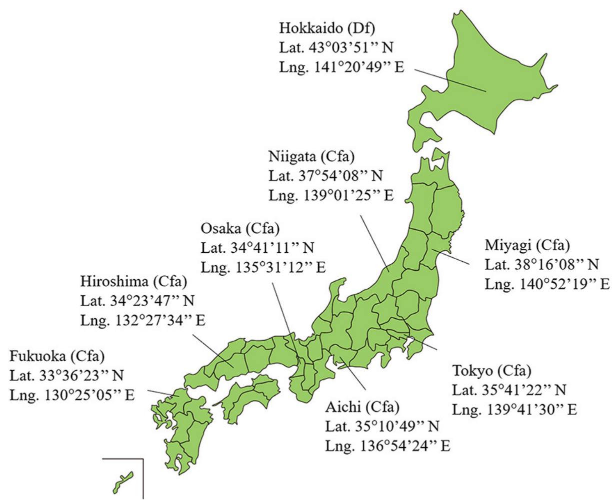

FIGURE 1
Location of eight prefectures in Japan selected for this study. Japan includes 47 prefectures. The Köppen climate classification in each prefecture are also presented.

Three datasets were utilized in this study. The first dataset includes the daily ambient temperature provided by Japan Meteorological Agency, Japan (24). The second describes the age composition of the population in each prefecture, as provided by Official Statistics of Japan (25).

The final dataset reports the number of people transported by ambulance owing to heat-related illnesses, provided by the Fire and Disaster Management Agency under the Ministry of Internal Affairs and Communications, Japan, between 2013 and 2019 (13). They provided the daily number of ambulance dispatches owing to heat-related illness in each prefecture from June to September annually. Data regarding the transported patients have been collected by prefectures by date and age categories (infant, child, adult, and elderly) since 2013, and the categories of occurrence location were added from 2017. The number of people transported *via* ambulance due to heat-related illness in Japan can be used as a surrogate marker because the number of transported people and that of the number of patients are correlated with each other (26). The dataset for the number of transportations from 2013 to 2016 that were not classified by occurrence location was substituted by dividing the total number by mean percentage transported from indoor locations/homes and outdoor locations/workplaces from 2017 to 2019.

Table 1 shows the daily average and maximum ambient temperatures per summer from June 1 to September 30 from 2013 to 2019, the average population and the population density from 2013 to 2019, and the average number of heat illness patients per million population per summer from June 1 to September 30 from 2013 to 2019 in each prefecture.

Table 2 shows the percentage of heat illness patients transported from indoor/home and outdoor/workplace from 2017 to 2019. The variation in the ratio of the transported people from the indoor/home and outdoor/workplace over the 3 years showed a ≤8% variation. Unlike a definition

TABLE 1 Daily average and maximum ambient temperature per summer from June 1 to September 30, average population and population density, and average number of patients due to heat-related illness per million population per summer from June 1 to September 30, all data from 2013 to 2019.

	Average ambient temperature (°C)	Maximum ambient temperature (°C)	Population (millions)	Population density per km^2	Number of patients per million
Hokkaido	20	33.7	5.3	63.7	192.9
Miyagi	22.4	35.6	2.3	319.1	391.8
Niigata	23.9	36.9	2.3	181.3	497.3
Tokyo	25.1	37.4	13.6	6205	330.5
Aichi	25.9	38.1	7.5	1449.9	506.4
Osaka	26.4	37.8	8.8	4634.6	469.2
Hiroshima	26	36.8	2.8	333.7	529.4
Fukuoka	26.2	37.3	5.1	1022.8	458.9

TABLE 2 Percentage of heat illness patients transported from indoor/home and outdoor/workplace from June 1 to September 30 from 2017 to 2019.

Prefecture	Location	2017	2018	2019	Average
Miyagi	Indoor	40.8	41.3	48.0	43.9
	Outdoor	59.2	58.7	52.0	56.1
Niigata	Indoor	40.7	40.7	40.7	40.7
	Outdoor	59.3	59.3	59.3	59.3
Tokyo	Indoor	37.3	40.5	40.3	39.9
	Outdoor	62.7	59.5	59.7	60.1
Aichi	Indoor	32.8	39.0	35.2	36.5
	Outdoor	67.2	61.0	64.8	63.5
Osaka	Indoor	34.5	38.2	32.7	35.6
	Outdoor	65.5	61.8	67.3	64.4
Hiroshima	Indoor	42.5	42.7	43.2	42.8
	Outdoor	57.5	57.3	56.8	57.2
Fukuoka	Indoor	37.0	40.5	38.0	38.7
	Outdoor	63.0	59.5	62.0	61.3

of Fire and Disaster Management Agency, places that are not related to their homes were classified as outdoor considering the consistency of non-external heat-related illness in the elderly.

2.2. Equation for estimating number of transported patients owing to heat-related illness

In our previous studies (19, 20), we proposed an equation for estimating the number of transported people owing to heat-related illness. In particular, the classification of indoor/home and outdoor/workplace was considered in Nishimura et al. (20), which are approximately surrogate for non-exertional and exertional heat stroke. The number of transported people can be estimated as follows:

$$y(x) = y_{in}(x) + y_{out}(x), \tag{1}$$

$$y_{in}(x) = a_{in}\left[e^{k_{in}(0.6x_0+0.2x_1+0.2x_2)} + l_{in}\right] \cdot \sum_n \left\{P(n)\cdot\left(be^{cn}+d\right)\right\}, \tag{2}$$

$$y_{out}(x) = a_{out}\left(e^{k_{out}x_0} + l_{out}\right)\cdot\sum_n\left\{P(n)\cdot\left(be^{cn}+d\right)\right\}, \tag{3}$$

$$k_{in,out} = f_{in,out}\cdot\left(\sum_{i=1}^{J} w_i\cdot x_i\right) + g_{in,out}, \tag{4}$$

where y_{in} and y_{out} denote daily heat illness patients transported from indoor/home and outdoor/workplace, respectively. The variable x_i denotes the input variable i days ago; x_0 indicates the input variable for the predicted day. The parameters a, l, f, and g are fitting parameters. Three types of input variable were selected for daily average temperature, daily maximum body core temperature increase, and amount of sweating. Unlike Nishimura et al. (20), the daily maximum body core temperature increase and the amount of sweating were computed using our in-house computational code (Section 2.3).

The number of cases of heat illness with transportation from indoor locations [Equation (2)] is affected by the daily average temperature for three successive days; the weightings of x_0, x_1, and x_2 were 0.6, 0.2, and 0.2, respectively (19), in addition to qualitative discussion in Williams et al. (27). The numbers of patients transported from outdoor [Equation (3)] are affected by the climate on the corresponding day (28). Parameter n denotes age category [five-year age intervals; $n = 1$ (20–24 years old), ...,14 (85 years old and over)]; $P(n)$ denotes the age composition of population in each prefecture. The function $be^{cn} + d$ is the regression curve derived in Figure 4 in Kodera et al. (19) expressed the increase in the risk of heat-related illness with age; the parameters b (=0.171), c (=0.494), and d (=190.7) determined by the least-squares fitting method, based on the age components of heat illness patients in Japan.

Equation (4) represents the short-term heat adaption during the summer, i.e., the risk of heat-related illnesses k (coefficient of

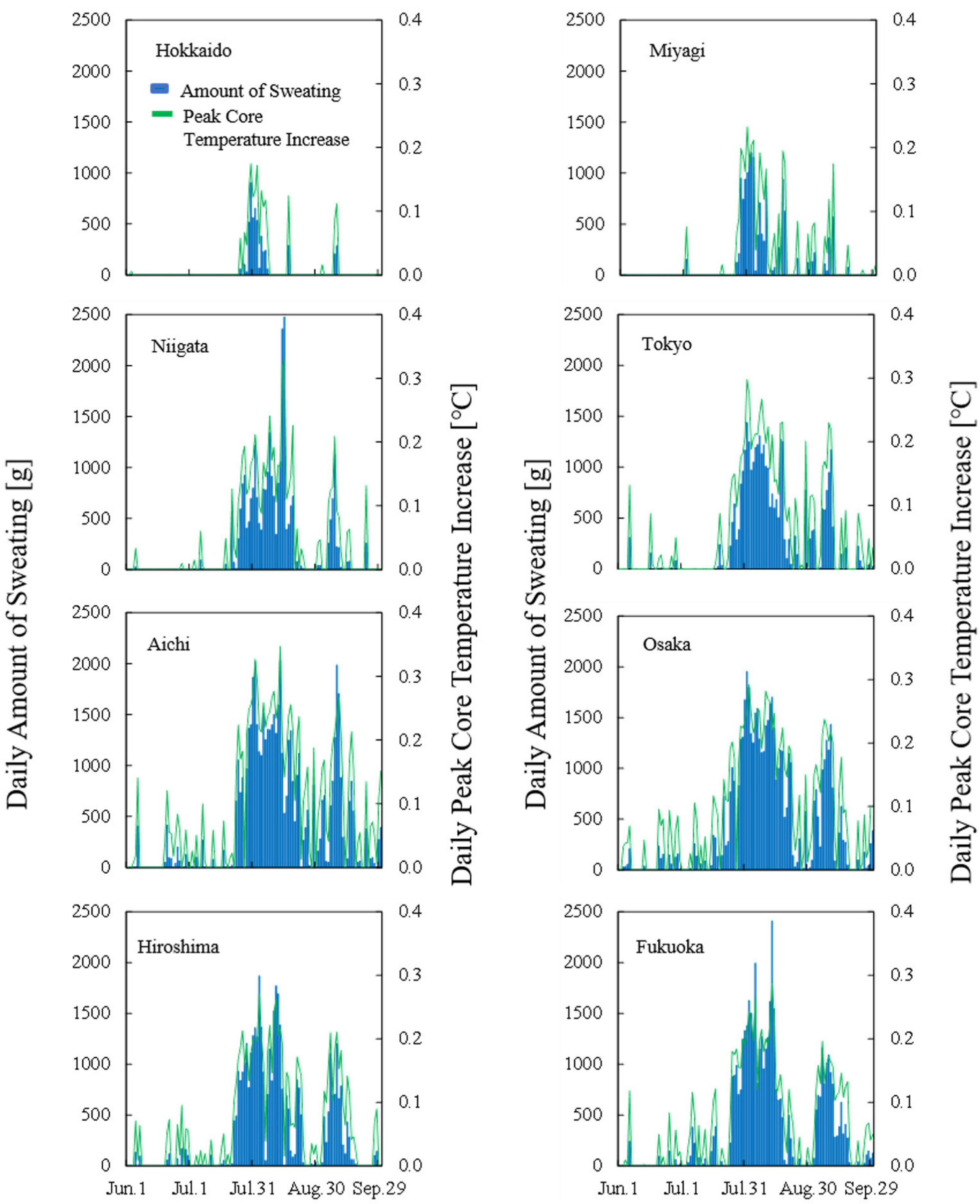

FIGURE 2
Time course of computed daily peak core temperature and total amount of sweating in each prefecture in 2019.

input variable x_i) with a decrease from the beginning to the end of summer, affected by climate over the previous several tens of days (29, 30). J provides the number of weighting days, and parameter w_i denotes weighted linear function. The input variables and optimal duration of J are evaluated in Section 3.2.

Fitting parameters a, l, f, and g were estimated to provide an expected number of cases of heat illness with transportation from indoor and outdoor locations, respectively. The parameters a and l were determined first, followed by f and g. All of the parameters were averaged over a 7-year time frame. Specifically, parameter fitting was iteratively conducted for convergence: 6 years of data (extracted over 7 years of data from 2013 to 2019) were used to determine the parameters, and then those for the remaining year were used through a leave-one-out cross-validation study (31). That is, data from 2013 to 2018 were used to determine the parameters for estimating the number of heat illness patients in 2019. Because the amount of sweating and the increase in body core temperature may be zero on days with a low heat load, we set $l = -1$ when these input variables were used, so that the number of transported patients converged to zero.

The estimation accuracy was evaluated in terms of the determination coefficient (R^2) and mean absolute error (MAE). The F-test was carried out for Equations (2, 3) with each input variable: daily average temperature, daily maximum increase in core temperature, and amount of sweating. All statistical analysis were conducted using Python 3.9.7. The threshold for a statistical significance was set at $p < 0.05$ (see Section 4 in the Supplementary material).

