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Air pollution as a risk factor affecting human health and economic costs

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Editorial: Air pollution as a risk factor affecting human health and economic costs

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Editorial on the Research Topic
Air pollution as a risk factor affecting human health and economic costs

This Research Topic focuses on the critical topic of air quality and its impact on public health, sustainable development, and economic growth. Air pollution is a significant global challenge, considered by the World Health Organization as a top environmental health risk. The Global Burden disease estimates that air pollution caused 6.7 million premature deaths worldwide (Fuller et al., 2022), ultimately leading to economic loss (World Bank, 2022). The 17 articles included in this Research Topic provide valuable insights into the inter disciplinary aspects of air pollution, offering innovative research, methodologies, and findings that contribute to the scientific understanding of this complex issue.

Air quality is of utmost importance as it directly influences human health, standards of living, healthcare costs, and the economies of nations. The World Health Organization (WHO) (Ambient outdoor air pollution, 2024) has recognized the detrimental effects of air pollution on public health, leading to millions of premature deaths each year (Babatola, 2018; Fuller et al., 2022; McDuffie et al., 2021). More specifically, air pollution has been linked to respiratory diseases, cardiovascular diseases, neurological disorders, and has a disproportionate impact on vulnerable populations such as children and the elderly (Yin et al., 2021). Therefore, understanding the sources and impacts of air pollution is crucial for developing effective strategies to mitigate its effects and improve public health and wellbeing (McDuffie et al., 2021; Reis et al., 2022). They have also been proven to be one of the potential causes of reduced intelligence and accelerated aging, as they promote neurodegenerative conditions (Zhang et al., 2018).

The 17 articles in this Research Topic cover a wide range of topics related to air quality, including the assessment of air pollution across European countries, the economic growth and pollutant emissions, the comparative risk assessment of behavioral, environmental, and occupational risks for various countries, and the spatial effects of economic growth, energy consumption, and environmental pollution in the provinces of China. Additionally, the articles explore the integration of the three dimensions of sustainable development, the evaluation of life-integrated bioelectrochemical-constructed wetland systems, and the

application of statistical methods in the construction of a model for identifying the combustion of waste in heating boilers (Liu et al.; Xiao et al.; Bielenia and Podolska; Liu et al.; Xiao et al.; Chou et al.; Colombo et al.; Enyew et al.; Jasińska-Biliczak and Ikwuwunna; Kim et al.; Sun et al.; Wang et al.; Xu et al.; Ye and Tao; Zhang et al.; Tsai et al.; Xia et al.).

Several articles focus on the specific challenges and initiatives in addressing air pollution in the European Union, particularly in the Po Valley, which is considered one of the most critical hotspots for pollution in Europe. The studies highlight the need for targeted policies, regional cooperation, and the reduction of emissions from industrial sources to improve air quality and public health. Furthermore, the articles emphasize the importance of aligning air quality standards with WHO recommendations and the development of progressive strategies to reduce air pollution and its impact on health and natural ecosystems.

The findings and methodologies presented in these articles contribute to a deeper understanding of the sources, impacts, and management of air pollution, providing valuable insights for policymakers, researchers, and practitioners. The research in this Research Topic offers innovative approaches, such as the use of decision support models, spatial econometrics models, and bioelectrochemical-constructed wetland systems, to assess air quality and its economic and health implications. The articles also highlight the importance of integrating scientific, educational, and production efforts to address air pollution and promote sustainable development.

The case in China illustrates a clear positive correlation between economic growth and industrial pollution. Industrial pollution accompanies the growth of foreign direct investment (FDI), which, in turn, promote economic growth, adversely affecting the environment. This aspect was extensively analyzed in the article: “Evaluation of the triangle-relationship of industrial pollution, foreign direct investment, and economic growth in China’s transformation”. While the peculiarities of China’s economy are different from other markets, they certainly illustrate a trend that can be replicated in other countries and should serve as a warning to other governments that are shaping environmental policies and the relationship between foreign investment and the consequences of industrial development on pollution emissions (Zhang et al.). Departing from traditional research, this study delves into the intricate interactions between industrial pollution, FDI, and economic growth in China. Using a dynamic simultaneous equation model, it reveals the dual role of FDI in promoting economic growth and contributing to environmental degradation. Policymakers are urged to optimize industrial structure for sustainable development.

Differences in shaping the consequences of economic growth exist not only between countries, but even within countries, depending on the province. China, whose economy has grown rapidly in recent years and at the expense of high consumption of raw materials and energy, is experiencing economic stratification between the provinces. Provinces closer to the coast represent the more developed part of the country, which at the same time better combines economic development with public health development. Central and western provinces are less effective in shaping tools to control economic growth, health, and air quality to a lower degree. ‘These results are presented in the article The dynamic relationship among economic development, air pollution, and health production in China: the DNSBM efficiency model, which analyzed as many as 30 Chinese provinces over a 5-year period’. A mature mathematical model was created to analyze seemingly disparate parameters such as economic development, health quality and air quality (Ye and Tao). This study addresses the intricate relationships between economic development, air pollution, and health in China. The research spans from 2015 to 2020 across 30 Chinese provinces. The findings emphasize the need for improved efficiency in the transition from economic production to health outcomes, highlighting disparities among regions and the importance of tailored policies for sustainable development. The study is important in advancing the knowledge of the distributional effects of air quality, linking economic development and air quality issues to public health.

Although studies show a positive relationship between economic growth and air pollution (Ye and Tao; Zhang et al.), there is at the same time a legitimate concern that, as a further consequence, air pollution could have such far-reaching negative consequences that it would even threaten economic growth. The consequences of air pollution can affect many aspects of life on the planet, not only directly related to human health, but also the quality of life of other species, or the productivity of crops. While rapid and uncontrolled industrialization may be the cause of deteriorating air quality, in the aftermath, this reduction in quality can contribute to risks affecting the rate of economic growth. Lower population health can lead to reduced productivity, as well as more frequent absenteeism, due to deteriorating health (Jasińska-Biliczak and Ikwuwunna). A key challenge facing modern society, therefore, is to reduce harmful emissions in or-der to minimize the pressure of transportation on air pollution, as well as health. The impact of air pollutants, which are largely emitted by road transport, has been repeat-edly highlighted in the impact on the phenomenon under study. In particular, these are nitrogen oxides and particulate matter. In this regard, it would be necessary to expand the infrastructure that takes road traffic out of the agglomeration. An-other investment to improve the current situation should be to increase the green fleet of public transportation (Czechowski et al., 2022).

It is the health consequences for society that are the focus of this issue. Understanding the causes of the air pollution phenomenon is important for policies to manage it and find potential solutions. In order to implement appropriate measures, it is important to determine the consequences that result from the adverse composition of the air, including the presence of particulate matter. Determining the causality of air pollution on health is a very difficult issue and requires many years of cross-sectional studies. Such studies have been carried out in a number of geographic locations on different samples of study participants and have diagnosed a number of potential problems that are direct or indirect consequences of poor air quality.

Studies on the effects of particulate matter on the quality of respiratory function were conducted in China on a sample of men and women. Differences in impact were shown by gender and types of particulate matter, but indicated significant positive relationships between exposure to inhaled particulate matter and the development of certain respiratory abnormalities (Liu et al.). Examining the impact of different-sized particulate matter on pulmonary function, this study spans South and North China, encompassing

1,592 participants. The results underscore significant associations between ambient PM exposure and reduced lung function, emphasizing the need for region-specific considerations in air quality management and respiratory health promotion. Individual studies conducted in different scientific fields (social economics and medicine) can mutually reinforce each other's formulated conclusions, leading to unambiguous conclusions regarding the causes of health deterioration and its consequences, beyond biological measures.

Further research into the impact of air quality on health, lead to the discovery of numerous links between air conditions and the risk of developing diseases of civilization, including cardiovascular diseases (CVDs). The findings are described within the article Causality of Particulate Matter on Cardiovascular Diseases and Biomarkers (Wang et al.). Addressing the limitations of observational studies, this research employs Mendelian randomization to explore the causality between particulate matter (PM) and cardiovascular diseases (CVDs) and biomarkers. The findings suggest a significant causal relationship between PM2. 5 and myocardial infarction, heart failure, and lipid traits. The study emphasizes the necessity of ongoing efforts in air pollution abatement for preventing cardiovascular diseases.

Attention should be paid to additional non-environmental risk factors that may enhance the negative effects of poor air quality. The original research study on smoking cigarettes discusses a study conducted in Taiwan to investigate the potential joint effects of cigarette smoking and exposure to particulate matter (PM2.5) on the risk of metabolic syndrome (MS) in adults. The study included 126,366 Taiwanese adults between 30 and 70 years old with no history of cancer. The researchers analyzed data from the Taiwan Biobank and the Taiwan Environmental Protection Administration to assess the prevalence of MS based on PM2.5 exposure and cigarette smoking. The findings indicated a significant association between higher PM2.5 levels and an increased risk of MS, with odds ratios ranging from 1.058 to 1.185 for different PM2.5 quartiles. Additionally, the risk of MS was significantly higher among former and current smokers, with odds ratios of 1.062 and 1.531, respectively, suggesting a dose-dependent relationship. The interaction between PM2.5 and cigarette smoking regarding MS was also found to be significant. Stratified analyses revealed a higher risk of MS due to PM2.5 exposure among nonsmokers, and current smokers were observed to have a higher risk of MS regardless of PM2.5 levels. The study concluded that PM2.5 and cigarette smoking independently and jointly contribute to a higher risk of MS, with the combined exposure of both factors compounding the risk of MS.

The study also provides essential background information on metabolic syndrome (MS), emphasizing its public health impact and association with various chronic diseases, including cancer, stroke, diabetes, and cardiovascular diseases. It highlights the contributing factors to MS, including age, unhealthy diet, obesity, alcohol consumption, physical inactivity, cigarette smoking, and exposure to PM2.5. Moreover, it discusses the significant role of cigarette smoking as a preventable promoter of global cardiovascular mortality and morbidity and its controversial association with MS. Similarly, it underscores the urgent global public health concern of air pollution, particularly PM2.5, and its significant impact on neurological and cardiovascular morbidity and mortality. The paper mentions conflicting findings regarding the relationship between PM2.5 and MS in various studies, emphasizing the need for robust investigations on the combined effect of PM2.5 and cigarette smoking on MS.

The significant findings of the study were presented, including the prevalence of MS based on PM2.5 exposure and cigarette smoking, as well as the interaction between these factors regarding MS. Additionally, the demographic characteristics of the study participants were summarized, highlighting the differences in PM2.5 exposure, cigarette smoking status, and other variables between individuals with and without MS.