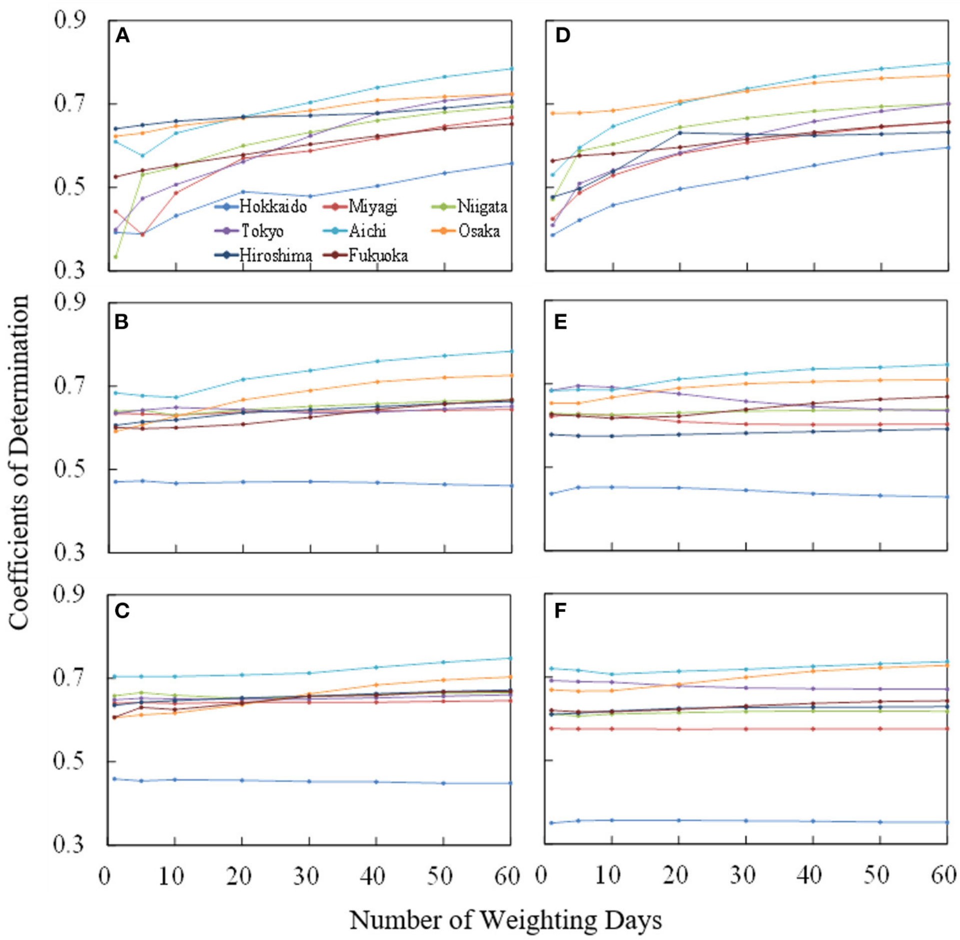

FIGURE 3
Variation of coefficient of determination averaged over 7 years (from June 1 to September 30 from 2013 to 2019) for the number of days over which an input variable is averaged, corresponding to *J* in Equation (4). For the number of patients transported the indoor locations, the **(A)** ambient temperature, **(B)** amount of sweating, and **(C)** body core temperature increase were considered. The same evaluation was conducted for patients transported from outdoor locations in **(D–F)**.

2.3. Computation of core temperature and water loss due to sweating

Body core temperature increase and amount of sweating, which were derived by computation, were used as surrogates for estimating the daily number of transported people using the non-linear analysis, in addition to the daily average ambient temperature. Ambient temperature showed a good correlation with the mobility of heat-related illness (14–16). The increase in body core temperature and the amount of sweating were computed in the time domain using our in-house computational code, taking into account the time series of ambient temperature and relative humidity from 2013 to 2019 (see Figure S2) (24).

Our computation combines thermodynamics in biological tissues and thermoregulation, including vasodilatation and sweating due to increased body temperature. Our computational code is summarized in the Section 2 in Supplementary material. To accelerate the computation, the in-house computational code was vectorized and parallelized and subsequently implemented on an SX-Aurora TSUBASA system named AOBA (32). A detailed and validation of our in-house computational code was presented in our previous studies (33, 34).

3. Results

3.1. Computed body core temperature and sweating

Figure 2 shows the computed daily peak core temperature and daily amount of sweating for each prefecture in 2019. The thermophysiological response to ambient heat stress was significant in early August across Japan. In Hokkaido, body core temperature increase and sweating amount were low even in August. It should also be noted that the distributions of body core temperature increase and sweating resembled each other. Their correlation coefficient was more than 0.93 ($p < 0.05$) for each prefecture.

TABLE 3 The parameters in Equations (2–4) for estimating patients transported from indoor and outdoor locations for average ambient temperature, amount of sweating, and body core temperature increase.

Input variables		Miyagi	Niigata	Tokyo	Aichi	Osaka	Hiroshima	Fukuoka
Indoor/home								
Average temperature	*a*	3.55×10^{-7}	7.01×10^{-7}	2.01×10^{-8}	2.83×10^{-8}	3.05×10^{-9}	2.49×10^{-9}	2.44×10^{-7}
	l	-3.07×10^{3}	-2.51×10^{3}	-2.33×10^{4}	-3.08×10^{4}	-1.09×10^{4}	-2.14×10^{-2}	-4.79×10^{3}
	f	-8.25×10^{-3}	-7.87×10^{-3}	-6.97×10^{-3}	-7.62×10^{-3}	-3.90×10^{-3}	-8.84×10^{-3}	-5.41×10^{-3}
	g	5.85×10^{-1}	5.50×10^{-1}	6.31×10^{-1}	6.45×10^{-1}	6.08×10^{-1}	7.60×10^{-1}	5.07×10^{-1}
Amount of sweating	*a*	1.87×10^{-1}	1.01	4.85×10^{-2}	8.41×10^{-3}	6.30×10^{-3}	2.08×10^{-2}	3.43×10^{-1}
	l	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00
	f	-1.50×10^{-7}	-2.04×10^{-8}	-7.10×10^{-8}	-3.42×10^{-7}	-3.95×10^{-7}	-1.94×10^{-7}	-1.80×10^{-8}
	g	2.01×10^{-4}	2.72×10^{-5}	2.34×10^{-4}	1.01×10^{-3}	1.09×10^{-3}	5.74×10^{-4}	4.00×10^{-5}
Body core temperature increase	*a*	9.27×10^{-3}	3.10×10^{-2}	6.65×10^{-3}	1.39×10^{-3}	5.18×10^{-4}	1.71×10^{-3}	3.44×10^{-3}
	l	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00
	f	-2.09×10^{1}	−8.39	−5.22	-1.94×10^{1}	-3.59×10^{1}	-2.78×10^{1}	−8.60
	g	8.97	3.18	5.28	1.30×10^{1}	1.89×10^{1}	1.47×10^{1}	8.28
Outdoor/workplace								
Average temperature	*a*	1.21×10^{-7}	8.36×10^{-6}	3.42×10^{-7}	1.85×10^{-7}	2.30×10^{-8}	5.25×10^{-6}	4.31×10^{-6}
	l	-5.13×10^{3}	-4.55×10^{2}	-3.92×10^{3}	-9.62×10^{3}	-2.50×10^{3}	-2.99×10^{2}	-7.42×10^{2}
	f	-8.69×10^{-3}	-6.40×10^{-3}	-5.86×10^{-3}	-6.78×10^{-3}	-3.04×10^{-3}	-2.22×10^{-3}	-3.96×10^{-3}
	g	6.35×10^{-1}	4.38×10^{-1}	5.19×10^{-1}	5.76×10^{-1}	5.34×10^{-1}	3.34×10^{-1}	3.88×10^{-1}
Amount of sweating	*a*	1.00×10^{2}	2.02×10^{2}	2.02	8.03×10^{-2}	2.85×10^{-2}	7.76	4.70×10^{1}
	l	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00
	f	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	g	3.34×10^{-7}	1.24×10^{-7}	7.39×10^{-6}	1.91×10^{-4}	3.79×10^{-4}	1.93×10^{-6}	2.81×10^{-7}
Body core temperature increase	*a*	7.94×10^{-2}	2.76×10^{1}	1.57×10^{-2}	8.92×10^{-3}	3.35×10^{-3}	1.15×10^{-2}	2.53×10^{-2}
	l	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00	−1.00
	f	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	g	1.58	4.54×10^{-3}	3.21	5.08	8.08	4.56	2.42

The parameters are derived for data from June 1 to September 30 from 2013 to 2019.

3.2. Duration of short-term heat adaptation

To clarify the duration that characterizes short-term heat adaptation, the correlation between observed and estimated numbers of patients transported from indoor/home and outdoor/workplace locations were evaluated in each prefecture for different input parameters. The evaluation period ran from June 1 to September 30 in 2013–2019. Figure 3 shows the coefficient of determination R^2 averaged over the 7 years for the number of days over which an input variable is averaged, corresponding to J in Equation (4). The coefficients of determination of Hokkaido were lower than those of the remaining prefectures. The amount of sweating and core temperature increase were relatively small due to its milder climate. In the remainder of this report, our discussion focuses on the characteristics of the seven prefectures, excluding Hokkaido.

For the average ambient temperature, R^2 increases with increase of averaging days (J) and then reached a plateau. The value of R^2 is high in Tokyo, Aichi, and Osaka, where the population density is large. Even for the remaining prefectures, high coefficients of determination were observed. R^2 reached a plateau at 40 days and 30 days of weighted days for the patients from indoor/home and outdoor/workplace locations, respectively.

The R^2 in terms of computed core temperature and sweating were less sensitive to the averaged days than those for average ambient temperature, regardless of whether patients were transported from indoor/home or outdoor/workplace locations. Estimation accuracy was improved only in Aichi, Osaka, Hiroshima, and Fukuoka, where average summer temperatures are higher than in the other prefectures studied (see Table 1).

The optimal parameters for the equation for estimating the number of patients transported from indoor and outdoor locations are listed in Table 3. Note that the number of parameters used for fitting was four for ambient temperature and two for the core temperature and amount of sweating. The validity of the equations

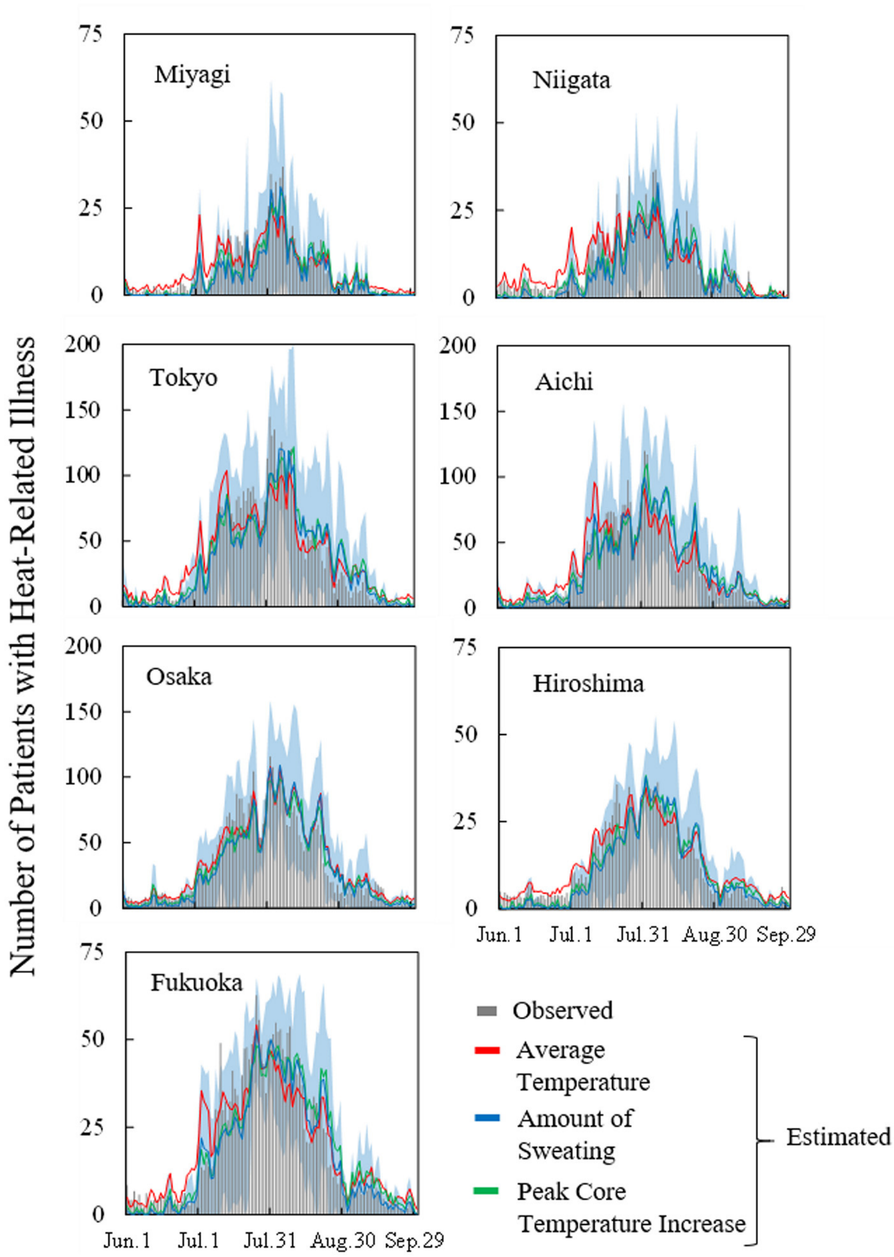

FIGURE 4
Observed and estimated number of patients with heat illness in seven prefectures (averaged over the period from 2013 to 2019) for average ambient temperature, amount of sweating, and body core temperature increase. Blue region represents the 95% confidence interval of estimation using computed daily amount of sweating.

using the parameters in Table 3 is shown in Section 4 of the Supplementary material.

3.3. Estimation of heat illness morbidity in seven prefectures

Figure 4 shows the observed and estimated numbers of daily patients, averaged over 7 years, for each prefecture. Moreover, the confidence interval region (95%) when estimating with daily amount of sweating is also presented. R^2 and MAEs per million population are listed in Table 4. The coefficient of determination R^2 exceeded 0.6 and was particularly high for Tokyo, Aichi, and Osaka. No significant difference was observed in R^2 between input parameters. MAEs have a mild correlation with the number of patients per million population. Because more patients were transported from outdoor locations, MAEs from those locations were larger than those from indoor locations. As seen in Figure 4, the estimated number of transported people is lower than the actual value and the variation is large just after the end of the rainy season (around July 20) in each prefecture, but actual value is almost within the 95% confidence interval. The number of

TABLE 4 Coefficient of determination R^2 and MAEs per million population in seven prefectures (averaged over the period from 2013 to 2019).

	R^2 [All (Indoor/Outdoor)]			MAEs per million population [All (Indoor/Outdoor)]		
	Average temperature	Amount of sweating	Body core temperature increase	Average temperature	Amount of sweating	Body core temperature increase
Miyagi	0.65 (0.62/0.61)	0.65 (0.64/0.58)	0.66 (0.64/0.61)	1.68 (0.77/1.02)	1.71 (0.76/1.07)	1.68 (0.77/1.01)
Niigata	0.70 (0.66/0.67)	0.66 (0.66/0.59)	0.68 (0.66/0.63)	1.97 (0.84/1.25)	1.95 (0.80/1.32)	1.90 (0.82/1.25)
Tokyo	0.68 (0.68/0.62)	0.71 (0.65/0.69)	0.69 (0.64/0.66)	1.25 (0.50/0.82)	1.11 (0.48/0.72)	1.20 (0.51/0.77)
Aichi	0.77 (0.74/0.74)	0.76 (0.73/0.71)	0.76 (0.76/0.68)	1.55 (0.61/1.05)	1.56 (0.61/1.12)	1.63 (0.57/1.22)
Osaka	0.74 (0.71/0.73)	0.71 (0.68/0.67)	0.74 (0.71/0.65)	1.47 (0.56/0.97)	1.55 (0.58/1.09)	1.48 (0.57/1.09)
Hiroshima	0.71 (0.68/0.63)	0.67 (0.66/0.61)	0.66 (0.65/0.57)	1.76 (0.76/1.21)	1.92 (0.81/1.22)	1.91 (0.81/1.25)
Fukuoka	0.64 (0.62/0.62)	0.67 (0.66/0.61)	0.66 (0.64/0.63)	1.77 (0.71/1.14)	1.67 (0.68/1.12)	1.74 (0.68/1.13)

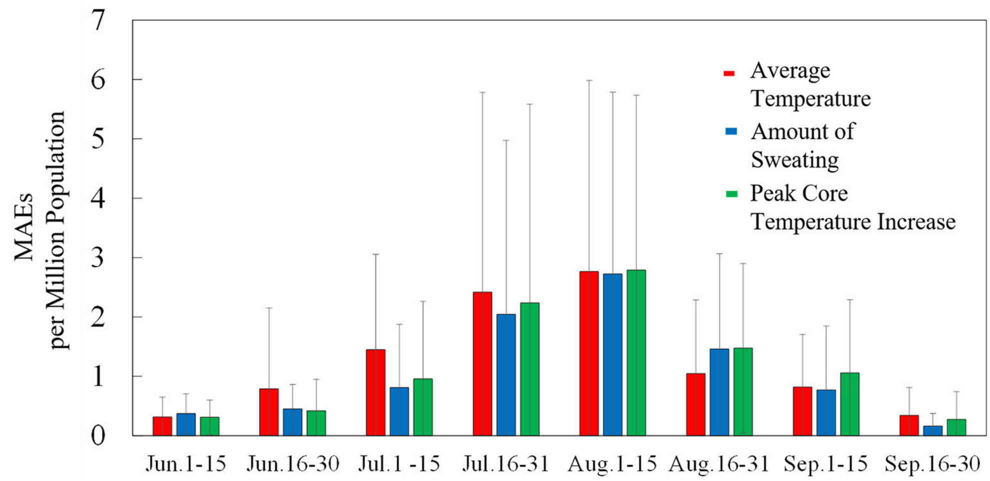

FIGURE 5
Time series of MAEs per million population in Tokyo for average ambient temperature, amount of sweating, and body core temperature increase (averaged over the period from 2013 to 2019). Standard deviations are indicated by error bars.

transported patients was overestimated around early July for the average ambient temperature, while from mid-August to mid-September, the amount of sweating and body core temperature increase.

To clarify the findings from Figures 4, 5 shows the time series of MAEs averaged over the period from 2013 to 2019 in Tokyo. MAEs were greatest from mid-July to mid-August, when the number of patients was highest. Differences in estimation accuracy were seen among the input variables, as shown by the trends identified in Figure 4. In July, the estimation accuracy was high for the computed core temperature and sweating, and in late August, the accuracy was high for ambient temperature.

Ambulance allocation is crucial for days when the number of transported patients. To evaluate the effectiveness of the method of estimation for 3 months, we focus on accuracy where the ambient temperature is large. To calculate heat-related risk, wet-bulb global temperature (WBGT) (35) is often used, a value that takes into account humidity and solar radiation in addition to ambient temperature. In Tokyo, the daily average number of heat illness cases was 136 for WBGT $\geq$ 31°C. In Figure 6, we present a comparison of estimation accuracy among the input variables for WBGT $\geq$ 31°C. The criterion approximately corresponds to $\geq$10 transported patients per million population.

In Figure 6, comparable accuracy was observed for seven prefectures. The difference in MAE per million population, defined as observed value minus estimated value, was distributed on the negative side (overestimation) for computed core temperature and sweating, relative to that for average ambient temperature. Table 5 summarized the MAE per million population for the days of WBGT $\geq$ 31°C. From Table 5, for the amount of sweating and the increase in body core temperature, the values of MAE were marginally small, suggesting a better agreement for estimated and observed values for hot days with larger numbers of transported patients.

4. Discussion

In this study, core temperature and sweating were computed to estimate the morbidity of heat illness patients for different

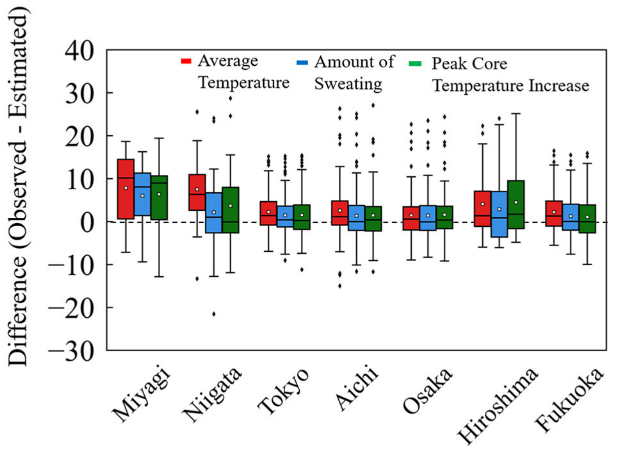

FIGURE 6
Difference from observed to estimated patients per million population in the days of WBGT ≥ 31°C. This approximately corresponds to a rate of transported patients per million population of ≥10 in seven prefectures from 2013 to 2019.

TABLE 5 Average MAEs per million population and number of days with WBGT ≥ 31°C for seven prefectures in Figure 6.

	Average temperature	Amount of sweating	Body core temperature increase	Number of days
Miyagi	9.75	7.84	9.26	14
Niigata	9.27	7.86	7.31	20
Tokyo	3.73	3.29	3.7	130
Aichi	4.45	4.46	4.32	102
Osaka	4.28	4.41	4.04	93
Hiroshima	5.89	6.35	6.55	29
Fukuoka	3.63)	3.71	4.03	173

prefectures of Japan. Eight prefectures were used that range from humid continental to subtropical climates (see Figure 1) (23).

In our analysis, Hokkaido, which belongs to Df in the Köppen climate classification scheme, was not well correlated with any input parameters because in that prefecture, body core temperature increase and sweating were low, even in August (see Figure 2). In other words, the number of hot days was limited, and thus, heat acclimatization is different or non-existent. One potential reason for this is that Hokkaido has a mild climate with only occasional heat waves. Thus, estimations covering very mild and extreme hot temperatures have less accuracy than those in the remaining prefectures. We then excluded Hokkaido for the remainder of the analysis.

As seen in Figure 2, the difference in daily peak core temperature and daily sweating amount were similar due to the daily course of ambient conditions. For the remaining seven prefectures, we derived parameters to estimate transported people in terms of Equations (2–4) with the parameters listed in Table 3. Note that the additional two parameters (f and l) were needed to obtain comparable accuracy in estimation of ambient temperatures to that shown in the sweating and core temperature.

As shown in Figure 3, the R^2 reached plateau at 40 days and 30 days of weighted days for patients from indoor and outdoor locations, respectively. This takes into account the human acclimatization to heat in the environment for a certain period (a few weeks). The R^2 values for computed core temperature and sweating were less sensitive to averaging days than that for average ambient temperature, regardless of whether patients were transported from indoor or outdoor locations. The R^2 values for patients transported from outside is high even at 1 day (without averaging) or at least higher than the R^2 for indoor patients with weighted average of $<$20 days. This suggests that the effects of heat adaptation are not crucial for outdoor patients (especially for workers). This hypothesis indicates that heat acclimatization is not crucial for outdoor patients in reality, rather adjustments to behavior, such as changing clothing with changes in the season. For the indoor patients, some heat accumulation was observed for $<$3 weeks. The numbers of patients transported from indoor and outdoor locations in Nagoya, Japan, were correlated with ambient temperature averaged over 50 and 20 days, respectively, in our previous study (20). The values obtained here are comparable to those data, from one city and one input variable.

Let us review heat accumulation further. Most previous studies investigated short-term adaptation *via* exercise (36–38). In Nakamura et al. (29), heat accumulation in daily life was investigated in a single region of Japan with a sample of five individuals, and it was found that 10 days were needed for intermittent heat exposure and 48 days for more continuous head adaptation. By contrast, this is a population-level study, and some difference can be observed (39, 40).

Smaller numbers of parameters were needed to estimate the numbers of transported people in terms of the computed thermophysiological responses, and these estimations provided better accuracy. An additional two parameters (f and l) were used in the estimation with ambient temperature, corresponding to heat accumulation (f) and additional tuning for accuracy compensation (l). Note that no physiological rationale exists for parameter (l) or a variable for different prefectures.

The estimated numbers of heat illness patients are in good agreement with observed values in seven prefectures. The proposed equations are applicable to different prefectures once weather, thermophysiological data, population, and age are incorporated. However, the estimation accuracy was variable for different seasons, as shown in Figure 5. In particular, the estimated numbers of people were smaller than the observed values following the rainy season, as shown in Figure 4. On those hot days, estimations with thermophysiological responses provided better accuracy (Figure 6).

The proposed equations have been used more than 20 times in the TV programs in Japan for public awareness. Fire departments in Nagoya City (Aichi prefectures) have introduced this system, sharing information with hospitals. The expected number of people transported owing to heat-related illness by using the proposed equations considering long-term temperature changes and the aging of the population in each region could be useful as a manner for future emergency systems. However, this system is tentatively suspended in COVID-19 epidemic.

This study was limited by the small number of extreme hot days included in the development of equations. Specifically, in 2018, the maximum ambient temperature was recorded in some prefectures. However, the estimation obtained on such days is an extrapolation, and thus accuracy is not warranted. Intense heat waves are expected to continue in the future, and thus the formula and parameters should also be revisited in the future.

Data availability statement

Publicly available datasets were analyzed in this study. The details can be found in the article/Supplementary material.