In summary, the study provides crucial insights into the independent and joint associations of PM2.5 and cigarette smoking with the risk of metabolic syndrome in Taiwanese adults, contributing valuable evidence to the understanding of the health effects of air pollution and smoking on metabolic health. The findings underscore the importance of considering both environmental and behavioral factors in public health interventions targeting metabolic syndrome and related chronic diseases.

Many correlations have been detected between health and air pollution. Potentially dangerous observations were made not only on organs, directly related to the respiratory system, but also on semen quality. There have also been studies of correlations between air quality and liver cancer risk.

There is some controversy surrounding the impact of air pollution on semen quality. The meta-analysis of Chinese men explores the potential effects of six pollutants on semen quality. The study identifies associations between PM2.5, PM10, NO2, SO2 exposure and reduced total sperm number and motility. The findings emphasize the necessity of limiting air pollution exposure to protect semen quality (Liu et al.).

Using Mendelian randomization, (Sun et al.) investigates the causal relationship between air pollution and primary liver cancer in European and East Asian populations. While no statistical association is found between air pollution and primary liver cancer, nitrogen oxides show a causal relationship with the biomarker Arginase-1. The study provides valuable insights into the complex interactions between air pollution and liver cancer (Sun et al.). The study conducted a Mendelian randomization (MR) analysis to investigate the causal relationship between air pollution and primary liver cancer in both European and East Asian populations. The study focused on the effects of air pollution, including particulate matter (PM2.5, PM2.5–10, PM10), nitrogen dioxide, and nitrogen oxides, on the risk of primary liver cancer. The results of the MR analysis in both populations did not show any evidence of a causal relationship between air pollution and primary liver cancer risk. This was consistent across multiple methods used in the analysis, and no significant heterogeneity or pleiotropy was found. Additionally, the study examined the association between air pollution and primary liver cancer biomarkers, including Alpha-fetoprotein, Osteopontin, Glypican-3, and Arginase-1. Similarly, the results did not show any causal association between air pollution and these biomarkers. The findings of the study contribute to the understanding of the lack of statistical causality between air pollution and primary liver cancer. The study's conclusions reduce the possibility of clinical relevance and refute the role of air pollution in the etiology of primary liver cancer. These findings complement and update the methodology of several cohort studies that have reached similar conclusions. In

summary, the study provides evidence that air pollution is not statistically causally related to primary liver cancer, and it emphasizes the importance of considering genetic factors and conducting MR analyses to improve the reliability and credibility of research conclusions.

The importance of this issue is that it allows a broad understanding of the causes of the phenomenon, generally described as environmental pollution, and its consequences, especially in terms of the many health implications for society. Studies conducted in various geographic areas, allow far-reaching conclusions to be drawn regarding the consequences of air pollution on the health of society.

Negative health effects resulting from poor air quality do not go unaddressed by relevant decision-making institutions. Numerous actions are being carried out in the context of air pollution management and control, which are analyzed in this Research Topic.

The article "New directions for the realization of SDG given the economic and welfare costs incurred by air pollution" by Jasinska-Biliczak and Ikwuwunna is a valuable addition to the Research Topic of the scientific journal. The subject of the article is particularly relevant to the Research Topic as it addresses the economic and welfare costs associated with air pollution, which is a critical aspect of air quality research. The findings of the study shed light on the impact of air pollution on human health, standards of living, health treatment, and the economies of states, emphasizing the need for new directions in the implementation of Sustainable Development Goals (SDG).

The research employs a comparative and statistical approach, focusing on the particulate matter factor and its implications for workforce productivity, absence from work, mortality, and crop yields. The study also contributes to the knowledge base of factors affecting human development and expands the statistical data based on a comparison between Poland and Germany in air quality tests. The methods used in the study provide a novel approach to understanding air pollution as a focus of research for the realization of SDG.

The main findings of the article highlight the significant impact of air pollution on both economic growth and public health, particularly in emerging economies. The study emphasizes the need for targeted actions to address air pollution and enhance population health, providing valuable insights for policymakers and researchers in the field of air quality research. The research also underscores the importance of aligning air quality standards with the recommendations of the World Health Organization (WHO) to reduce air pollution to levels that are no longer harmful to health and natural ecosystems.

In conclusion, the article presents a comprehensive analysis of the economic and welfare costs incurred by air pollution, offering valuable insights into the complex relationship between air quality, economic growth, and public health. The study's findings and conclusions provide a solid foundation for future research and policy development in the field of air quality and sustainable development.

The Research Topic prefaces as many as two articles that clearly demonstrate the possibilities of reducing emissions and the positive impact of pollution reduction.

An attempt to reduce emissions was made in the Po Valley area of Italy, which can be considered as one of the most polluted areas in europe. The work, "Assessing the Impacts and Feasibility of Emissions Reduction Scenarios in the Po Valley," investigates the feasibility of reducing Pm2.5 precursor emissions by 80% in order to achieve air quality compliance with WHO guidelines in the Po Valley region (Colombo et al.). Despite notable emission reductions of 50% and 80%, the study reveals that recommended pollutant levels are unlikely to be met across most areas of the Po Valley region. Implementing the finest available technologies across various sectors, particularly within the Lombardy region, is insufficient without simultaneous reductions in activity levels such as vehicle miles traveled, energy consumption for heating, and industrial, agricultural, and livestock production. The article also discusses the use of chemical transport models (CTMs) to understand the transport and transformation of air pollutants, providing insight into the sources atubution for pollution and their impact on public health. The study concludes that achieving improved air quality in the Po Valley requires a multifaceted endeavor involving numerous stakeholders and diverse strategies.

Moreover, achieving an 80% reduction in emissions within the Lombardy Region, would necessitate drastic reductions in activities such as vehicle usage, energy consumption for domestic heating, industrial activities, and livestock production. The study emphasizes the challenges of achieving an 80% reduction solely through technical measures and highlights the complexity of meeting air quality limits, which requires the adoption of source-specific emissions standards and the development of comprehensive air quality plans at the national, regional, and local levels.

The article "China's air quality improvement strategy may already be having a positive effect: evidence based on health risk assessment" presents a comprehensive analysis of the impact of PM2.5 pollution on public health in Shandong Province, China (Xu et al.). The study utilized exposure response functions, the cost of illness (COI) method, and the value of statistical life (VSL) method to estimate the health risks and economic losses associated with PM2.5 pollution. The findings revealed that despite a 30 μg/m3 reduction in PM2.5 baseline concentration, there was no significant increase in health risks and economic losses. The study also highlighted the potential positive effects of China's air quality improvement strategies. The authors emphasized the importance of regional difference analysis and long-term assessment for evaluating air quality prevention and control strategies in China. The ultimate goal of reducing population health risks through improved air quality was underscored as a key conclusion of the study. This article provides valuable insights into the effectiveness of air quality improvement strategies and their impact on public health, making it a significant contribution to the field of environmental health research.

All in all, this Research Topic highlights the importance of studying air pollution at local to regional scales across the globe. It adds to the ever-growing body of scientific evidence on the adverse health impacts of air pollution. It demonstrates both the causal effects on human health and the critical need for effective policies to mitigate these effects. Additionally, it emphasizes the importance of incorporating health risks and the impacts of air pollution into the evaluation of environmental policies. This issue speaks directly to decision-makers who are committed to making science-informed decisions.

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Evaluation of the triangle-relationship of industrial pollution, foreign direct investment, and economic growth in China's transformation

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Unlike previous research on foreign direct investment (FDI), economic growth, and pollution, this study focuses on investigating complex interactions specifically. A dynamic simultaneous equation model is adopted, together with the one-step systematic GMM, drawn upon to empirically analyze 30 Chinese provinces between 2006 and 2017. The results show that FDI does promote economic growth in China which, in turn, positively affects FDI. However, FDI inflow and economic growth both have negative environmental effects. A higher level of environmental pollution corresponds with FDI becoming more attractive. In the case of China, therefore, the pollution-haven hypothesis holds weight. Specifically, industrial environmental pollution is found to positively affect economic growth, indicating this growth to fall on the left side of the environmental Kuznets Curve. Accordingly, therefore, policymakers should look to optimize China's industrial structure, guide the inflow of high-quality FDI, and promote healthy and sustainable development under the country's new development philosophy.

KEYWORDS

triangle-relationship, foreign direct investment, industrial pollution, economic growth, China

1 Introduction

FDI brings funds to a host country and stimulates economic growth *via* foreign-funded enterprises that settle in undeveloped regions. For China's "economic miracle," FDI has played a key role in promoting the country's transformation from a planned to a market-oriented economy. Nevertheless, extensive FDI can trigger numerous problems, such as environmental pollution and resource depletion. The inflow of FDI into developing countries and regions where energy consumption industries are highly concentrated has resulted in environmental degradation (Grimes and Kentor, 2003; Shah et al., 2022). In response, some countries have implemented strict environmental protection policies. For instance, the 2030 Climate and Energy Policy Framework agreement stipulates that, by 2030, the EU plans to reduce its greenhouse gas (GHG) emissions by 40%. The United States has also committed to reducing its GHG emissions by half by 2030, as well as confirming a commitment to zero emissions by 2050. Developing countries with low infrastructure levels,

such as Tunisia, Morocco, and Egypt, are more likely to have poor environmental standards. However, despite having environmental protection policies in place, the economic development in China, India, and Vietnam has not seen such policies strictly enforced. These countries mainly receive their FDI from the United States, Japan, and the EU, which can generate a double-edged impact.

Under the impact of a series of major emergencies, such as the complex international situation and the COVID-19 pandemic, global FDI fluctuated sharply. The COVID-19 pandemic has significantly impacted pollution emissions and air quality, ecology, economic development, and FDI (Chossière et al., 2021; Miyazaki et al., 2021; Pei et al., 2021; Su et al., 2021; Syarifuddin and Setiawan, 2022), causing unprecedented economic and social disruption (Azomahou et al., 2021). The impact of the crisis depends mainly on economic conditions and governance before the COVID-19 pandemic (Azomahou et al., 2021). Mukanjari and Sterner (2020) found that establishing formal ESG "climate change policies" does not affect firm performance during the pandemic. Companies with higher carbon intensity were more affected by crisis events. Calls for a green economic recovery have intensified since the COVID-19 pandemic, with events such as the COVID-19 pandemic making it clear that we need to rethink how we live. In response to the impact of significant events such as the COVID-19 crisis, a correct review of the relationship between FDI, economic growth, and industrial pollution will help improve the ability to cope with crises in the social and economic development process and realize the modernization of the country.