Author contributions

Conceptualization: AH, RE, MN, and SK. Methodology and formal analysis: AH, SK, and MN. Investigation and data curation: SK and AT. Resources and writing—review and editing: RE and HT. Writing original draft preparation: AT, SK, and AH. Project administration: AH, KS, and HT. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1061135/full#supplementary-material

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Ruoyu Wang,
University of Edinburgh, United Kingdom

REVIEWED BY
Peter James Franklin,
University of Western Australia, Australia
Xiangrong Zheng,
Xiangya Hospital, Central South University, China

*CORRESPONDENCE
Pablo Mariscal-Aguilar
✉ pmaguilar91@gmail.com

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Relationship between air pollution exposure and the progression of idiopathic pulmonary fibrosis in Madrid: Chronic respiratory failure, hospitalizations, and mortality. A retrospective study

Pablo Mariscal-Aguilar[1,2,3,4]*, Luis Gómez-Carrera[1,2,3,4], Carlos Carpio[1,2,3,4], Ester Zamarrón[1,2,3,4], Gema Bonilla[2,3,5], María Fernández-Velilla[2,3,6], Isabel Torres[2,3,6], Isabel Esteban[2,3,7], Rita Regojo[2,3,7], Mariana Díaz-Almirón[2], Francisco Gayá[2], Elena Villamañán[2,3,8], Concepción Prados[1,2,3,4] and Rodolfo Álvarez-Sala[1,2,3,4]

[1]Department of Respiratory Medicine, Hospital Universitario La Paz, Madrid, Spain, [2]Research Institute of Hospital Universitario La Paz (IdiPAZ), Madrid, Spain, [3]Department of Medicine, Universidad Autónoma de Madrid, Madrid, Spain, [4]Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Madrid, Spain, [5]Department of Rheumatology, Hospital Universitario La Paz, Madrid, Spain, [6]Department of Radiology, Hospital Universitario La Paz, Madrid, Spain, [7]Department of Pathological Anatomy, Hospital Universitario La Paz, Madrid, Spain, [8]Department of Pharmacy, Hospital Universitario La Paz, Madrid, Spain

Introduction: Air pollution has a significant impact on the morbidity and mortality of various respiratory diseases. However, this has not been widely studied in diffuse interstitial lung diseases, specifically in idiopathic pulmonary fibrosis.

Objective: In this study we aimed to assess the relationship between four major air pollutants individually [carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), and nitrogen oxides (NO_x)] and the development of chronic respiratory failure, hospitalization due to respiratory causes and mortality in patients with idiopathic pulmonary fibrosis.

Methods: We conducted an exploratory retrospective panel study from 2011 to 2020 in 69 patients with idiopathic pulmonary fibrosis from the pulmonary medicine department of a tertiary hospital. Based on their geocoded residential address, levels of each pollutant were estimated 1, 3, 6, 12, and 36 months prior to each event (chronic respiratory failure, hospital admission and mortality). Data was collected from the air quality monitoring stations of the Community of Madrid located <3.5 km (2.2 miles) from each patient's home.

Results: The increase in average values of CO [OR 1.62 (1.11–2.36) and OR 1.84 (1.1–3.06)], NO_2 [OR 1.64 (1.01–2.66)], and NO_x [OR 1.11 (1–1.23) and OR 1.19 (1.03–1.38)] were significantly associated with the probability of developing chronic respiratory failure in different periods. In addition, the averages of NO_2, O_3, and NO_x were significantly associated with the probability of hospital admissions due to respiratory causes and mortality in these patients.

Conclusion: Air pollution is associated with an increase in the probability of developing chronic respiratory failure, hospitalization due to respiratory causes and mortality in patients with idiopathic pulmonary fibrosis.

KEYWORDS

air pollution, idiopathic pulmonary fibrosis, chronic respiratory failure, hospital admissions, mortality

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common progressive fibrosing lung disease among idiopathic interstitial pneumonias. IPF is the interstitial lung disease with the worst prognosis, with an approximate median survival from the time of diagnosis of between 3 and 5 years (1–4). There is various prognosis factor of this disease (older age, smoking status, lower lung function…) and some studies recently suggested an association between air pollution and clinical course or mortality of IPF (5–11).

There are numerous short- and long-term effects that air pollution can have on the incidence and prognosis of different respiratory pathologies. The impact of urban air pollution has been associated with alterations in lung maturation and development, increased incidence of chronic obstructive pulmonary disease (COPD), COPD exacerbations, poorly controlled asthma, and increased mortality from respiratory causes (12, 13).

Increased emissions from transportation and industry, the rapid urbanization of different regions and the consumption of energy have currently exposed the respiratory system to an exponential increase in atmospheric pollutants (14). Carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), and nitrogen oxides (NO_x) are among the most important pollutants to assess in terms of their effect on the respiratory system (15).

Polluted air, when it comes into direct contact with and damages the epithelium of the bronchial tree, can induce epigenetic changes leading to increased collagen deposition and abnormal repair of the affected cells (16, 17). We have found several articles that assess the effects of pollution on IPF. In fact, there are some protocols that have related air pollution with acute exacerbations, lung function and mortality of IPF (5–11).

We hypothesized that major urban air pollutants (CO, NO_2, O_3, and NO_x) could impact individually to the development of chronic respiratory failure and hospitalization due to respiratory causes in patients with IPF and we have not found studies that evaluated it. Furthermore, we also investigated the relationship between air pollution and mortality in patients with IPF with different periods of exposure.

In addition, the length of time studied for high concentrations of CO, NO_2, O_3, and NO_x to cause these outcomes is heterogeneous in studies and it has not been defined. We aimed to focus on pollution levels over 1, 3, 6, 12, and 36 months before an event because it has been demonstrated that measuring mean air pollution over longer periods often results in stronger associations with lung changes (18–23).

Abbreviations: CO, Carbon Monoxide; COPD, Chronic obstructive pulmonary disease; DLCO, Carbon monoxide diffusing capacity of the lung; FEV_1, Forced expiratory volume on the first second; FVC, Forced vital capacity; IPF, Idiopathic pulmonary fibrosis; KCO, Carbon monoxide transfer coefficient; NO_2, Nitrogen dioxide; NO_x, Nitrogen oxides; O_3, Ozone; OR, Odds ratio; PM_{10}, Particulate matter with an aerodynamic diameter <2.5 µm; $PM_{2.5}$, Particulate matter with an aerodynamic diameter <10 µm; RR, Relative risk; SO_2, Sulfur dioxide; sPAP, Systolic pulmonary artery pressure; TLC, Total lung capacity.

Materials and methods

Subjects

Patients included were diagnosed according to the consensus criteria of the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (1, 2). Patients whose basic data (address, age, sex, complementary tests, and treatments) were not available in the medical records, who failed to attend more than two consecutive visits, or lived more than 3.5 km from the nearest air quality station were excluded. Patients whose home address changed during the study period and those who presented incomplete data during follow-up were withdrawn.

Protocol

This is a exploratory retrospective panel study of a cohort of patients in follow-up for diffuse interstitial lung disease at the Pulmonary Fibrosis Specialty Clinic of the Hospital Universitario La Paz Pneumology Department. The follow-up period was from 2011 to 2020. Patients were evaluated every 3–4 months in the clinic in compliance with the IPF follow-up protocol established in clinical practice guidelines, collecting different clinical data: a questionnaire to assess dyspnea level, symptoms, diagnostic tests, treatments received, results of complementary tests and diagnoses of other diseases. Patients were considered to be under treatment with antifibrotics when such therapy extended beyond 45 days (24).

Exposure assessment

The Integral Air Quality System of *Ayuntamiento de Madrid* and *Comunidad de Madrid* provides hourly reports through air quality control stations on the concentrations of NO_2, O_3, and NO_x measured in μg/m^3 and CO measured in mg/m^3 (25, 26). Each patient was assigned air pollutant levels obtained from the surveillance station closest to their home; in the event that the station did not measure a specific pollutant, they were associated with another nearby station provided that this was <3.5 km from their home. The distance between surveillance stations and each patient's residence was determined through the coordinates provided by Google Maps. Distance-related averages were used to relate them. We could not control meteorogical factors (temperature and relative humidity) because we have only found meteorogical data in some stations from *Comunidad de Madrid* (26), while we have not obtain it from the *Ayuntamiento de Madrid* (25).

Outcome measures

The onset of chronic respiratory failure was defined as those patients who had a partial pressure of oxygen of <60 mmHg in baseline arterial blood gases (27). Hospitalizations due to respiratory causes were specified based on the diagnosis reflected in patients' medical record at the time of each admission. In addition, every patient who had a hospitalization were made a respiratory virus test (Influenza, Respiratory Syncytial Virus or SARS-CoV2) and before each hospital admission. Data related to mortality were obtained from each patient's medical record.

Baseline arterial blood gases were obtained by puncture of the radial artery, after ensuring the existence of adequate collateral circulation using the Allen maneuver, in accordance with SEPAR (Spanish Society of Pneumology and Thoracic Surgery) recommendations (28). The arterial blood sample obtained while the patients were breathing room air was measured with an ABL90 blood gas analyzer (Radiometer Medical ApS, Brønshøj, Denmark).

Ethics

This study was conducted in accordance with the standards of good clinical practice and the ethical principles of the Declaration of Helsinki. It was approved by the La Paz University Hospital Clinical Research Ethics Committee (Code PI-3742, June 20, 2019). Given the retrospective nature of the study, informed consent was not required.

Statistical method

To calculate the value of each pollutant relative to the period between patient visits, the average of each pollutant was taken, weighted by the inverse of the squared of the distance from the patient's home to the nearest air quality station (maximum distance of 3.5 km).

Correlated data were analyzed using a generalized linear mixed model with the restricted maximum pseudo-likelihood method. Three events were assessed: chronic respiratory failure, hospitalization due to respiratory causes and mortality. A random intercept and unstructured covariance matrix were added to the generalized linear mixed model with binomial distribution and logit link function to estimate the "likelihood of the event". Each air pollutant was added to the model, estimating the relationship with the binary outcome in terms of the OR. To estimate the average values of air pollutants, a random intercept and unstructured covariance matrix were added to the generalized linear mixed model with normal distribution and an identity link function.

A Poisson log-linear model with robust standard errors ("sandwich" method) was used to study the association between air pollutants and the risk ratio of two events: hospitalization due to respiratory causes and mortality. Non-linear associations for each air pollutant with a risk ratio were tested using a likelihood ratio test comparing a model with the exposure fitted on a spline with a model assuming a linear exposure-outcome relationship. Spline smoothness was selected after determining two and three degrees of freedom. The p-value for non-linearity of <0.05 suggests evidence against the linearity assumption.

Three multivariate analysis were calculated (once for each outcome, chronic respiratory failure, hospitalizations and mortality). The Generalized Linear Mixed Model (GLMM) with the Restricted Maximum Pseudo-Likelihood Method (RMPL) was considered to estimate "Probability of the event" with a binomial distribution and logit link function.

Seasons have been controlled and no significant differences were found between hospitalizations and mortality in each period. We have taken two definitions of each season. The first one based on Sesé et al. (8), who defined "cool season" from November to April. Secondly, it has been taken the definition according to Johannson et al. (6) and Dales et al. (29) who stablished "cool season" from October to March. In both cases there were no significant differences between hospitalizations and mortality (Supplementary Tables 1–4). In addition, in order to include season as a potential confounder, seasons have been incorporated in multivariate analyses as categorical regressor variable in the Generalized Linear Mixed Model where it has been taken "cool season" definition from October to March and "warm season" from April to September (6, 29).

On the other hand, statistical models used were also adjusted for age, sex, smoking status, FVC, and DLCO at the time of the first visit, antifibrotic treatment regimen and pulmonary hypertension.

In general, two-tailed p-values of <0.05 were considered statistically significant. Analyses were conducted in R Statistical Software V4.0.4 (2021-02-15) with the mgcv package (mgcv_1. 8-33) and SAS Enterprise Guide 8.2 statistical program (SAS Institute Inc., Cary, North Carolina).

Results

Of the 71 patients initially included in the cohort, two whose place of residence was unknown and one who lived more than 3.5 km from the station were excluded. The baseline characteristics of all included patients may be observed in Table 1. Of the 69 enrolled patients with IPF, 22 developed chronic respiratory failure, 29 were hospitalized at least once for respiratory causes, and 22 died. Results were obtained with calculations adjusted for age, sex, smoking status, lung function and antifibrotic treatment. Of the 22 patients who developed chronic respiratory failure, 13 (59%) were hospitalized due to respiratory causes at least once, and 16 died (72.7%). Of the 29 patients who were hospitalized at least once, 13 (44.8%) developed chronic respiratory failure and 15 (51.7%) died. Finally, of 22 patients who died, 15 (68.1%) had at least one hospital admission and 16 (72.7%) developed chronic respiratory failure. here were significant differences between hospitalizations and mortality. On the other hand, there were too significant differences between chronic respiratory failure and mortality. Patient exposure levels appear in Supplementary Table 5.