From one perspective, scholars confirm a pollution-haven hypothesis (Hoffmann et al., 2005; Acharyya, 2009; Caglar, 2020; Singhania and Saini, 2021). This theory blames FDI for transferring polluting investments to low-income countries in order to reduce production costs. Furthermore, when countries are in the process of expanding their economic scale, they consume more energy and emit more pollutants that gradually damage environmental quality (Sapkota and Bastola, 2017; Shao, 2017). Alternative research, however, finds that FDIs in OECD countries have aggravated CO_2 emissions (Pazienza, 2015), although these factors need to be weighed against the funds, advanced technologies, and knowledge that FDI brings in to drive an economy. Economic growth improves people's living standards, which in turn is conducive to improving environmental quality. All these suppositions lead to the pollution-halo hypothesis (Bergh and Nijkamp, 1994), which theorizes that to abate the negative effects of FDIs some countries have implemented strict environmental regulation policies forcing the use of environmental technologies. The problem with this approach, however, is that the adoption of these technologies only increases FDI costs, thereby generating a crowding-out effect and resulting in economic damages.

In the early 21st century, Asian countries prioritized achieving economic take-off *via* industrialization, rather than addressing environmental problems. Consequently, China's ascendency has shed light on the dynamics at play between FDI, economic growth, and the environment. Given the environmental impact of expanding production scales, economic growth has inevitably led to environmental degradation, with Pakistan being one obvious example of economic development pursued at the expense of its environment (Abbasi and Riaz, 2016; Álvarez-Herránz et al., 2017; Ullah et al., 2022). Other research has explored how the economic growth of 17 countries in the Middle East and North Africa has resulted in a similar negative effect (Abdouli and Hammami, 2017a). China government has begun to shift their focus to improving environmental quality. Such aims, however, may result in conflict with economic development and lead to social issues (Blonigen, 2005; Paul and Singh, 2017).

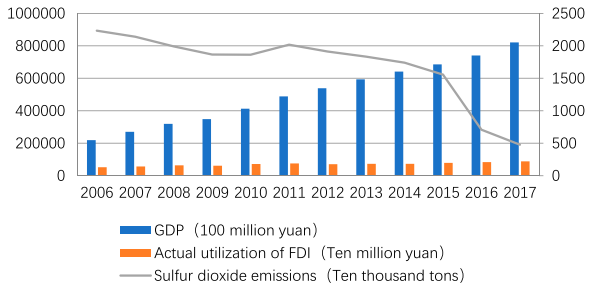

FIGURE 1
China's FDI, industrial pollution, and economic growth.

As a major source of environmental harm, addressing industrial pollution needs prioritizing. The pollutants discharged by industrial enterprises cause serious environmental damage. The 1997 World Bank report China in 2020: Development Challenges in the New Century reveals China to have one of the most serious urban pollution levels in the world, with polluting enterprises and activities estimated to account for 3%–8% of annual GDP. Urbanization inevitably affects environmental quality, with each urbanization stage exerting a different degree of impact.

Figure 1 shows China's economic growth and industrial pollution emissions from 2006 to 2017. To promote green and sustainable development and to comprehensively improve utilization efficiency, China has initiated a green transformation of its economic and social development model. However, the interaction between FDI, economic growth, and industrial pollution is still uncertain. The following questions need to be answered: first, whether China's rapid economic development can be sustained and whether this growth will come at the expense of the environment; Second, whether China's rapid economic development has the potential to attract FDI and whether FDI can become a driving force to promote economic growth; Thirdly, whether FDI inflow improves or worsens China's ecological environment, and whether the more serious environmental pollution is, the more FDI inflow will be attracted. Based on the above considerations, the research objective of this paper is to construct a simultaneous equation model to comprehensively investigate the dynamic evolution characteristics of FDI, industrial pollution, and economic growth in 30 provinces of China during 2006–2017. Furthermore, it explores the interaction effect among the three and provides suggestions on coordinating the relationship between them to achieve green, circular, and sustainable development.

The main contribution of this study to the literature is twofold. Firstly, by combing previous studies on industrial pollution, FDI, and economic growth, the dynamic simultaneous equation model is utilized to evaluate the relationship complexity, including by taking the endogenous problem into consideration. By extending the two-

element analysis framework, a simultaneous equation model is constructed capable of analyzing three elements and evaluating their interactive relationships. Secondly, as previous studies on the relationship between environmental pollution and economic growth mostly conclude that economic growth affects environmental pollution, the GMM method is adopted here to study the bidirectional causality. The results show that FDI does promote economic growth in China which, in turn, positively affects FDI. However, FDI inflow and economic growth both have negative environmental effects. A higher level of environmental pollution corresponds with FDI becoming more attractive. Specifically, industrial environmental pollution is found to positively affect economic growth, indicating this growth to fall on the left side of the environmental Kuznets Curve.

2 Literature review

2.1 Relationship between pollution and FDI

Foreign capital and environmental pollution studies are mainly divided into three streams. The first stream labels FDI's negative effects as resulting from "Pollution Havens" (Copeland and Scott, 1994; Farooq et al., 2023; Pan H et al., 2023; Shah et al., 2023; Wu and Wang, 2023). Some researchers argue that countries have different policies and environmental standards, with developed countries usually adopting stricter environmental control policies and advanced technologies to reduce environmental pollution (Abdouli and Hammami, 2017b). Other research has confirmed that the challenge of attracting foreign investment and achieving rapid economic development has led to some countries avoiding strict environmental regulations (Shahbaz et al., 2015). Indeed, the strategy of embracing low environmental standards for profit has become increasingly obvious as, to reduce costs, foreign companies place investments in countries with relatively loose environmental regulations. These same investments then contribute to environmental deterioration within the host country, which is transformed into a pollution haven. By using the GMM method to investigate 21 high-polluting developed and developing countries between 1990 and 2016, previous studies have shown how FDI can aggravate environmental pollution, especially in developing countries labeled "pollution havens" (Caglar, 2020; Monica and Neha, 2021). This pollution-haven hypothesis is only valid for low-income countries, however. A positive correlation between pollution emissions and FDI in Latin America, for example, has been identified, calling into question whether low-income countries are capable of improving environmental health by attracting clean and energy-efficient industries through FDI. A study by Hadj and Ghodbane (2021), focusing on the effect of FDI on pollution *via* energy consumption, confirmed close links by using fixed and variable effect models, which validated the pollution-paradise hypothesis.

The second stream focuses on the positive effects of the pollution-halo hypothesis, positing that FDI brings advanced technologies and management experience to less developed regions, improving both resource-use efficiency and environmental quality (Pan X et al., 2023; Teng et al., 2023; Wang et al., 2023; Xie et al., 2023; Yilanci et al., 2023). Examining the location choices of United States Fortune 500 companies from 1972 to 1978 shows a greater interest in benefiting from a high-quality environment than having low-level environmental protection (Bartik, 1988). One research examining five Asian countries between 1981 and 2011 found different factors to have heterogeneous effects on carbon emissions (Zhu et al., 2016). So, although FDI can increase carbon emissions, its effect is not always judged significant. The pollution-paradise hypothesis tends to hold in low-emission countries, but in middle-to-high-emission countries FDI can be conducive to the overall reduction of carbon emissions. Utilizing a dynamic panel data model with generalized moment's estimation for 54 countries between 1990 and 2011 showed that an increase in carbon dioxide emissions will lead to a decrease in FDI inflows (Omri et al., 2014). Hence, FDI flowing to industrialized economies was beneficial to developing countries and conducive to the improvement of China's environmental quality (Ashraf et al., 2020). A causal relationship has been found between FDI and PM2.5 pollution in 11 emerging countries and regions, with the overall effect of FDI on PM2.5 negative, thereby supporting the pollution-halo hypothesis (Xie and Sun, 2020).

The third stream argues that FDI has an uncertain environmental impact (Guo et al., 2023). On the one hand, FDI aggravates environmental pollution *via* scale and structural effects. On the other, FDI reduces environmental pollution *via* technological effects, which differ for capital- and labor-intensive industries. One study analyzed China's FDI and sulfur dioxide emissions, finding these factors to have an inverted U-shaped relationship and that technology adoption increases coal consumption but does not reduce sulfur dioxide emissions. Another study compared 65 countries along "the Belt and Road," finding FDI to have a pollution-haven effect in low- and middle-income countries and a pollution-halo effect in high-income countries (Muhammad and Long, 2020; Xu et al., 2020). A Turkish study revealed that an FDI decrease leads to a long-term decline in emission growth rate, thereby confirming the asymmetric pollution-halo hypothesis. However, FDI has no effect on environmental pollution in the five BRIC countries: Brazil, Russia, India, China, and South Africa (Shao et al., 2019).

The impact of FDI on environmental pollution in host countries is controversial and can be divided into three categories: first, the pollution-haven hypothesis; The pollution-halo hypothesis; Third, FDI has both positive and negative impacts on the host country's environment. Such a result is mainly due to scholars' analysis of the relationship between the two from different perspectives, such as specific industries and specific regions.

Accordingly, hypothesis 1 is proposed: there is a positive (negative) relationship between industrial pollution and FDI inflow, which is consistent with the pollution-haven (halo) hypothesis, and FDI leads to higher emissions in places with weak (strong) environmental regulations.

2.2 Relationship between industrial pollution and economic growth

Previous economic growth and environmental pollution studies have mainly focused on the environmental Kuznets curve (EKC),

which assumes an inverted U-curve relationship between economic output and environmental pollution (Omri et al., 2014; Tiba and Omri, 2016; Wu and Wang, 2023). One research avenue argues that environmental pollution increases with economic growth during the early stages of economic development, then decreases with economic growth after the economy reaches a certain level, hence, highlighting the existence of an EKC curve (Isik et al., 2018; Altinoz et al., 2020; Dogru et al., 2020; Alvarado et al., 2021). Some researchers have applied GMM to verify the EKC effect of carbon emissions from 24 emerging economies, finding carbon emissions and economic growth to have an inverted U-shape relationship (Hove and Tursoy, 2019). Other research has used a combined mean group (PMG), panel FMOLS, and panel DOLS to validate the environmental EKC hypothesis for OECD countries. This EKC hypothesis was further validated by the interaction between infrastructure investment in the transportation system and environmental degradation of 21 OECD countries (Erdogan, 2020). Elsewhere, the dynamic link between Pakistan's CO_2 emissions and industrial development was examined for effectiveness, with the variables found to be co-integrated, involving both long- and short-term dynamics that validate the hypothesis (Ali et al., 2021).

An alternative research avenue argues that the EKC curve does not exist (Shah et al., 2023; Farooq et al., 2023). To confirm the hypothesis, therefore, other factors must be considered, such as technological effects, resources, and scale of development. Xie et al. (2023), Khan (2023), and Farooq et al. (2023) found that economic growth has a positive linear relationship with environmental pollution. Within OECD countries, both economic growth and carbon emissions were found to follow a U-shaped relationship (Sohag et al., 2019). Higher levels of economic development, however, contributed to lower levels of pollution emissions, thereby rejecting the EKC hypothesis (Dogan and Inglesi-Lotz, 2020). It was found that CO/CO_2 and NO_2/CO_2 ratios in most developed cities marginally increase along with GDP, but these increase more substantially along with GDP in developing cities, such as Mumbai and Tianjin, whose pollutant emission ratios are very high or even comparable to developed cities (Park et al., 2021). When exploring the effects of economic growth on the use of SO_2, NO_2, and PM2.5 registered air pollutants, researchers found a U- or N-shaped relationship present between GDP *per capita* and air pollutants in eastern, western, and central China. These results suggest that the relationship between air pollutants and economic growth is associated with regional factors and the choice of variables (Xu et al., 2019).

The research on the relationship between economic growth and environmental pollution has not reached a consensus conclusion, mainly including linear and non-linear relationships. Therefore, hypothesis 2 is put forward that there is a positive (negative) relationship between industrial pollution and economic growth, and places with light (severe) pollution will promote (hinder) economic growth.

2.3 Relationship between FDI and economic growth

The relationship between FDI and economic growth has received a great deal of research, one stream of which reveals a positive relationship due to FDI directly promoting economic growth (Romer, 1986; Narteh-Yoe et al., 2022; Asafo-Agyei and Kodongo, 2023; Khan and Imran, 2023). Specifically, FDI inflow increases the host country's capital stock and access to variable funds for financial development, brings in advanced technologies, and promotes economic progression. A higher economic growth sends a positive signal that attracts more FDI (O'Doherty et al., 2003; Jalil and Mahmud, 2009; Saini and Singhania, 2018; Saini and Singhania, 2019).

The Granger causality test has been applied to determine the two-way association between FDI and economic growth within 62 countries between 1975 and 1978, and for 51 countries between 1983 and 1986. The vector error correction model was equipped with an autoregressive distributional lag test to examine the interrelationship among FDI, international trade, and economic growth within 15 selected MENA countries (Kalai and Zghidi, 2019). The results showed the long-standing unidirectional effect of FDI on economic growth. The causal relationship existing among environmental quality, FDI, and economic growth was also analyzed, showing the one-way causal relationship between direct investment stock and economic growth to support the growth hypothesis. In other words, increasing the FDI stock promotes economic growth. By embracing this as a key tool for economic growth, therefore, both developed and developing countries are eager to engage in foreign-to-foreign investment.

Other research finds the relationship between FDI and economic growth to be insignificant or even negative (Pradhan, 2009). As far as its potential (industrial, commercial and financial resources) is concerned, Russia does not attract all the FDI it matches (Fabry and Zeghni, 2002). Economic growth and financial development can develop independently, while FDI cannot affect economic growth by influencing financial development. It has also been argued that FDI can block economic growth by hindering domestic economic development due to lax policies and privatization, with the presence of financial liberalization limiting the role of economic development in attracting FDI inflows (Boyd and Smith, 1992). Furthermore, the OLS method has found no significant short- or long-term relationship between FDI and economic growth in Turkey (Temiz and Gkmen, 2014).

Whether theoretically or empirically, FDI has a positive or negative impact on the host country's economic growth. This impact is related to the host country's development potential. However, the inflow of foreign capital can bring advanced technology and financial support to the host country, which is conducive to economic development. The sustainable economic development of the host country is attractive to the inflow of foreign capital. Therefore, hypothesis 3 is that FDI inflow will promote economic growth, which can attract FDI inflow.

2.4 Relationship between pollution, FDI, and economic growth

FDI accelerates economic development and promotes employment but is also a double-edged sword in that its effects may be negative too, such as with environmental

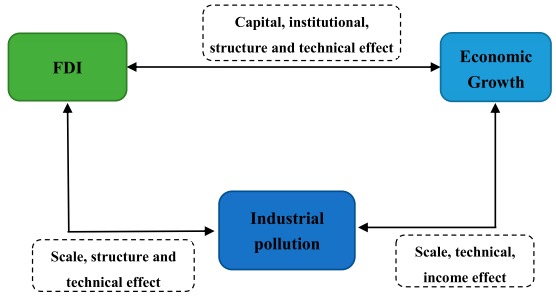

FIGURE 2
The interrelationship of FDI, economic growth, and industrial pollution.

pollution and damage (Bildirici and Çoban Kayıkçı, 2023). An empirical study analyzed the relationship between FDI, economic growth, and pollution for 14 Latin American countries, based on time series data from 1980 to 2010, concluding FDI to be positively associated with environmental pollution, thereby supporting the EKC hypothesis (Sapkota and Bastola, 2017). The researchers added that Latin America should focus on FDI policies that attract clean and energy-efficient industries with the potential to improve environmental health and promote economic growth. This theoretical analysis reveals a complex interrelationship that should be further explored, while the existing problems also need to be addressed to enable further economic development. Accordingly, strategies for managing a healthy relationship between FDI and environmental protection have become a key research problem.

In response, researchers should systematically investigate the influencing mechanisms among the key factors. Specifically, the relationship between FDI and environmental pollution should be further analyzed based on the pollution-haven and pollution-halo hypotheses, which point to the presence of scale, structural, and technology effects as defining (Behera and Dash, 2017; Liu, et al., 2019; Caglar, 2020). The EKC curve model illustrates the interactions between economic growth and pollution *via* the effects of scale, technology, income, and policy (Brock and Taylor, 2005; Lin et al., 2016). Meanwhile, the capital, technology, institutional, and structural effects between FDI and economic growth should be understood based on economic growth theory (Welela, 2018).

In short, many studies have examined the relationship between FDI and environmental pollution, economic growth and FDI, and FDI and economic growth. However, only some studies have analyzed the impact of environmental pollution on economic growth. Moreover, the relationship between the three is complicated (as shown in Figure 2 below), so putting them into the same framework and studying their mutual relationship is necessary. Therefore, this paper constructs a simultaneous equation model and uses the GMM method to evaluate the dynamic evolution characteristics and interaction effects of FDI, economic growth, and industrial pollution in the era of comprehensive green economic and social development transformation.

3 Models and data

3.1 Simultaneous equation models

As shown in previous studies investigating interactions between industrial pollution, FDI, and economic growth, a single regression analysis cannot comprehensively portray the interrelationships. Plus, using the Cobb–Douglas (C–D) production function form to build a simultaneous equation model cannot solve the endogeneity problem caused by two-way causality (Omri et al., 2014; Liu et al., 2018). The basic form of the C–D production function is $Y = AK^{\alpha}L^{\beta}$, which, after introducing environmental pollution and FDI into the economic growth equation, is transformed into the following (Ang, 2008; Anwar and Sun, 2011):

$$Y = AK^{\alpha}P^{\lambda}(FDI)^{\psi}L^{\beta} \tag{1}$$

Where Y denotes economic growth, A denotes total factor productivity, L denotes labor force, K denotes capital stock, and FDI denotes the actual amount of FDI utilized. At this point, we have $\alpha + \lambda + \psi + \beta = 1$. Following previous literature, total factor productivity (A) is excluded from the model to avoid multicollinearity, and both sides of Eq. 1 are simultaneously divided by labor force (L) and logarithmically processed to obtain the following economic growth equation:

$$\ln\left(\frac{Y}{L}\right)_{it} = \alpha_0 + \alpha_1 \ln\left(\frac{FDI}{L}\right)_{it} + \alpha_2 \ln\left(\frac{P}{L}\right)_{it} + \alpha_3 \ln\left(\frac{K}{L}\right)_{it} + \varepsilon_{it} \tag{2}$$

Where i and t denote the situation of the ith province in year t. By setting output *per capita* $y = \frac{Y}{L}$, capital stock *per capita* $k = \frac{K}{L}$, FDI *per capita* $fdi = \frac{FDI}{L}$, and pollutant emissions *per capita* $p = \frac{P}{L}$, Eq. 2 can be written as Eq. 3:

$$\ln(y)_{it} = \alpha_0 + \alpha_1 \ln(fdi)_{it} + \alpha_2 \ln(p)_{it} + \alpha_3 \ln(k)_{it} + \varepsilon_{it} \tag{3}$$

According to economic growth theory, capital stock (K) is an important factor. Plus, in addition to sulfur dioxide emissions, FDI, and GDP *per capita*, economic growth may be affected by population size (pop), technology level (tec), government intervention (gov), and trade openness ($open$). These control variables are added to Eq. 3 as part of the econometric analysis to control for their effects on the dependent variable. Eq. 4 is an economic growth model that describes the effects of industrial pollution (P), FDI, and control variables [6, 22, 63]:

$$\begin{aligned}\ln(y)_{it} = {} & \alpha_0 + \alpha_1 \ln(fdi)_{it} + \alpha_2 \ln(p)_{it} + \alpha_3 \ln(k)_{it} + \alpha_4 tec_{it} \\ & + \alpha_5 \ln(pop)_{it} + \alpha_6 gov_{it} + \alpha_7 open_{it} + \varepsilon_{it}\end{aligned} \tag{4}$$

P and Y affect FDI at a certain level, and FDI considers production costs, such as workers' wages and human capital level (hum). According to international trade theory, labor cost is an important measure of a country's comparative advantage, which China has been attracting foreign investment with. However, given that pollution control level (reg) and trade openness ($open$) are two other important factors that influence FDI, they are used as control variables in the pollution model to obtain the following equation (Wang and Chen, 2014):

$$\begin{aligned}\ln(fdi)_{it} = {} & \beta_0 + \beta_1 \ln(y)_{it} + \beta_2 \ln(p)_{it} + \beta_3 \ln(wage)_{it} + \beta_4 reg_{it} \\ & + \beta_5 open_{it} + \beta_6 \ln(hum)_{it} + \nu_{it}\end{aligned} \tag{5}$$

Another equation is established to describe the effect of *FDI* and economic growth (*Y*) on industrial pollution (*P*). Given that the pollution level is also closely related to environmental regulation (*reg*), technology level (*tec*), urbanization level (*urb*), trade openness (*open*), and industrial structure (*str*), all of these variables are added to Eq. 6 as control variables. The following industrial pollution model is then obtained (Dogan and Inglesi-Lotz, 2020; Li et al., 2020):

$$\ln(p)_{it} = \gamma_0 + \gamma_1 \ln(fdi)_{it} + \gamma_2 \ln(y)_{it} + \gamma_3 tec_{it} + \gamma_4 reg_{it} + \gamma_5 urb_{it} + \gamma_6 open_{it} + \gamma_7 str_{it} + \mu_{it} \quad (6)$$