Effects of pollution on the development of chronic respiratory failure

The increment in the average values of CO, NO_2, and NO_x was significantly associated with an increase in the probability of the development of chronic respiratory failure in different periods. In the case of CO, an OR of 1.62 (1.11–2.36) was observed for each 0.1 mg/m^3 ($p = 0.01$) increase during the 3 months prior to the event and an OR of 1.84 (1.1–3.06) over the previous 6 months (Supplementary Figure 1). Regarding NO_2, an OR of 1.65 (1.01–2.66) ($p = 0.04$) was obtained for each 10 μg/m^3 increase with exposure 6 months before the event (Supplementary Figure 2). NO_x yielded results with an OR of 1.12 (1.01–1.23) ($p = 0.03$), and OR 1.20 (1.03–1.38) ($p = 0.01$) for each 10 μg/m^3 increase at 3 and 6 months of exposure prior to the event, respectively (Supplementary Figure 3). Regarding multivariate analysis, the association between each pollutant and chronic respiratory failure was not affected by the inclusion of other pollutants in the models. In addition, there was no effect of seasons in these results (Supplementary Tables 6–10).

Effects of pollution on admissions due to respiratory causes

The increase in the averages of NO_2, O_3, and NO_x were significantly associated with an increase in the probability of hospital admission due to respiratory causes in these patients. In the case of NO_2, a significant relationship was obtained with an exposure of 6, 12, and 36 months before admission (Supplementary Figures 4–6). The positive results obtained with respect to O_3 involved an exposure of 1 month prior to admission (Supplementary Figure 7). In the case of NO_x the association between the probability of hospitalization for respiratory causes occurred with an exposure of 6, 12, and 36 months (Supplementary Figures 8–10). Regarding multivariate analysis, the association between each pollutant and hospitalizations due to respiratory causes was not affected by the inclusion of other pollutants in the models. In addition, there was no effect of seasons in these results (Supplementary Tables 11–15).

TABLE 1 Baseline characteristics of IPF patients.

Baseline characteristics	Mean ± standard deviation or number (percentage)
Sex, number (%)	
Women, number (%)	16 (23.2)
Men, number (%)	53 (76.8)
Age, years	73.70 ± 7.72
Height, cm	72.85 ± 14.12
Weight, kg	165.5 ± 10.32
Body mass index, Kg/m^2	26.40 ± 3.92
Smokers, number (%)	
Non-smoker	39 (56.5)
Current smoker	30 (43.5)
Packs per year	22.65 ±13.97
Charlson Index	2 ± 1.5
Dyspnea (modified Medical Research Council)	1 ± 0.65
Total lung capacity (TLC), % predicted	77.69 ± 14.76
Pulmonary carbon monoxide diffusing capacity (DLCO), % predicted	63.45 ± 20.54
Carbon monoxide transfer coefficient (KCO), % predicted	91.8 ± 17.9
Forced expiratory volume in the first second (FEV_1) % prebronchodilator, % predicted	88.20 ± 18.3
Forced vital capacity (FVC) % prebronchodilator, % predicted	82.42 ± 18.39
6 min walk test, m	488.89 ± 101.69
Initial oxygen saturation, %	94 ± 2.2
Final oxygen saturation, %	85.83 ± 5.2
pH	7.42 ± 0.01
Partial pressure of oxygen in baseline arterial blood, mmHg	72.40 ± 10
Partial pressure of carbon dioxide in baseline arterial blood, mmHg	37.4 ± 4.1
Systolic pulmonary artery pressure (sPAP)	32.6 ± 7.16
Antifibrotic treatment > 45 days	61 (88.4)
Pirfenidone > 45 days	48 (69.5)
Nintedanib > 45 days	21 (30.5)
Chronic respiratory failure	22 (31.9)
Hospitalizations (respiratory cause)	29 (42)
Deaths	22 (31.9)

Effects of pollution on mortality

Increases in the averages of NO_2, O_3, and NO_x were significantly associated with an increase in the probability of death in patients with an exposure to these pollutants of 1 and 3 months in the case of O_3 and of 12 and 36 months in the case of NO_2 and NO_x (Supplementary Figures 11–16). Regarding multivariate analysis, the association between each pollutant and mortality was not affected by the inclusion of other pollutants in the models. In addition, there was no effect of seasons in these results (Supplementary Tables 16–20).

Discussion

Our data show that air pollution may be associated with the development of chronic respiratory failure irrespective of other factors such as sex, age, smoking status, lung function, or antifibrotic therapy in patients with IPF. The results obtained indicate that increases in the average values of CO, NO_2 and NO_x are related to an increased probability of the development of chronic respiratory failure in different periods of exposure (three and 6 months prior to the event).

To date, we have found no works in the literature consulted that study the association between the pollution caused by CO, NO_2, and NO_x and the probability of developing chronic respiratory failure in patients with IPF. However, we have identified protocols that do so with variations in oxygen saturation whose conclusions partially coincide with those of our study (30, 31). Such is the case of work carried out by DeMeo et al. (30) who demonstrated that for each 11.45 $\mu g/m^3$ increase in $PM_{2.5}$ oxygen saturation decreased by 0.172% (−0.313 to −0.031). Similar research developed by Luttmann-Gibson et al. (31) analyzing NO_2, SO_2, $PM_{2.5}$, O_3, $SO_4{}^{2-}$, and elemental carbon concluded that an increase of 13.4 $\mu g/m^3$ in $PM_{2.5}$ on the previous day was associated with a decrease of −0.18% (−0.31 to −0.06) in oxygen saturation, while an increase of 5.1 $\mu g/m^3$ in $SO_4{}^{2-}$ was associated with a decrease of −16% (−0.27 to −0.04) in pulse oximetry.

The possible disparity in results may be due to all protocols we consulted examined oxygen saturation measured by pulse oximetry, while we used baseline arterial blood gases, which is more accurate (28). Secondly, our study included a larger sample size compared to the subjects included in these studies. In addition, our study used stations close to patients' homes, while DeMeo et al. (30) only monitored pollution data at the study site.

Regarding to hospitalizations due to respiratory deterioration we observed that increases in NO_2, O_3, and NO_x were significantly associated with the increase in the number of hospitalizations for this cause in patients with IPF with relatively long periods of exposure compared to other studies (5, 6, 8, 29). We have found no research that examines the association between pollution and the probability of hospitalization due to respiratory causes in patients with IPF. However, we have observed that there are studies (5, 6, 8, 29) that analyze other variables.

Our results regarding NO_2 and O_3 partially coincide with those obtained by Dales et al. (29) who obtained a significant association between the levels of CO_2, NO_2, SO_2, $PM_{2.5}$, PM_{10}, and O_3 and hospitalizations although they do not do so in the same time interval. This may be due to the fact that this study measured not only admissions due to respiratory causes, as in our work, but hospitalizations of patients with IPF due to any pathology, which may constitute a confounding factor with respect to the exposure time necessary for the disease to lead to hospital admission. Tomos et al. (5) obtained similar results to our study because of the impact of NO_2 in the increase of exacerbations. On the other hand, the results obtained in our protocol correspond more closely with those found by Johannson et al. (6) who demonstrated that pollution caused by increased levels of NO_2 and O_3 increased the risk of acute exacerbations. Finally, Sesé et al. (8) found consistent results relating to O_3 levels and acute exacerbations. Nevertheless, although they did not examined the same exposure period and they have only assessed exacerbations of IPF. The differences in outcomes could be due to dissimilarities in the data sources, as well as in the composition of the air, which may have influenced the time course of these particles leading to patient hospitalization for IPF.

The increase in hospitalizations due to pollutants that we have detected may be supported by the effect that these pollutants have on the respiratory system. NO_2 and NO_x derive from the combustion of motorized vehicles and can reach the lower airway, causing inflammation and changes in its caliber. Finally, excessive ozone can decrease ventilatory capacity (32). These demonstrated effects of pollutants in the respiratory system add more power to our data, since they are highly consistent.

Our data indicate that the action of certain pollutants, namely NO_2, O_3, and NO_x may have a significant impact on the mortality of these patients with different exposure times. In this regard, we have found several works in the literature that evaluate IPF mortality and pollution with some discrepancies in results. Sesé et al. (8) did not find positive results in NO_2, and O_3 maybe because they had different sample size characteristics with more mortality than ours (53.4 vs. 31.9%) and, as same as the study of Johannson et al. (6), they used 42-day exposure time, which could be insufficient time for the pollutants to contribute to increasing the mortality of patients with IPF. In addition, Mariscal et al. (33) reported an increased risk of mortality with CO and this results differ with our protocol because the measurement was from a single surveillance station in central Madrid while in ours we have used all the stations in the region. Finally, Yoon et al. (11), with a larger sample size, observed a clear influence of NO_2 levels on the mortality of these patients.

Discrepancies may also be due to the different levels of exposure and toxicity, the study populations in different climatic zones, and the criteria for diagnosing and admitting patients with IPF. Therefore, although these works have similar objectives, the comparison of results must be performed with caution, since the methodology was different.

Regarding the correspondence between our study outcomes and those of Yoon et al. (11), we believe that our protocol coincides in the finding that NO_2 is the pollutant most associated with the deterioration of IPF, whether in terms of chronic respiratory failure, hospital admissions or mortality. Therefore, it seems reasonable to think that this particle, which is linked to road traffic, causes inflammation and an increase in surface tension in the alveoli that contributes to the progression of IPF in various aspects. This suggests that a correct action in reducing the levels of NO_2, O_3, and NO_x through stricter control of traffic and motor vehicle emissions could promote a better clinical course for IPF patients residing in cities with high pollution levels.

This research project has several limitations. First, it is a single-center study with a limited number of subjects, insofar as it is a low prevalence disease, although the cohort comes from an interstitial lung disease unit with a not insignificant sample size. Second, exposure to air pollution in the workplace, which could play an important role in this type of study, was not taken into account. No information on temperature and relative humidity was available. Regarding potential confounding factors, it was not possible to control for all of them, since there are many more particles in the air than those studied in this protocol, which could have prevented the demonstration of other effects of air pollution. Finally, although 3.5 km was the best available exposure assessment in our protocol, an important limitation of the study was the error in the exposure measurements.

However, our study also has its strengths. It is a work that simultaneously analyzes a greater number of pollutants than most other published protocols (5–11) in this case up to four (CO, NO_2, O_3, and NO_x), selected according to the evidence available in this type of research.

In addition, the indicators assessed (blood gas, hospitalizations, and mortality) are decisive in the clinical course of patients with idiopathic pulmonary fibrosis and to the best of our knowledge there is no other article that considers all these variables together. Our work also includes the averages of each pollutant during 1, 3, 6, 12, and 36 months so this results could be useful to hypothesize with caution that both short and long term exposure to air pollution could be harmful to the clinical course of the patient (18–22).

The foregoing adds significant value to this protocol analyzing the impact of environmental pollution on the clinical course and mortality of idiopathic pulmonary fibrosis.

Conclusions

In conclusion, the findings of this study suggest that environmental pollution, specifically that caused by four main pollutants (CO, NO_2, O_3, and NO_x), can increase cases of chronic respiratory failure, hospitalizations due to respiratory causes and mortality in patients with IPF. These results are in line with the WHO recommendations for reducing polluting emissions and could encourage changes in environmental policies to improve the follow-up and clinical course of these patients. It is necessary to continue this line of research with future protocols that allow for more precise quantifications of ambient air quality, paying special attention to these pollutants.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the La Paz University Hospital Clinical Research Ethics Committee (Code PI-3742, June 20, 2019). Given the retrospective nature of the study, informed consent was not required. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: PM-A, LG-C, CP, and RÁ-S. Methodology: PM-A, CC, LG-C, MD-A, FG, and RÁ-S. Software and formal analysis: PM-A, CC, MD-A, and FG. Validation: CC, IT, PM-A, MF-V, and RÁ-S. Research: LG-C, CC, EZ, EV, and RÁ-S. Resources: CC, EZ, PM-A, MD-A, FG, and RÁ-S. Data curation: PM-A and GB. Writing—original draft preparation: PM-A and RÁ-S. Writing—review and editing: CC, PM-A, IE, RR, and RÁ-S. Visualization: CC, PM-A, CP, and RÁ-S. Supervision: LG-C, CC, and RÁ-S. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1135162/full#supplementary-material

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EDITED BY
Yunquan Zhang,
Wuhan University of Science and Technology, China

REVIEWED BY
Fangchao Liu,
Chinese Academy of Medical Sciences and Peking Union Medical College, China
Ying Wu,
Southern Medical University, China

*CORRESPONDENCE
Shichao Han
✉ hanshichaohome@163.com
Zhiping Niu
✉ zhiping_niu@whu.edu.cn

†These authors have contributed equally to this work

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Associations of long-term exposure to air pollution, physical activity with blood pressure and prevalence of hypertension: the China Health and Retirement Longitudinal Study

Jinglong Zhang[1†], Fen Zhang[2†], Chao Xin[3], Zhizhou Duan[4], Jing Wei[5], Xi Zhang[6], Shichao Han[7]* and Zhiping Niu[7]*

[1]Department of Cardiovascular Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, China, [2]Department of Hepatobiliary Surgery, Xijing Hospital, The Fourth Military Medical University, Xi'an, China, [3]PLA Rocket Force Characteristic Medical Center, Beijing, China, [4]Preventive Health Service, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, China, [5]Department of Atmospheric and Oceanic Science, Earth System Science Interdisciplinary Center, University of Maryland, College Park, MD, United States, [6]The First Clinical Medical College, Anhui Medical University, Hefei, Anhui, China, [7]Department of Urology, Xijing Hospital, The Fourth Military Medical University, Xi'an, China

Background: Long-term exposure to air pollution and physical activity (PA) are linked to blood pressure and hypertension. However, the joint effect of air pollution and PA on blood pressure and hypertension are still unknown in Chinese middle-aged and older adults.

Methods: A total of 14,622 middle-aged and older adults from the China Health and Retirement Longitudinal Study wave 3 were included in this study. Ambient air pollution [particulate matter with diameter≤2.5μm ($PM_{2.5}$), or ≤10μm (PM_{10}), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), carbonic oxide (CO)] were estimated using satellite-based spatiotemporal models. PA was investigated using International Physical Activity Questionnaire. Generalized linear models were used to examine the associations of air pollution, PA score with blood pressure [systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP)], and the prevalence of hypertension. Subgroup analysis was conducted to investigate the effects of air pollution on blood pressure and the prevalence of hypertension in different PA groups.

Results: The results showed that for each inter-quartile range (IQR) increase in $PM_{2.5}$ (25.45μg/m^3), PM_{10} (40.56μg/m^3), SO_2 (18.61μg/m^3), NO_2 (11.16μg/m^3), CO (0.42mg/m^3) and PA score (161.3 MET/h-week), the adjusted odd ratio (OR) of hypertension was 1.207 (95% confidence interval (CI): 1.137, 1.281), 1.189 (95%CI: 1.122, 1.260), 1.186 (95%CI: 1.112, 1.266), 1.186 (95%CI: 1.116, 1.260), 1.288 (95%CI: 1.223, 1.357), 0.948 (95%CI: 0.899, 0.999), respectively. Long-term exposure to $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO was associated with increased SBP, DBP, and MAP levels. For example, each IQR increase in $PM_{2.5}$ was associated with 1.20mmHg (95%CI: 0.69, 1.72) change in SBP, 0.66mmHg (95%CI: 0.36, 0.97) change in DBP, and 0.84mmHg (95%CI: 0.49, 1.19) change in MAP levels, respectively. Each IQR increase in PA score was associated with −0.56mmHg (95%CI: −1.03, −0.09) change in SBP, −0.32mmHg (95%CI: −0.59, −0.05) change in DBP, and −0.33mmHg (95%CI: −0.64, −0.02) change in MAP levels, respectively. Subgroup analysis found that the estimated effects in the sufficient PA group were lower than that in the insufficient PA group.

Conclusion: Long-term exposure to air pollutants is associated with increased blood pressure and hypertension risk, while high-level PA is associated with decreased blood pressure and hypertension risk. Strengthening PA might attenuate the adverse effects of air pollution on blood pressure and hypertension risk.

KEYWORDS

air pollution, blood pressure, hypertension, physical activity, middle-aged and older adults, cardiovascular system

1. Introduction

Hypertension has become the top leading risk factor for attributable death, accounting for ~10.8 million deaths each year (1). Moreover, hypertension is one of the most significant risk factors for other cardiovascular diseases (CVDs) and always leads to organs damage and dysfunction of the organs, such as the heart, brain, and kidney (2–4). Previous studies showed that both blood pressure and the risk of hypertension increase significantly with age (5), and middle-aged and older adults were identified as the population at high risk for hypertension and other CVDs (3, 6). With the deepening aging of society, the burden of hypertension and hypertension-related diseases will greatly increase in the next few decades (1). Therefore, it is critical to identify the risk factor of hypertension and further explore its intervention strategies for the health promotion of middle-aged and older adults.

Several studies have indicated that exposure to ambient air pollution was associated with increased blood pressure and the prevalence of hypertension (8–11). A systematic review and meta-analysis indicated that long-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 was associated with increased diastolic blood pressure (DBP) levels, and $PM_{2.5}$ was associated with an increased prevalence of hypertension (11). A cross-sectional study in rural China found that exposure to $PM_{2.5}$, PM_{10}, and NO_2 was associated with increased SBP, DBP (except for PM_{10}), mean arterial pressure (MAP) and the prevalence of hypertension (7). However, some studies have reported opposite results or insignificant associations (12). For example, a longitudinal study from the Jackson Heart Study found negative associations between $PM_{2.5}$ and blood pressure, while no significant association between $PM_{2.5}$ and hypertension was observed (12). Therefore, no consistent conclusion was reached, and evidence from middle-aged and older adults with higher CVD risks was still scarce. Moreover, most of the published studies were focused on the effects of particulate matter ($PM_{2.5}$, PM_{10}) and NO_2, further studies are needed to determine whether exposure to other air pollutants (such as SO_2, CO) can increase blood pressure and hypertension risk.

Physical activity (PA) has been demonstrated as an effective way against hypertension and other CVDs (13–15).

Numerous studies have found that higher PA levels could reduce blood pressure levels and hypertension risk (16–18). A meta-analysis of cohort studies found that each 10 metabolic equivalents of task (MET) hour/week increase in PA was associated with a 6% decrease in hypertension risk (16). After Liu et al.'s study, a longitudinal study of 12,511 adults from the China Health and Nutrition Survey found that people with higher PA levels had lower hypertension risk and blood pressure (SBP and DBP) levels (18). However, some studies reported inconsistent results (19, 20). For example, a national cross-section study of 18,231 Malaysian adults found that PA level was positively associated with SBP levels, whereas no significant association was observed for DBP level (20). In addition to the uncertainty of results, the majority of studies focused on the separate effect of PA, and litter attention was paid to the effects of PA in different environmental conditions, such as air pollution.

It cannot be ignored that PA also increases the risk of exposure to higher air pollution and leads to higher inhaled air pollutants, which might reduce or even negate the benefits of PA (21). Several studies have examined the joint effects of air pollution and PA on blood pressure (21, 22). For example, a nationwide cohort study of the Prediction for Atherosclerotic Cardiovascular Disease Risk in China (China-PAR) examined the modification effect of long-term exposure to $PM_{2.5}$ in the associations between PA and hypertension incidence and indicated that PA was associated with decreased hypertension only among participants with low $PM_{2.5}$ exposure (22). As for blood pressure, a cohort study of the China Health and Retirement Longitudinal Study (CHARLS) found that exposure to higher $PM_{2.5}$ could attenuate the beneficial effects of PA on blood pressure (21). However, those two studies only examined the modification effects of PA in the associations of air pollution with hypertension and/or blood pressure, the health effects of air pollution on blood pressure and hypertension risk among different PA groups have still not been investigated. Moreover, to our knowledge, those published studies focused on $PM_{2.5}$, the effects of other air pollutants among different PA groups have not been examined, especially gaseous pollutants. Further studies with more air pollutants are warranted to provide more comprehensive evidence of the adverse effects of air pollution on blood pressure and hypertension among different PA groups.

In this study, we aimed to examine the associations of air pollution ($PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO) and PA with three blood pressure components (SBP, DBP, and MAP) and the prevalence of hypertension, and investigate the effects of air pollution on blood pressure and prevalence of hypertension in different PA groups.

2. Methods

2.1. Study population

This study used the data from the China Health and Retirement Longitudinal Study (CHARLS), which is established to collect a wide range of high microdata of middle-aged and older adults.

Detailed description of the CHARLS study has been reported in previous studies (23–25). Briefly, a nationally representative sample of Chinese adults who aged 45 years or older was recruited using a four-stage stratified probability sampling method and participants were recruited from 450 communities, 150 county-level cities in 28 provinces. Four nationwide surveys were conducted in 2011, 2013, 2015, and 2018, respectively. Since blood pressure was only examined in 2011 and 2015, and the estimation of air pollution was mainly performed after 2013, we conducted a cross-sectional study of the CHARLS study wave 3 in 2015. A total of 16,406 participants completed blood pressure examinations. After excluding participants who aged below 45 years, without 3-time blood pressure measurements or air pollution data, 14,622 participants were included in the study.

All participants signed informed consent and the CHARLS was approved by the Institutional Review Board of Peking University (Code: IRB00001052-11015).

2.2. Assessment of air pollution

The concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO were estimated at 0.1 degree (≈10 km) with space–time extremely randomized trees models using ground-based measurements, remote sensing products, and atmospheric re-analysis, and are collected from the ChinaHighAirPollutants (CHAP) dataset.[1] The cross-validation R^2 (root-mean-square error, RMSE) were 0.92 (10.76 μg/m^3), 0.90 (21.12 μg/m^3), 0.84 (10.07 μg/m^3), 0.84 (7.99 μg/m^3) and 0.80 (0.29 mg/m^3) for daily $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO, respectively. Detailed information of the air pollution estimation is described in our previous study (26–29). Annual concentrations of air pollutants of each individual were matched according to their residential cities. Three-year average concentrations of air pollutants were defined as long-term exposure for the main effect models (7, 30, 31), while 2-year average was used in the sensitivity analysis.

2.3. Assessment of PA

PA was estimated using International Physical Activity Questionnaire (IPAQ) via face-to-face interviews. Briefly, the frequency and duration of different intensities activity (including vigorous, moderate, and light intensity) during a week were investigated. PA duration score was calculated as the frequency (times/week) × duration (hour/time). And then PA score was assessed using metabolic equivalent (MET) a: PA score = 8.0 × vigorous PA duration +4.0 × moderate PA duration +3.3 × light PA duration (32, 33). According to the World Health Organization (WHO) recommendation on PA for adults, participants were further categorized into "sufficient PA group (total score of vigorous and moderate PA ≥600 MET-hour/week)" and "insufficient PA group (total score of vigorous and moderate PA <600 MET-hour/week)" (34, 35).

2.4. Blood pressure measurement and definition of hypertension

Three-time SBP and DBP measurements were completed using electronic blood pressure monitors (HEM-7200 Monitor, Omron, Japan). Participants were asked not to eat, exercise, smoke or drink alcohol within 30 min before the blood pressure measurement. MAP was defined as DBP + 1/3 (SBP-DBP) (36). The three-time average blood pressure was used in statistical analysis. Hypertension individual was defined as a participant with SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, having clinical-diagnosed hypertension, or taking anti-hypertension medicine (7, 37).

2.5. Covariates

Numerous potential confounders were included in our study according to previous studies of long-term exposure to air pollution with blood pressure and/or hypertension, including meteorological factors (38–40), sociodemographic variables, socioeconomic variables and health behaviors (7, 41–43). Meteorological factors (temperature and relative humidity) data were available from the China Meteorological Administration.[2] Sociodemographic (age, sex), socioeconomic variables (residence, education, marital status), and health behaviors (smoking and drinking status) were collected via face-to-face interviews (8, 7, 37, 40, 43). Education level was categorized into "elementary school or below," "middle, high, vocational school and associate degree" and "college and above." Marital status was classified into "married and living with a spouse" "married but living without a spouse" or "single, divorced, and widowed" groups. Smoking status was classified into "smoker" and "non-smoker." Drinking status was categorized into "non-drinker," "drink but less than once a month" and "drink more than once a month"(6).

2.6. Statistical analysis

The characteristics of participants were described as mean ± standard deviation (SD) for continuous variables and counts (percentage, %) were described for categorical variables, respectively. The difference of continuous variables between the hypertension group and non-hypertension group was tested using Student's *t*-test, and the distribution discrepancy of categorical variables between the hypertension group and non-hypertension group was examined using Chi-square test (33, 44). The rate in parentheses was represented as percentage of different subgroups in total, non-hypertension, and hypertension groups, respectively.

Generalized linear models (GLMs) were performed to examine the associations of air pollution with blood pressure and the prevalence of hypertension. The results were presented as change in mmHg for blood pressure and odd ratio (OR) for hypertension per inter-quartile range (IQR) increase in air pollutants. We first performed crude model without any

1 Available at: https://weijing-rs.github.io/product.html.

2 http://www.cma.gov.cn/

adjustments. Then, temperature and relative humidity were adjusted in adjusted model 1. Finally, sociodemographic, socioeconomic variables, and health behaviors were additionally adjusted in adjusted model 2.

To further explore the effect of PA on blood pressure/hypertension prevalence and the modification effects of PA in the associations of air pollution with blood pressure and the prevalence of hypertension, a two-stage analysis was developed. We first used GLM models to examine the associations of PA score with blood pressure and prevalence of hypertension. Then, subgroup analysis was performed to examine whether PA score could modify the adverse effects of air pollution on blood pressure and prevalence of hypertension by including an interaction term of air pollution and different PA groups (Sufficient PA group *v.s.* Insufficient PA group) (31, 32).