One period of dependent variable lag level (i.e., economic growth, FDI inflow, and industrial pollution) can affect current levels. The lag term of the dependent variables, therefore, is introduced in Eq. 4–6 to construct the following dynamic simultaneous equation models:

$$\begin{cases} \ln(y)_{it} = \alpha_0 + \alpha_1 \ln(y)_{it-1} + \alpha_2 \ln(fdi)_{it} + \alpha_3 \ln(p)_{it} + \alpha_4 \ln(k)_{it} + \alpha_5 tec_{it} + \alpha_6 \ln(pop)_{it} + \alpha_7 gov_{it} + \alpha_8 open_{it} + \varepsilon_{it} \\ \ln(fdi)_{it} = \beta_0 + \beta_1 \ln(fdi)_{it-1} + \beta_2 \ln(y)_{it} + \beta_3 \ln(p)_{it} + \beta_4 \ln(wage)_{it} + \beta_5 reg_{it} + \beta_6 open_{it} + \beta_7 \ln(hum)_{it} + \nu_{it} \\ \ln(p)_{it} = \gamma_0 + \gamma_1 \ln(p)_{it-1} + \gamma_2 \ln(fdi)_{it} + \gamma_3 \ln(y)_{it} + \gamma_4 tec_{it} + \gamma_5 reg_{it} + \gamma_6 urb_{it} + \gamma_7 open_{it} + \gamma_8 str_{it} + \mu_{it} \end{cases} \quad (7)$$

3.2 Variables selection

Economic growth is expressed in terms of GDP and converted to actual values by using CPI, taking 2006 as the base period. Industrial pollution (*P*) is expressed as industrial sulfur dioxide emissions, while FDI is expressed as the actual amount of FDI utilized by each region, which is initially converted to RMB using the annual average exchange rate of USD to RMB, then converted to actual 2006 values by using CPI.

Among the control variables, capital stock is calculated as follows using the perpetual inventory method: $K_{it} = (1 - \delta_{it})K_{it-1} + I_{it}$, where K_{it} denotes the total fixed asset formation in city i in year t and takes 2006 as the base period, while δ_{it} is the depreciation rate and takes a fixed value of 9.6%. Meanwhile, labor force (*L*) is expressed as the average number of employees on the job, technology level (*tec*) is expressed as the ratio of national internal expenditure on R&D funds to GDP, population size (*pop*) is expressed as the total population at the end of the year, and government intervention (*gov*) is expressed as the GDP share of government general public budget expenditure.

The level of openness to the outside world (*open*) is expressed as the share of total imports and exports of goods in regional GDP, *wage* is expressed as the average wage, environmental regulation level (*reg*) is expressed as the investment in environmental pollution control as a share of GDP, urbanization level (*urb*) is measured by the share of urban population, human capital level (*hum*) is expressed as the average number of students in higher education per 100,000 population, and industrial structure (*str*) is expressed as secondary industry share (Soytas et al., 2007; Zhu L et al., 2019; Zhu W et al., 2019).

Considering the availability, reliability, and accuracy of the data, this study selected the panel data of 30 provinces and cities in China from 2006 to 2017 for empirical analysis (Tibet was excluded due to missing data) as the observation object, while individual missing data were supplemented according to the mean value method. All data are obtained from the *Wind* database, China Statistical Yearbooks, China Environmental Statistical Yearbooks, China Urban Statistical Yearbooks, China Social Statistical Yearbooks, and the statistical yearbooks of provinces and cities. The symbols, names, and unit attributes of the above statistical variables are specified in Table 1.

3.3 Estimation methods

Given that explanatory variables with one-period lag are included in Eqs 4–6, using the classical OLS approach may lead to biased estimation results. Meanwhile, the generalized method of moments (GMM) can address the endogeneity problem in the models and obtain consistent estimates (Bond, 2002; Hille, 2018; Hashmi and Alam, 2019).

GMM offers two advantages for this study. Firstly, *per capita* pollutant emissions, *per capita* foreign direct inflows, and *per capita* GDP may be determined at the same time. Dynamic panel GMM can effectively control the endogeneity of the explanatory variables by selecting appropriate instrumental variables (Çoban and Topcu, 2013). Secondly, when the unobservable variables are related to explanatory variables or when some influencing factors are omitted, GMM uses differential conversion data to overcome the problem of missing variables. System GMM (SYS-GMM), which includes one- and two-step GMM, is used because the weight matrix of the two-step estimation depends on the estimated parameters and the standard deviation is biased downward, which provides neither significant efficiency improvements nor reliable estimators (Arellano and Bond, 1991; Arellano and Bover, 1995; Monica and Neha, 2021). To test the rationality of the estimation method, the results of one-step difference GMM and one-step SYS-GMM are also presented.

4 Results and discussion

4.1 Panel unit root tests

Given that this article uses large N small T panel data, the HT method is used in the panel unit root test to avoid the regression phenomena in the regression process and to ensure that the results are unbiased and effective. The test results are shown in Table 2.

The three indexes of the original sequence *ln(pop)*, *tec*, and *urb* are non-stationary variables, whereas the other variables are stable. However, after the first-order difference, each variable becomes stable. The next step, therefore, is to test for a long-term co-integration relationship among the variables.

4.2 Panel co-integration tests

Kao test is performed to test the co-integration among economic growth, FDI, and sulfur dioxide emissions for each influence factor. Table 3 reveals the *p*-values of each equation variable with economic

TABLE 1 Type, definition, and descriptive statistics of variables.

Type	Variable	Units of measurement	Mean	Max	Min	Std. Error
Endogenous variable	*y* (GDP *per capita*)	Chinese Yuan/person	331,533	728,251	3,096	108,731
	p (Industrial sulfur dioxide emissions *per capita*)	Tons/person	0.1940	0.8960	0.0005	0.1830
	fdi (Per capita actually utilized FDI)	Chinese Yuan/person	0.7770	4.1240	0.0065	0.6920
Exogenous variable	*k* (Net value of fixed assets *per capita*)	Chinese Yuan/person	1,294,000	4,069,000	11,241	593,531
	hum (Average number of students in colleges and universities per 100,000 population)	Person	2,404	6,897	903.9000	974.1000
	pop (Total population at the end of the year)	10,000 people	4,467	11,169	548	2,678
	L (Average number of employees)	Person	5,445,000	370,400,000	210,900	19,570,000
	urb (Proportion of urban population)	Percentage	53.4900	89.6000	27.4600	13.7400
	tec (The ratio R&D expenditure to GDP)	Percentage	1.4520	6.0100	0.2000	1.0650
	gov (The government's general public budget expenditure as a proportion of GDP)	Percentage	0.2220	0.6270	0.0837	0.0963
	open (The proportion of total import and export of goods in GDP)	Percentage	0.2960	1.6680	0.0116	0.3360
	reg (Investment in environmental pollution control as a proportion of GDP)	Percentage	1.3720	4.2400	0.3000	0.6880
	wage (Average on-the-job salary)	Chinese Yuan	36,388	103,347	357.5000	14,778
	str (Proportion of secondary industry)	Percentage	46.2700	59.3000	19.0000	8.1070

Note: All data are obtained from the *Wind* database, China Statistical Yearbooks, China Environmental Statistical Yearbooks, China Urban Statistical Yearbooks, and China Social Statistical Yearbooks.

TABLE 2 Results of the HT unit root test of variables.

Variable	Original sequence	First order differential
ln(y)	(0.0000)	(0.0000)
ln(fdi)	(0.0000)	(0.0000)
ln(p)	(0.0000)	(0.0000)
ln(k)	(0.0000)	(0.0000)
ln(L)	(0.0000)	(0.0000)
tec	(0.8618)	(0.0000)
ln(pop)	(0.4258)	(0.0000)
gov	(0.9998)	(0.0007)
(open)	(0.1363)	(0.0049)
ln(wage)	(0.0000)	(0.0000)
reg	(0.0000)	(0.0000)
lnhum	(0.0084)	(0.0000)
urb	(0.4584)	(0.0000)
str	(0.9556)	(0.0000)

Notes: The estimated *p*-values are enclosed in parentheses.

growth, FDI, and SO_2 emissions to be less than 0.1, which passes the significance test and so indicates the presence of a long-term co-integration relationship among economic growth, FDI, and SO_2 emissions.

4.3 Empirical results and analysis

Table 4 presents the estimations obtained using Stata16.0, one-step differential GMM, and one-step system GMM methods, using economic growth, FDI, and industrial pollution and their lagged variable as endogenous variables. For those problems related to order sequence, the regression results of each equation are valid. The Hansen-J value indicates that the selected instrumental variable passes the over-identification test and meets the requirements of correlation and exogeneity. SYS-GMM outperforms differential GMM in terms of the significance of the explanatory variable's coefficient and the Hansen-J value. The SYS-GMM estimation results, therefore, are used for analysis reference.

Model (2) in Table 4 shows that the coefficient of *lnfdi* is 0.149 in the economic growth equation, which is significant at the 1% level. In other words, for every 1 percentage point increase in *FDI per capita*, the regional economy increases by 0.149 percentage points, thereby suggesting that FDI promotes regional economic growth. Meanwhile, the coefficient of *Lnp* is 0.041, which means that, for every 1 percentage point increase in industrial sulfur dioxide emissions *per capita*, the regional economy increases by 0.041 percentage points at the 10% significance level. This positive correlation supports the assumption that China endures environmental damage for the sake of economic growth and confirms the country to be in a stage of rapid industrialization, with high-pollution manufacturing as the supporting industry. Among the control variables, the coefficient of *lnk* is 0.71 and significantly positive, indicating

TABLE 3 Results of the Kao panel co-integration test.