Sensitivity analysis was also performed to evaluate the robustness of our results based on the full-adjusted model. Firstly, we examined the association of 2-year exposure with blood pressure and the prevalence of hypertension. Then, we excluded participants who were taking anti-hypertension medicine and evaluated whether the associations of air pollution with blood pressure were responsible for anti-hypertension medicine (7, 12, 45). Finally, we performed generalized linear mixed models (GLMMs) and included community ID as a random effect term in the models to adjust the different lifestyle characteristics in different regions.

All the statistical analyses were performed by R version 4.1.2 and the missing data for PA was imputed by using "mice" package (32, 33). A two-tailed p-value < 0.05 was set as statistical significance.

3. Results

3.1. Descriptive statistics

A total of 14,622 participants from 430 communities in 120 county-level cities were included in this study. The distribution of participants in 27 Chinese provinces is shown in Figure 1. A total of 5,191 participants were identified as hypertension cases, with a prevalence of 35.50%. A higher prevalence of hypertension was observed in the insufficient PA group than sufficient PA group. More detailed information about participants is shown in Table 1.

Table 2 presents the descriptive statistics of blood pressure, air pollution, and PA score. The average levels of SBP, DBP, MAP was 128.46 ± 19.86 mmHg, 75.42 ± 11.38 mmHg, 93.10 ± 13.14 mmHg, respectively. Three-year average concentrations of $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO were 61.87 ± 18.60 μg/m^3, 103.13 ± 32.34 μg/m^3, 33.74 ± 14.07 μg/m^3, 31.94 ± 7.61 μg/m^3, 1.28 ± 0.38 mg/m^3, respectively. Person correlation analysis found high co-linearity among different air pollutants (Supplementary Table S1). The average level of PA was 127.07 ± 108.95 MET/h-week.

3.2. Associations of air pollution with blood pressure and prevalence of hypertension

Higher $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO exposure were associated with increased SBP, DBP and MAP in both crude model and adjusted models (Table 3). After adjusting for potential confounding factors, each IQR increase in $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO was associated with 1.20 mmHg (95%CI: 0.69, 1.72), 1.09 mmHg

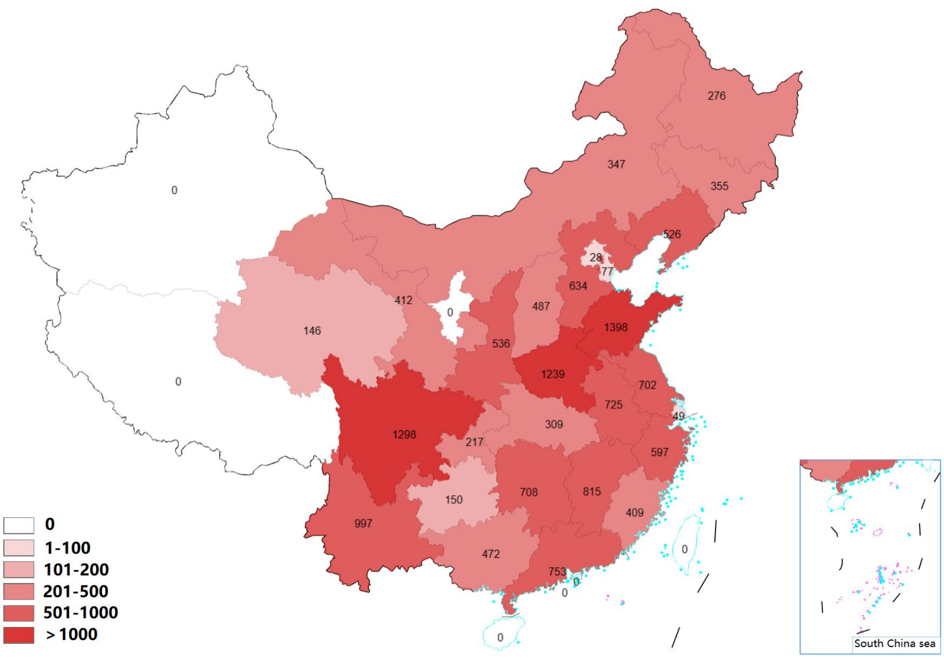

FIGURE 1
The geographical distribution of participants.

TABLE 1 Basic characteristics of the study population.

Characteristics[a]	Total (*n* =14,662)	Non-hypertension (*n* =9,471)	Hypertension (*n* =5,191)	*p*-value[b]
Age, years	60.38 ± 10.05	58.59 ± 9.67	63.64 ± 9.93	<0.001
Age group				<0.001
≥65 years	9,833 (67.1)	2,479 (26.2)	2,350 (45.3)	
Sex[c]				0.121
Male	6,834 (46.6)	4,351 (45.9)	2,483 (47.8)	
Residence				<0.001
Rural	9,074 (61.9)	5,960 (62.9)	3,114 (60.0)	
Education[d]				<0.001
Elementary school or below	2,564 (17.5)	1,620 (22.9)	944 (22.2)	
Middle, High, Vocational school and associate degree	5,427 (37.0)	3,154 (44.7)	2,273 (50.6)	
College and above	3,508 (23.9)	2,255 (31.9)	1,253 (27.9)	
Marital status				<0.001
Married and living with a spouse	12,047 (82.2)	7,964 (84.1)	4,083 (78.7)	
Married but living without a spouse	678 (4.6)	472 (5.0)	206 (4.0)	
Single, divorced, and widowed	1937 (13.2)	1,035 (10.9)	902 (17.4)	
Smoking status[e]				<0.001
Non-smoker	10,023 (68.4)	5,825 (61.5)	4,197 (80.9)	
Drinking status[f]				0.009
Non-drinker	3,899 (26.6)	2,451 (25.9)	1,448 (27.9)	
Drink but less than once a month	1,271 (8.7)	805 (8.5)	466 (9.0)	
Drink more than once a month	9,484 (64.7)	6,211 (65.6)	3,273 (63.1)	
PA categories				<0.001
Sufficient PA	7,754 (53.0)	5,293 (55.9)	2,461 (47.4)	

[a]Mean ± standard deviation for continuous variable, and count (percentage) for categorical variables. The rate in parentheses was represented as percentage of different subgroups in total, non-hypertension, and hypertension participants, respectively.
[b]*p*-value for the mean difference of continuous variable between non-hypertension participants and hypertension participants using Student's *t*-test, and the distribution discrepancy of categorical variables between the hypertension group and non-hypertension group using Chi-square test.
[c]146 missing data existed in sex.
[d]3,132 missing data existed in education.
[e]32 missing data existed in smoking status.
[f]32 missing data existed in drinking status.

(95%CI: 0.58, 1.59), 1.81 mmHg (95%CI: 1.25, 2.38), 1.05 mmHg (95%CI: 0.52, 1.57), 1.44 mmHg (95%CI: 0.98, 1.89) increase in SBP, respectively. Each IQR increase in $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO was associated with 0.66 mmHg (95%CI: 0.36, 0.97), 0.56 mmHg (95%CI: 0.26, 0.85), 0.79 mmHg (95%CI: 0.45, 1.12), 0.54 mmHg (95%CI: 0.24, 0.85), 0.76 mmHg (95%CI: 0.50, 1.03) increase in DBP, respectively. And each IQR increase in $PM_{2.5}$, PM_{10}, SO_2, NO_2 and CO was associated with 0.84 mmHg (95%CI: 0.49, 1.19), 0.73 mmHg (95%CI: 0.39, 1.08), 1.13 mmHg (95%CI: 0.74, 1.52), 0.71 mmHg (95%CI: 0.35, 1.06), 0.99 mmHg (95%CI: 0.68, 1.29) increase in MAP, respectively.

Exposure to air pollution was associated with increased prevalence of hypertension. After fully adjusting for potential confounders, each IQR increase in $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO was associated with 20.7% (OR = 1.207, 95%CI: 1.137, 1.281), 18.9% (OR = 1.189, 95%CI: 1.122, 1.260), 18.6% (OR = 1.186, 95%CI: 1.112 1.266), 18.6% (OR = 1.186, 95%CI: 1.116, 1.260), 28.8% (OR = 1.288, 95%CI: 1.223, 1.357) increase in the prevalence of hypertension, respectively (Table 3).

3.3. Association of PA score with blood pressure and hypertension

PA score was negatively associated blood pressure and prevalence of hypertension. In the adjusted model, each IQR increase in PA score (161.3 MET/h-week) was associated with an −0.56 mmHg (95%CI: −1.03, −0.09), −0.32 mmHg (95%CI: −0.59, −0.05), −0.33 mmHg (95%CI: −0.64, −0.02) change in SBP, DBP and MAP, respectively. As for the prevalence of hypertension, each IQR increase in PA score was associated with a 5.2% (OR = 0.948, 95%CI:0.899, 0.999) decrease in the prevalence of hypertension (Table 4).

TABLE 2 Descriptive statistics of blood pressure, air pollution, temperature, relative humidity, and PA score.

Variables	Mean	SD	P25	P50	P75	IQR
Blood pressure						
SBP (mmHg)	128.46	19.86	114.00	126.00	140.00	26.00
DBP (mmHg)	75.42	11.38	67.33	74.67	82.67	15.34
MAP (mmHg)	93.10	13.14	83.67	92.11	101.33	17.66
Air pollutants						
$PM_{2.5}$ (μg/m^3)	61.87	18.60	48.64	59.80	74.09	25.45
PM_{10} (μg/m^3)	103.13	32.34	79.77	99.15	120.33	40.56
SO_2 (μg/m^3)	33.74	14.07	23.92	28.27	42.53	18.61
NO_2 (μg/m^3)	31.94	7.61	25.87	30.52	37.03	11.16
CO (mg/m^3)	1.28	0.38	1.01	1.13	1.43	0.42
Meteorological factor						
Temperature (°C)	15.49	4.20	13.87	16.10	18.03	4.16
Relative Humidity (%)	67.49	9.83	61.33	70.00	75.00	13.67
Physical activity (PA)						
PA score (MET/h-week)	127.07	108.95	35.00	92.40	196.31	161.31

3.4. Subgroup analysis by different PA groups for the association of air pollution with blood pressure and hypertension

Exposure to air pollution was associated with increased blood pressure and prevalence of hypertension in both sufficient and insufficient PA group. When comparing the estimated effects in different PA groups, we found that the increased levels of blood pressure and prevalence were all lower in the sufficient PA group than that in insufficient PA group, even if the *P-interaction* was not significant (Table 5).

3.5. Sensitivity analysis

Except for associations of SO_2 with DBP, MAP, and hypertension, the sensitivity analysis using 2-year average concentration of air pollutants showed consistent results (Supplementary Table S2). And the adverse effects of air pollution on blood pressure and the prevalence of hypertension were also observed after excluding the participants taking anti-hypertension medicine (Supplementary Table S3). Sensitivity analysis by including community ID as a random effect term in the GLMM models also showed similar results (except for PM_{10}, and NO_2 with DBP; Supplementary Table S4).

4. Discussion

In this study, we found that long-term exposure to ambient air pollutants was associated with increased blood pressure and the prevalence of hypertension. PA was associated with decreased blood pressure levels and prevalence of hypertension. While the *P-interaction* values were not significant, subgroup analysis by different PA groups showed consistent trend that the estimated effects of air pollution on blood pressure and hypertension were all higher in the insufficient PA group than that in insufficient PA group, suggesting that PA might attenuate the adverse effects of air pollution on blood pressure and hypertension risk. Further studies are warranted to confirm our findings about the health effects of air pollution blood pressure and hypertension risk among people with different PA levels.

Our study suggested that exposure to air pollution was related to increased blood pressure levels and the prevalence of hypertension, which was in line with previous studies (7, 11, 46). For example, A cross-sectional study of 39,259 Chinese rural adults indicated that long-term exposure to $PM_{2.5}$, PM_{10}, and NO_2 could significantly increase the prevalence of hypertension and blood pressure (SBP, DBP, and MAP), except for PM_{10} with SBP (7). Insignificant association between PM_{10} and SBP may be due to limited study regions, population characteristics, and chemical components of PM_{10}. Additionally, we noticed that those studies were mainly focused on the effects of $PM_{2.5}$, PM_{10}, and NO_2, litter attention was paid to other air pollutants. As important products of fossil fuel combustion, the health effects of exposure to SO_2 and CO on blood pressure levels and hypertension should be noticeable (47). Our study indicated that long-term exposure to SO_2 and CO may increase the prevalence of hypertension and blood pressure levels, including SBP, DBP, and MAP, which provided new evidence of adverse effects of SO_2 and CO on cardiovascular system. Several potential biological mechanisms have been proposed to explain the adverse effects of air pollution on blood pressure and hypertension risk. Firstly, air pollution could increase oxidative stress, systemic inflammation and cause autonomic nervous system imbalance (11). Those pathways change would result from endothelial dysfunction (48), thrombotic pathway changes (49), epigenetic changes (50, 51), atherosclerosis (52), and activation of hypothalamic and pituitary–adrenal axis (HPA) (53) and further lead to hypertension risk and blood pressure levels increase (54).