Kao test for Eq. 4	Statistic	*p*-value
Modified Dickey–Fuller t	−1.7544	0.0397
Dickey–Fuller t	−2.7230	0.0032
Augmented Dickey–Fuller t	−3.5927	0.0002
Unadjusted modified Dickey–Fuller t	−1.3797	0.0838
Unadjusted Dickey–Fuller t	−2.5222	0.0058
Kao test for Eq. 5	**Statistic**	***p*-value**
Modified Dickey–Fuller t	−6.0756	0.0000
Dickey–Fuller t	−6.1627	0.0000
Augmented Dickey–Fuller t	−3.6641	0.0001
Unadjusted modified Dickey–Fuller t	−6.2033	0.0000
Unadjusted Dickey–Fuller t	−6.2032	0.0000
Kao test for Eq. 6	**Statistic**	***p*-value**
Modified Dickey–Fuller t	−5.8443	0.0000
Dickey–Fuller t	−6.8921	0.0000
Augmented Dickey–Fuller t	−2.4383	0.0074
Unadjusted modified Dickey–Fuller t	−8.2939	0.0000
Unadjusted Dickey–Fuller t	−7.7031	0.0000

that the stock of fixed capital can positively contribute to the development of China's economy (Hamdi et al., 2014). A comparison of the *lnfdi* and *lnk* coefficients reveals that, during the study period, domestic fixed capital achieves a greater contribution to China's economic development compared with FDI. The coefficient of *lnpop* is 0.137, which is significant at the 1% level, whereas the coefficient of *tec* is 0.055, which is significantly positive at the 10% level. China, therefore, is dominated by labor-intensive industries, featuring a level of technology that, to a certain extent, can also contribute to its economic growth. The coefficient of *gov* is significantly positive at the 1% statistical level, indicating that the Chinese government can reasonably allocate local general budget expenditure costs, allowing them to effectively and reasonably utilize financial resources. The coefficient of *open* is positive yet insignificant, thereby suggesting that foreign opening levels do not have a significant role in promoting economic growth.

In Model (4), the coefficient of *lny* is 0.774 and significant at the 10% level, suggesting that for every 1 percentage point increase in the economy *FDI per capita* increases by 0.774 percentage points. The host country's economic development level is among the key factors that foreign investors consider. A larger scale of economic development indicates a greater market potential and higher potential for attracting foreign investors (Omri and Sassi-Tmar, 2015). The coefficient of *lnp* is 0.141 and significant at the 5% level, suggesting that for every 1 percentage point increase in industrial SO_2 emissions *per capita FDI* increases by 0.141 percentage points. In other words, a greater amount of industrial sulfur dioxide emissions results in more serious environmental pollution. This finding may be ascribed to the fact that, for some industries, higher pollution lowers environmental standards, whereas lower expenditure on environmental protection for foreign investors corresponds to lower costs and greater FDI inflows (Blanco et al., 2013; Bildirici and Çoban Kayıkçı, 2023). Among the control variables, the coefficient of *lnwage* is −0.152 and insignificant, suggesting that even though labor cost can affect FDI entry to some extent, this factor is not of high consideration among foreign investors. The coefficient of *reg* is −0.225 and significant at the 5% level, indicating that environmental regulation has a suppressive effect on FDI inflows. This result validates the pollution-haven hypothesis that a greater degree of pollution can effectively attract more FDI. The coefficient of *lnhum* is significantly positive, indicating that FDI is closely related to local human capital level and that human capital enhances the ability of cities to attract FDI.

In Model (6), the coefficient of *lny* is 0.52 and significant at the 5% significance level, suggesting that for every 1 percentage point increase in economic growth, *per capita* sulfur dioxide emissions increase by 0.52 percentage points. China's economic development stays on the left side of the EKC curve, while the degree of environmental pollution increases with economic growth (Shahbaz et al., 2015; Lau et al., 2014; Bildirici and Çoban Kayıkçı, 2023). The coefficient of *lnfdi* is 0.254 and significant at the 10% significance level, suggesting that for every 1 percentage point increase in *per capita FDI*, *per capita* industrial sulfur dioxide emissions increase by 0.254 percentage points (He, 2006; Acharyya, 2009; Ren et al., 2014; Wu and Wang, 2023). In other words, FDI inflow leads to further environmental degradation, thereby verifying the pollution-haven hypothesis. Among the control variables, the coefficient of *open* is 0.143 and insignificant, thereby indicating that the degree of openness is not the main cause of pollution. Meanwhile, the coefficient of *reg* is 0.161 and significant at the 10% level, indicating that China's environmental regulation is ineffective, that the country may still be in the early stages of implementing environmental protection policies, and that its technical equipment and policy methods are not effective in improving the environment. The coefficient of *urb* is −0.031 and significant at the 1% level, indicating that a higher level of urbanization can reduce industrial pollution for two possible reasons. Firstly, urban areas are not conducive to the establishment of large factories. Secondly, a higher level of development increases people's awareness of the importance of environmental protection and inspires environmental protection initiatives, thereby contributing to pollution reduction. The coefficient of *tec* is 0.065 and insignificant, suggesting that technology level does not have a suppressive effect on SO_2 emissions.

The first-order lagged coefficients of *lny*, *lnfdi*, and *lnp* are all significantly positive. This result also supports the validity of using the dynamic panel model. The coefficient of *L.lnfdi* is 0.446, suggesting that for every 1% increase in FDI during the previous period the current period increases by 0.446%. FDI shows an agglomeration effect because foreign investors tend to focus on location when choosing investments. To reduce the risks posed by uncertain factors such as culture, economy, market situation, and

TABLE 4 GMM estimation results for pollution, FDI, and economic growth.

Variable	Diff-GMM (1) *lny*	Sys-GMM (2) *lny*	Diff-GMM (3) *Lnfdi*	Sys-GMM (4) *lnfdi*	Diff-GMM (5) *lnp*	Sys-GMM (6) *lnp*
lny			1.1090*** (3.4500)	0.7740* (1.8700)	1.3420*** (3.4100)	0.5200** (2.7500)
lnfdi	0.2320*** (4.6500)	0.1490*** (3.5900)			−0.3450 (−0.9000)	0.2540* (1.9400)
lnp	0.1090*** (4.7800)	0.0410* (1.8100)	0.0610 (1.1300)	0.1410** (2.1000)		
lnk	0.8250*** (11.1600)	0.7100*** (9.0300)				
tec	0.0660 (1.0700)	0.0550* (2.0000)				
gov	−0.6160 (−1.0400)	1.0330*** (2.8200)				
lnpop	1.0370 (1.4600)	0.1370*** (3.7000)				
Open	−0.3540** (−2.1600)	0.0350 (0.5600)	0.3490 (0.9300)	0.4230 (1.4700)	1.7000** (2.1800)	0.1430 (0.8200)
reg			0.0080 (0.2100)	−0.2250** (−2.4500)	0.1430*** (2.9900)	0.1610* (1.9300)
Lnwage			−0.1200 (−0.4200)	−0.1520 (−0.6100)		
lnhum			−1.0870* (−1.8600)	0.9900** (2.3400)		
urb					−0.0930*** (−4.590)	−0.0310*** (−2.8100)
tec					0.1110 (0.5200)	0.0650 (0.4900)
str					0.0610*** (3.6300)	0.0100 (0.9600)
L.lny	0.3620* (1.9900)	0.1520** (2.0500)				
L.lnfdi			0.1710 (1.2400)	0.4460* (1.7500)		
L.lnp					0.4050 (1.6800)	0.8230*** (3.5000)
N	300	330	300	330	300	330
AR (2)	(0.1180)	(0.1380)	(0.6030)	(0.2750)	(0.7610)	(0.2760)
Hansen-J	(0.0810)	(0.9340)	(0.5660)	(0.8940)	(0.5010)	(0.6150)

Notes: The estimated *p*-values are enclosed in parentheses. The Hansen J-test refers to the over-identification test for GMM, estimation restrictions according to the original hypothesis that there is no over-identification of the equation perturbation terms. The AR(2) test refers to the Arellano–Bond test for the existence of a second-order autocorrelation in first differences. ***, **, and * indicate significance at the 1%, 5%, and 10% levels, respectively.

host country preferential policies, foreign investors tend to be drawn to those areas where foreign capital is relatively concentrated. Meanwhile, the flow of foreign capital into the high-emission manufacturing industry will increase industrial sulfur dioxide emissions and intensify environmental pollution. For the environment, pre-pollution will significantly aggravate the deterioration of current environmental levels. Timely population control measures, therefore, should be adopted to avoid ecosystem destruction.

5 Conclusion

By using a dynamic panel coefficient model, this paper analyzes the panel data of 30 provinces and cities in China between 2006 and 2017 with the aim of understanding whether introducing foreign investments produces a pollution-haven or pollution-halo effect on China's environment, whether economic growth and foreign investment inflow have a mutual promotion effect, and whether an EKC exists between economic growth and pollution.

On the one hand, FDI inflows promote China's economic growth, but economic growth also brings harm to the environment. Seeing that a high level of environmental pollution is conducive to FDI taking place, these inflows do pose a threat to China's environment, thereby validating the pollution-paradise hypothesis. So, despite the negative relationship between environmental regulations and FDI inflows, China's present environmental regulations do not actually benefit the country's environment. Moreover, foreign investors choose to invest in those areas with poor environmental standards, thereby exacerbating these complications. On the other hand, the scale of economic development positively affects FDI, indicating that economic growth and FDI inflows can promote each other. Actively introducing FDI while supervising and improving foreign investment access policy can promote China's economic growth yet deteriorate its environment at the same time. Green thresholds should be established, therefore, ensuring that the inflow of highly polluting foreign investment is strictly gated and managed, the industrial structure of FDI is balanced, and the development of

high-tech industries accelerated. When foreign investors consider green industries, some preferential treatment may be advisable to encourage additional investments in sustainable development.

Economic growth harms the environment, whereas industrial pollution positively affects economic growth. In this case, China's economic development leans on the left side of the EKC curve, meaning that the country sacrifices its environment for the sake of economic development. Therefore, China needs to change its economic development model and emphasize the quality of economic growth. At the same time, the government should strengthen environmental supervision, introduce high-quality FDI, and play the role of foreign investment in improving the environment.

6 Limitations and future directions

Although this study supplements the research on the relationship between FDI, economic growth, and industrial pollution under the same framework, it still has shortcomings that need further improvement. First of all, due to the limitations of data availability and data processing methods, only *per capita* industrial sulfur dioxide emission is selected as the proxy variable of industrial pollution, which has certain defects in measuring industrial pollution. Subsequent studies can expand this based on data richness. Secondly, this study did not analyze the relationship mechanism among the three. In the follow-up study, more in-depth research should be carried out on the theoretical and specific effect mechanisms of the interaction between the three. Finally, the panel data of 30 provinces in China from 2006 to 2017 are studied in this paper. In future work, the scope of the study can be expanded to other regions with different economic and social conditions, which is conducive to the comparison and generalization of the research results.

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

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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Association between long-term exposure to ambient particulate matter and pulmonary function among men and women in typical areas of South and North China

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Background: Studies comparing the effects of different sizes and concentrations of ambient particulate matter (PM) on pulmonary function in different regions and sexes remain sparse.

Objectives: To investigate the associations of different sizes and levels of long-term ambient PM exposure with pulmonary function among people of different sexes in typical areas of South and North China.

Methods: In 2021, a total of 1,592 participants aged 20–73years were recruited to participate in the pulmonary function test from the baseline survey of the Diverse Life-Course Cohort (DLCC) in typical areas of Guangdong Province and Hebei Province. The three-year (2018–2020) average ambient PM concentrations were assessed from the ChinaHighPM_1 dataset, ChinaHigh$PM_{2.5}$ dataset and ChinaHighPM_{10} dataset. Mean differences in pulmonary function were used in multilevel models for different regions and sexes.

Results: We discovered significant associations of ambient PM exposure with reduced forced vital capacity (FVC) and increased forced expiratory volume in 1 s/forced vital capacity ratio (FEV_1/FVC) among men and lower levels of FEV_1 and FVC among women, such that a 5-μg/m^3 concentration increase in PM_1, $PM_{2.5}$, and PM_{10} was associated with decreases in FVC of 122.1ml (95% confidence interval (CI): 30.8, 213.4), 54.6ml (95% CI: 15.8, 93.3) and 42.9ml (95% CI: 12.7, 73.1) and increases in FEV_1/FVC of 2.2% (95% CI: 0.6, 3.9), 1.1% (95% CI: 0.4, 1.9) and 0.9% (95% CI: 0.3, 1.5) among men and decreases in FEV_1 of 51.1ml (95% CI: 9.7, 92.4), 21.6ml (95% CI: 4.3, 38.9) and 16.7ml (95% CI: 3.3, 30.1) and in FVC of 77.8ml (95% CI: 10.0, 145.6), 38.7ml (95% CI: 9.0, 68.5) and 31.1ml (95% CI: 8.1, 54.1) among women in Hebei Province. There was no association between ambient PM and pulmonary function in Guangdong Province.

Conclusion: Long-term exposure to different sizes and concentrations of ambient PM were associated with FEV_1 and FVC among men and women differently. The impact of ambient PM on FVC should be of greater concerned.

KEYWORDS

PM_1, $PM_{2.5}$, PM_{10}, pulmonary function, restrictive ventilatory dysfunction

1. Introduction

Particulate matter (PM) is a major risk factor for disease burden worldwide and long-term exposure to ambient PM is greatly associated with cardiovascular and respiratory diseases (1–4). In addition to resulting in multisystem disorders, including respiratory diseases, ambient PM seems to reduce pulmonary function directly (5–8). In general, PM_{10} is mostly released into the atmosphere through mechanical processes like the production of construction dust, wind-blown mineral soil and sea-salt, $PM_{2.5}$ is largely generated by human activities, such as power generation, industrial manufacturing, and residue emissions. While some sources are common, PM_1 mainly originates from direct emissions during the combustion process (9–11). The effect of PM on pulmonary function is associated with size because finer PM is more likely to reach the terminal bronchi (12, 13). In addition, smaller particles cause greater cytotoxic effects and inflammation (14). Thus, finer PM may have a greater impact on pulmonary function.

Pulmonary function is an objective indicator that reflects respiratory health, which can be measured by pulmonary function instruments. Portable and easy to operate, pulmonary function instruments are often used for large-scale population surveys to evaluate pulmonary health and screen for respiratory diseases. According to the 2019 Global Initiative for Chronic Obstructive Lung Disease guidelines, a postbronchodilator forced expiratory volume in 1 s/forced vital capacity ratio (FEV_1/FVC) < 0.70 is defined as chronic obstructive pulmonary disease (COPD) (15). Asthma, pulmonary fibrosis, lung cancer and other respiratory diseases are also accompanied by decreased pulmonary function. A study also indicated that decreased pulmonary function is a mediator of cardiopulmonary death (16).

Thanks to publicly available *in situ* measurements of $PM_{2.5}$ (particulate matter ≤2.5 μm in aerodynamic diameter) and PM_{10} (particulate matter ≤10 μm in aerodynamic diameter), there have been several studies on the associations between long-term exposure to $PM_{2.5}$ and PM_{10} and pulmonary function. All forced expiratory volume parameters decrease with increment in $PM_{2.5}$ and PM_{10} in the UK and Taiwan; Increase in $PM_{2.5}$ was associated with lower FEV_1 and FVC, but association with FEV_1/FVC ratio was weak or absent in the Northeastern United States; And a slight positive correlation between $PM_{2.5}$ and FEV_1 and FVC in some places of northwestern China (17–20). Although the findings were inconsistent, they all showed that pulmonary function declined at different levels with increasing $PM_{2.5}$ and PM_{10} concentrations. Governments worldwide have taken measures to improve air quality. Since the implementation of the Air Pollution Prevention and Control Action Plan in the Beijing-Tianjin-Hebei region (BTH region, one of the most polluted areas in China) in 2013, air quality has greatly improved but was still not adequate until 2018 (21). Evidence of the association between ambient PM and pulmonary diseases in the BTH region is limited. Moreover, studies on PM_1 are much rarer due to fewer ground monitoring stations. Presently, there are not large-scale population surveys on the relationship between PM_1 (particulate matter ≤1 μm in aerodynamic diameter) and pulmonary function. Evidence suggests that PM_1 exposure is associated with poorer pulmonary function in children and adolescents (22–24).In addition, regional and sex discrepancies in pulmonary function are substantial (25); however, few studies distinguished areas and sexes when exploring the association between ambient PM and pulmonary function and none of them compared the different effects of PM_1, $PM_{2.5}$ and PM_{10} on pulmonary function in the general population.

The BTH region is one of the world-class urban agglomerations in China that serves as the country's political center and third largest economy. With 8.1% of China's population in this region, it has witnessed rapid socioeconomic growth and urbanization, and, consequently caused severe air pollution and substantial changes in health-related behaviors (26). In Baoding (southern BTH region in North China), due to coal consumption and increasing numbers of private cars, ambient PM pollution is relatively serious. The annual average concentration of $PM_{2.5}$ exceeded 50 μg/m^3 for many years in Baoding (21), Hebei Province, which exceeded the World Health Organization (WHO) (27) Air Quality Guidelines (5 μg/m^3) by >10-fold (2021). Nonetheless, with the World Geopark Baishishan Mountain, the air quality of Laiyuan County is far better than that of Baoding city. We selected mountainous regions, coastal cities and islands in Shantou and Meizhou, Guangdong Province (South China) as clean controls outside Baoding and the average annual concentration of $PM_{2.5}$ is approximately 20 μg/m^3 in Shantou and Meizhou every year. This provides a natural condition with two clean controls inside and outside Baoding city to explore the different associations between high-level and low-level ambient PM and pulmonary function. In this comparative study, research was conducted by using the baseline survey of the Chaoshan-Hakka-Baoding-general population cohort (CHB cohort) in the Diverse Life-Course Cohort (DLCC) in Shantou and Meizhou, Guangdong Province (South China) and Baoding, Hebei Province (North China) to investigate the different associations between high-level and low-level exposure to ambient PM and pulmonary function.

2. Methods

2.1. Study population

This comparative study was based on a baseline survey of the CHB cohort in the DLCC. Detailed information on the whole

research has been described previously (28). Briefly, At Visit 2 of the DLCC, we singled out typical areas in Guangdong Province (South China) and Hebei Province (North China), including coastal Shantou city-Chenghai and Jinping, island-Nan'ao County, southern mountainous regions -Meizhou city and Jiaoling county, northern plains area-Baoding city and northern mountainous region-Laiyuan county. The newly enrolled areas have some unique characteristics in culture, dietary patterns, environmental risk factors (such as concentration of ambient PM), and noncommunicable chronic diseases (NCDs) prevalence, which enabled us to conduct comparative studies on the effects of different ambient pollution patterns on multiple health outcomes. The main aim of Visit 2 of the DLCC was to explore the associations of ambient pollutants and other environmental risk factors with NCDs in the general population in China.

Candidates who were 20-to 80-year-old permanent residents without severe physical or mental disease were included in the study sample. A total of 9,866 participants responded and completed the baseline survey. To ensure an adequate sample size and control for confounding factors related to pulmonary function, we selected as many nonsmoking participants under 50 years of age without a history of respiratory disease or an occupational history of high-risk respiratory disease as possible. If there were not enough participants in pulmonary function tests, we relaxed the criteria. Finally, only 1,592 participants aged 20–73 years whose pulmonary function parameters were valid were included.

Demographic characteristics, socioeconomic characteristics, health behavior, physician-diagnosed diseases and medication histories were collected via face-to-face questionnaire interviews by well-trained investigators. Height, weight, and pulmonary function were collected parameters from anthropometric measurements.

2.2. Ambient particulate matter exposure assessment

As air monitoring station data was not available in rural areas and there are no air monitoring stations on Nan'ao Island, we used well-established databases on ambient PM for PM assessment. The annual concentrations of PM_1, $PM_{2.5}$, and PM_{10} at a resolution of 1 km were estimated from ChinaHighPM_1 dataset, ChinaHigh$PM_{2.5}$ dataset and ChinaHighPM_{10} dataset with a space–time extremely randomized trees model (denoted the STET model) (29–32), which combined information from multiple data sources, including satellite data (Multi-Angle Implementation of Atmospheric Correction (MAIAC) and aerosol product, meteorological, land cover, surface topographic and population data. Comprehensive utilization of various factors related to ambient PM ensured the accuracy of ambient PM assessment. Although air monitoring stations data or MAIAC data may be missing, the model can generally provide particle concentration for different seasons across China, which was available to assess ambient PM in Guangdong Province and Hebei Province (The spatial coverage was average value of 79%, more than 98% and more than 93% for PM_1, $PM_{2.5}$, and PM_{10}). The out-of-station cross-validation coefficients of determination (CV-R^2) were 0.77, 0.88, and 0.82 for PM_1, $PM_{2.5}$, and PM_{10}, and, respectively. We calculated the three-year (2018–2020) average concentration before the baseline survey (2021) for each participant as the long-term exposure concentration of PM_1, $PM_{2.5}$, and PM_{10}, and assigned PM concentration estimates for each participant according to their geocoded residential address. ArcGIS Desktop (version 10.2, ESRI Inc., Redlands, CA, United States) was used to describe the distribution of particulate matter.

2.3. Pulmonary outcome assessment

Trained and certified technicians carried out pulmonary function tests before and after bronchodilator inhalation using the same MasterScreen Pneumo PC spirometers (Jaeger, Germany) according to a standard protocol (33). Daily calibration with a 3-L syringe was performed for spirometers.