PA is a well-established protective factor against chronic diseases. According to the WHO recommend, adults should take at least 75 min of vigorous PA or 150 min of moderate PA per week to reduce the risk of stroke, hypertension, diabetes and depression (55). Our study also found negative associations between PA with blood

TABLE 3 Associations of air pollution with blood pressure and prevalence of hypertension.

Air pollutants (IQR)	Blood pressure (mmHg and 95%CI)			Hypertension
	SBP	DBP	MAP	OR and 95%CI
$PM_{2.5}$ (25.45μg/m³)				
Crude model	1.34 (0.90, 1.78)***	0.89 (0.64, 1.14)***	1.04 (0.75, 1.33)***	1.227 (1.172, 1.285)***
Adjusted model 1	1.28 (0.75, 1.81)***	0.60 (0.30, 0.91)***	0.83 (0.48, 1.18)***	1.190 (1.125, 1.259)***
Adjusted model 2	1.20 (0.69, 1.72)***	0.66 (0.36, 0.97)***	0.84 (0.49, 1.19)***	1.207 (1.137, 1.281)***
PM_{10} (40.56μg/m³)				
Crude model	1.15 (0.74,1.55)***	0.97 (0.74, 1.20)***	1.03 (0.76, 1.30)***	1.213 (1.163, 1.265)***
Adjusted model 1	1.13 (0.61, 1.66)***	0.53 (0.23, 0.83)***	0.73 (0.38, 1.08)***	1.175 (1.112, 1.242)***
Adjusted model 2	1.09 (0.58, 1.59)***	0.56 (0.26, 0.85)***	0.73 (0.39, 1.08)***	1.189 (1.122, 1.260)***
SO_2 (18.61μg/m³)				
Crude model	1.54 (1.12, 1.97)***	1.21 (0.97, 1.46)***	1.32 (1.04, 1.60)***	1.226 (1.173, 1.282)***
Adjusted model 1	1.95 (1.36, 2.54)***	0.84 (0.50, 1.18)***	1.21 (0.82, 1.60)***	1.212 (1.140, 1.290)***
Adjusted model 2	1.81 (1.25, 2.38)***	0.79 (0.45, 1.12)***	1.13 (0.74, 1.52)***	1.186 (1.112, 1.266)***
NO_2 (11.16μg/m³)				
Crude model	1.46 (0.99, 1.93)***	0.89 (0.62, 1.16)***	1.08 (0.77, 1.39) ***	1.254 (1.193, 1.317) ***
Adjusted model 1	1.35 (0.81, 1.89)***	0.58 (0.27, 0.89)***	0.84 (0.48, 1.19) ***	1.226 (1.158, 1.299) ***
Adjusted model 2	1.05 (0.52, 1.57)***	0.54 (0.24, 0.85)***	0.71 (0.35, 1.06) ***	1.186 (1.116, 1.260) ***
CO (0.42mg/m³)				
Crude model	1.04 (0.68, 1.40)***	0.89 (0.68, 1.09)***	0.94 (0.70, 1.17) ***	1.179 (1.135, 1.223)***
Adjusted model 1	1.17 (0.70, 1.64)***	0.65 (0.39, 0.92)***	0.82 (0.52, 1.13) ***	1.193 (1.136, 1.253) ***
Adjusted model 2	1.44 (0.98, 1.89)***	0.76 (0.50, 1.03)***	0.99 (0.68, 1.29) ***	1.288 (1.223, 1.357) ***

*** For *p*-value < 0.001.

TABLE 4 Associations of PA score with blood pressure and the prevalence of hypertension.

Outcome	Crude model		Adjusted model	
	mmHg/OR and 95%CI	*p*-value	mmHg/OR and 95%CI	*p*-value
SBP (mmHg and 95%CI)	−0.80 (−1.27, −0.32)	0.001**	−0.56 (−1.03, −0.09)	0.019*
DBP (mmHg and 95%CI)	−0.21 (−0.48, 0.06)	0.133	−0.32 (−0.59, −0.05)	0.020*
MAP (mmHg and 95%CI)	−0.41 (−0.72, −0.09)	0.012*	−0.33 (−0.64, −0.02)	0.039*
Hypertension (OR and 95%CI)	0.893 (0.848, 0.939)	<0.001***	0.948 (0.899, 0.999)	0.048*

*For *p*-value < 0.05; **for *p*-value < 0.01; ***for *p*-value < 0.001.

pressure and prevalence of hypertension, which was consistent with the WHO recommendation. Moreover, the benefits of PA on blood pressure and hypertension risk were also reported in previous studies (16, 17, 56). For example, a meta-analysis of 29 cohort studies found that each 10 MET/hour-week increase of PA was associated a 6% (relative risk = 0.94, 95%CI: 0.92, 0.96) decrease in hypertension risk (16). A meta-analysis of 15 randomized controlled trials (RCT) studies indicated that PA significantly reduced 24-h, day-time, and night-time blood pressure of hypertension patients (57). The benefits of PA on blood pressure and hypertension risk might be explained by reducing cardiac output, plasma norepinephrine levels, sympathetic activity, and total peripheral resistance (16, 21).

Our study investigated the effects of long-term exposure to air pollution on blood pressure and prevalence of hypertension in different PA groups and found that the adverse effects of blood pressure and prevalence were lower in the sufficient PA group than that in insufficient PA group. Despite no similar study has been published previously, our findings could be supported by the following aspects. Firstly, several studies investigated the modification effect of air pollution in the associations of PA with blood pressure and hypertension risk and indicated long-term exposure to air pollution could attenuate the beneficial effects of PA on blood pressure and hypertension risk (21, 22). Secondly, several studies reported that PA could attenuate the adverse effects of air pollution on chronic diseases, including metabolic syndrome (32, 58), diabetes (59), CVDs (60) and cognitive function (61). Thirdly, previous studies suggested that exposure to higher levels of air pollution could lead to oxidative stress, systemic inflammation and autonomic nervous system imbalance, and result in declines in immunity stability (62, 63). On the contrary, several studies indicated that PA could improve

TABLE 5 Subgroup analysis by different PA groups for the associations of air pollution with blood pressure and prevalence of hypertension.

Air pollutants (IQR)	SBP		DBP		MAP		Hypertension	
	mmHg and 95%CI	P_{inter}	mmHg and 95%CI	P_{inter}	mmHg and 95%CI	P_{inter}	OR and 95%CI	P_{inter}
$PM_{2.5}$ (25.45 μg/m^3)		0.416		0.570		0.468		0.283
Sufficient PA group (n = 7,754)	1.01 (0.32, 1.70)**		0.58 (0.17, 0.98)**		0.72 (0.25, 1.19)**		1.176 (1.092, 1.268)***	
Insufficient PA group (n = 6,908)	1.36 (0.72, 2.00)***		0.72 (0.35, 1.10)***		0.93 (0.50, 1.37)***		1.241 (1.146, 1.343)***	
PM_{10} (40.56 μg/m^3)		0.696		0.703		0.681		0.210
Sufficient PA group (n = 7,754)	1.00 (0.34, 1.66)**		0.50 (0.12, 0.89)*		0.67 (0.22, 1.12)**		1.157 (1.078, 1.243)***	
Insufficient PA group (n = 6,908)	1.15 (0.54, 1.77)***		0.59 (0.23, 0.95)**		0.78 (0.36, 1.20)***		1.225 (1.136, 1.321)***	
SO_2 (18.61 μg/m^3)		0.832		0.919		0.964		0.542
Sufficient PA group (n = 7,754)	1.85 (1.16, 2.54)***		0.77 (0.36, 1.17)***		1.12 (0.63, 1.60)***		1.169 (1.081, 1.265)***	
Insufficient PA group (n = 6,908)	1.76 (1.05, 2.48)***		0.79 (0.38, 1.21)***		1.13 (0.66, 1.60)***		1.204 (1.110, 1.305)***	
NO_2 (11.16 μg/m^3)		0.680		0.683		0.662		0.211
Sufficient PA group (n = 7,754)	0.93 (0.21, 1.65)*		0.47 (0.05, 0.90)*		0.62 (0.13, 1.12)*		1.149 (1.064, 1.241)***	
Insufficient PA group (n = 6,908)	1.12 (0.46, 1.78)***		0.58 (0.19, 0.97)**		0.76 (0.31, 1.21)***		1.229 (1.130, 1.335)***	
CO (0.42 mg/m^3)		0.375		0.228		0.259		0.655
Sufficient PA group (n = 7,754)	1.27 (0.69, 1.84)***		0.63 (0.29, 0.97)***		0.84 (0.45, 1.23)***		1.276 (1.197, 1.361)***	
Insufficient PA group (n = 6,908)	1.58 (1.02, 2.14)***		0.88 (0.55, 1.20)***		1.11 (0.73, 1.49)***		1.299 (1.216, 1.389)***	

*For p-value < 0.05; **for p-value < 0.01; ***for p-value < 0.001.

immune responses to lower chronic low-grade inflammation and improve immune markers in several disease conditions (62, 64, 65).

Some limitations should be mentioned in our study. Firstly, since blood pressure were only measured in 2011 and 2015, and air pollution was estimated after 2013 in our study, longitudinal study was not conducted. The cause-and-effect of the associations with blood pressure and hypertension still needs further research. Secondly, anti-hypertension medication use might also affect blood pressure. However, the results of excluding anti-hypertension treatment participants indicated that our findings were robust (7). Thirdly, muti-pollutant models were not developed due to the high co-linearity of air pollutants (66). Fourthly, similar to previous studies of long-term effects of air pollution on blood pressure, blood pressure was assessed using three-time average levels in single day, which might cause some bias. Further studies with precise measurement of the individual's true blood pressure levels are needed to confirm our results. Fifthly, lifestyle and other potential confounders were not investigated in CHARLS, which might also influence blood pressure. However, in order to adjust the difference of lifestyle characteristics in different regions, we conducted sensitivity analysis by including the community ID as a random effect term and the results showed good consistency. Finally, although subgroup analysis by different PA groups showed consistent trends, the *P-interaction* was not significant. Further studies are warranted to confirm our results.

5. Conclusion

In conclusion, exposure to higher air pollution and lower PA are associated with increased blood pressure level and the prevalence of hypertension. The adverse effects of air pollution on blood pressure and prevalence of hypertension are lower in sufficient PA group than insufficient PA group, suggesting that PA might attenuate the adverse effects of air pollution on blood pressure and hypertension risk. Further studies are needed to confirm our findings about different effects of air pollution on blood pressure and hypertension among people with different PA levels.

Data availability statement

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

Ethics statement

All participants signed informed consents and the CHARLS was approved by the Institutional Review Board of Peking University (Code: IRB00001052-11015). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZN, SH, and JZ: conceptualization. JZ, FZ, JW, and ZD: data curation. JZ, FZ, ZN, and ZD: formal analysis. SH: funding acquisition. JZ, FZ, CX, XZ, and ZD: investigation. ZN and SH: methodology, supervision, and writing–review and editing. JZ, FZ, CX, and XZ: project administration. JZ and ZN: resources. JZ and FZ: software and roles and writing–original draft. ZN: validation. JZ, FZ, and ZN: visualization. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1137118/full#supplementary-material

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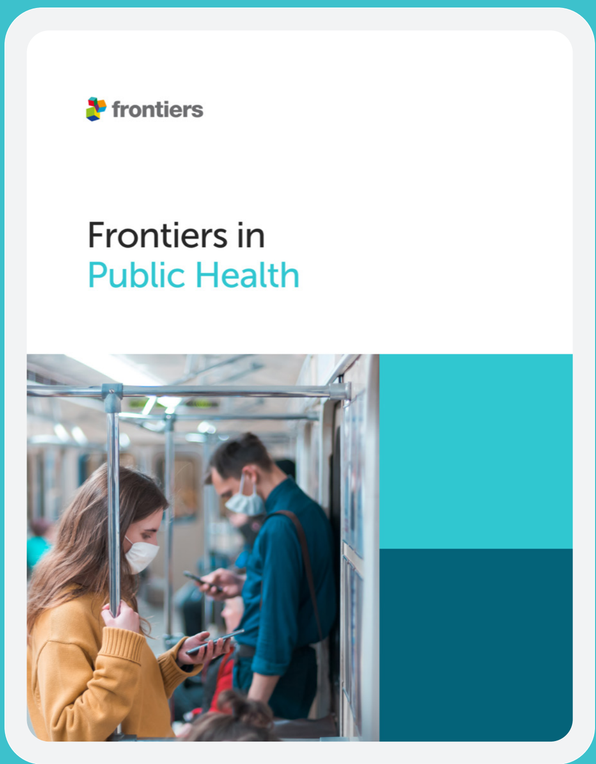

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