Pulmonary function tests were conducted from 8:00 to 12:00 a.m. each investigation day. We performed spirometric maneuvers with every participant in a seated position, wearing a nose clip, and using a disposable mouthpiece. Participants were required to perform up to eight forced expiratory maneuvers until the forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were reproducible within 150 ml. Inspiratory capacity (IC), and vital capacity (VC) were also tested. Predicted values of FEV1, FVC, and FEV_1/FVC ratio can be automatically generated by system only based on Asian standards. So, using previously published spirometry reference values for the population aged 7–80 years in China as the reference (34) we calculated the predicted values of forced expiratory volume parameters to further ensure the quality control of pulmonary function. If any measured values/predicted values ratio appeared too low, it would be excluded. Finally, forced expiratory volume parameters were included in models as continuous variables.

2.4. Covariates

Potential confounders were included based on the previous studies on ambient PM and the respiratory system (18): (1) demographic and socioeconomic characteristics, including: age (years, as a continuous variable), age groups(20–29 years/30–39 years/40–49 years/50- years), height (cm, as a continuous variable), weight (kg, as a continuous variable), body mass index (BMI) categories(underweight/normal weight/overweight/obesity), residential area (urban/rural), highest education attained (illiterate or elementary school / high school / college or above), and annual personal income (≤50,000 RMB/>50,000 RMB); and (2) health-related lifestyle factors, including: smoking (no/yes), alcohol consumption (no/yes), and self-reported respiratory diseases history.

2.5. Statistical analysis

We characterized the distributions of all the covariates according to the means and standard deviations (SDs) or the medians and interquartile ranges (IQR) for continuous variables, and counts and percentages for categorical variables. Differences in baseline characteristics between participants in the present study and those in the overall CHCN-BTH were tested using Student's *t*-test, the Wilcoxon rank sum test, or the chi-square test. Spearman rank

correlation coefficients were determined to assess the relationship between sizes of particulate matter.

Difference in pulmonary function parameters, including the means and 95% confidence intervals (CIs), every 5-μg/m^3 concentration increase in PM_1, $PM_{2.5}$, and PM_{10} were analyzed in multilevel models. As pulmonary function levels were substantially different among men and women in the two provinces and PM concentrations in Guangdong Province and Hebei Province have no overlap, we chose to conduct 4 multilevel models for men and women in different provinces, respectively. Individuals were treated as level 1 units, and different survey points (including Chenghai, Jinping, Nan'ao, Meizhou and Jiaoling in Guangdong Province and Baoding and Laiyuan in Hebei Province) were treated as level 2 units. Before analyses, a null model was fitted to test the random effects of the intercept term and evaluate whether the data was suitable for multilevel models. To ensure the comparability of the models, the same variables [age group (categorical variable), height (continuous variable), weight (continuous variable), education, annual personal income (categorical variable), smoking (categorical variable), alcohol consumption (categorical variable), and self-reported respiratory diseases (categorical variable)] were included in the models.

To identify the characteristics that might be significant in the association between ambient PM and pulmonary function, we performed stratified analyses according to BMI category (Under or Normal weight/ Overweight or Obesity) and age group (20–29 years/30–39 years/40–49 years/50-years). In addition, By performing analyses of participants without self-reported respiratory disease history, we conducted sensitivity analyses to assess the robustness of the associations between the 3 PM types and pulmonary function parameters.

All of the statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). A p-value <0.05 was considered statistically significant for a two-tailed test.

3. Results

3.1. Descriptive statistic

The descriptive statistics for the main characteristics of the study participants are presented in Table 1. There were 1,592 participants included in this study (420 men and 481 women in Guangdong Province and 260 men and 431 women in Hebei Province). The demographic characteristics (including age, age groups, height and weight) of men and women were similar in Guangdong Province and Hebei Province. In comparison with Hebei Province, the participants in Guangdong Province had higher income and education levels and mostly lived in urban areas. The smoking rate among men in Guangdong Province (55.2%) was lower than that among men in Hebei Province (62.7%), and the alcohol consumption rate among men was 48.8% in Guangdong Province, which was lower than that in Hebei Province (69.2%). The rates among women in Guangdong Province were similar. The rates of self-reported respiratory diseases were lower among both men (1.9%) and women (1.3%) in Guangdong Province. The characteristics of pulmonary function of the study participants are summarized in Table 2. All pulmonary function parameters were lower in Guangdong Province than in Hebei Province, and all pulmonary function parameters were higher among men than among women. The means ± SDs for FEV_1 were 3.4 ± 0.5 (L) and 2.6 ± 0.4 (L) for men and women, respectively, in Guangdong Province and 3.7 ± 0.6 (L) and 2.7 ± 0.4 (L) for men and women, respectively, in Hebei Province. The means ± SDs for FVC were 4.3 ± 0.6 (L) and 3.1 ± 0.5 (L) for men and women, respectively, in Guangdong Province and 4.7 ± 0.7 (L) and 3.4 ± 0.5 (L) for men and women, respectively, in Hebei Province.

The distributions of the 3-year average particulate matter concentrations and Spearman rank correlation coefficients from 2018 to 2020 are summarized. The PM_1, $PM_{2.5}$, and PM_{10} concentrations varied greatly across study sites with medians (IQRs) of 15.4 (1.2) μg/m^3, 24.4 (0.9) μg/m^3, and 41.2 (1.5) μg/m^3 in Shantou and Meizhou, Guangdong Province and 33.0 (9.1) μg/m^3, 57.0 (22.0) μg/m^3, and 98.9 (28.3) μg/m^3 in Baoding, Hebei Province, respectively. The 3-year average concentrations of PM_1, $PM_{2.5}$, and PM_{10} in Baoding were much greater than two times those in Shantou and Meizhou. With higher concentrations, the three ambient PM all showed a gradual upward trend from northwest to southeast in Baoding; however, the ambient PM concentrations were low and evenly distributed in Shantou and Meizhou, as shown in Figure 1. In addition, the 3-year average concentrations of the 3 PM types in Baoding city were much higher than those in Laiyuan county. Compared with Shantou and Meizhou, there were stronger correlations between the three kinds of PM in Baoding (Spearman rank correlation coefficients were 0.8, 0.8, and 0.9 in Baoding and 0.4, 0.5, and 0.9 in Shantou and Meizhou).

3.2. Associations between ambient PM and pulmonary function parameters

The associations of the 3 PM types with pulmonary function parameters are summarized. The discrepancy in the relationship between the 3 PM types and pulmonary function in Guangdong Province and Hebei Province was reflected in forced expiratory volume parameters. In Hebei Province, higher concentrations of PM showed significant associations with lower levels of FVC and higher levels of FEV_1/FVC among men, with a 5-μg /m^3 increase in PM_1, $PM_{2.5}$, and PM_{10}, decreases in FVC of 122.1 mL (95% CI: 30.8, 213.4), 54.6 ml (95% CI: 15.8, 93.3) and 42.9 mL (95% CI: 12.7, 73.1) and increases in FEV_1/FVC of 2.2% (95% CI: 0.6, 3.9), 1.1% (95% CI: 0.4, 1.9), and 0.9% (95% CI: 0.3, 1.5). Among women, higher concentrations of PM showed significant associations with lower levels of FEV_1 and FVC, with a 5-μg /m^3 increase in PM_1, $PM_{2.5}$, and PM_{10}, decreases in FEV_1 of 51.1 ml (95% CI: 9.7, 92.4), 21.6 ml (95% CI: 4.3, 38.9) and 16.7 ml (95% CI: 3.3, 30.1), respectively, and decreases in FVC of 77.8 ml (95% CI: 10.0, 145.6), 38.7 ml (95% CI: 9.0, 68.5) and 31.1 ml (95% CI: 8.1, 54.1), respectively. The effect on forced expiratory volume parameters was magnified with the decrease in PM size, and the association between ambient PM and FVC were greater than that with FEV_1 in Hebei Province. There were no statistically significant associations between the three ambient PM types and forced expiratory volume parameters in Guangdong Province.

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TABLE 1 Characteristics of the study population in different provinces in DLCC (*n*=1,592).

Characteristics	Guangdong			Hebei		
	Total (*n*=901)	Men (*n*=420)	Women (*n*=481)	Total (*n*=691)	Men (*n*=260)	Women (*n*=431)
Age, mean ± SD, (years)	41.5 ± 9.2	42.4 ± 10.1	40.7 ± 8.2	40.3 ± 9.1	40.2 ± 9.5	40.4 ± 8.9
Age group, years, n (%)						
20–29	106 (11.8)	50 (11.9)	56 (11.6)	97 (14.0)	37 (14.2)	60 (13.9)
30–39	248 (27.5)	110 (26.2)	138 (28.7)	222 (32.1)	85 (32.7)	137 (31.8)
40–49	420 (46.6)	163 (38.8)	257 (53.4)	267 (38.6)	96 (36.9)	171 (39.7)
50–73	127 (14.1)	97 (23.1)	30 (6.2)	105 (15.2)	42 (16.2)	63 (14.6)
Height, mean ± SD, (cm)	168.7 ± 5.8	168.7 ± 5.8	156.8 ± 5.4	163.1 ± 8.6	171.1 ± 5.9	158.5 ± 5.9
Weight, mean ± SD, (kg)	62.6 ± 12.4	68.6 ± 12.9	56.6 ± 8.8	67.5 ± 13.0	76.8 ± 12.3	61.9 ± 9.9
BMI categories, n (%)[a]						
Underweight	61 (6.8)	21 (5.0)	40 (8.3)	16 (2.3)	4 (1.5)	12 (2.8)
Normal weight	478 (53.0)	205 (48.8)	273 (56.8)	265 (38.4)	72 (27.7)	193 (44.8)
Overweight/Obesity	362 (40.2)	194 (46.2)	168 (34.9)	410 (59.3)	184 (70.8)	226 (52.4)
Residential area, n (%)						
Urban	550 (61.0)	286 (68.1)	264 (54.9	361 (52.2)	130 (50.0)	231 (53.6)
Rural	351 (39.0)	134 (31.9)	217 (45.1)	330 (47.8)	130 (50.0)	200 (46.4)
Education, n (%)						
Illiterate/Elementary school	61 (6.8)	27 (6.4)	34 (7.1)	70 (10.1)	23 (8.8)	47 (10.9)
High school	423 (47.0)	192 (45.7)	231 (48.1)	344 (49.8)	127 (48.8)	217 (50.3)
College or above	416 (46.2)	201 (47.9)	215 (44.8)	277 (40.1)	110 (42.3)	167 (38.7)
Annual personal income (CHY), n (%)						
≤50000RMB/year	441 (49.2)	147 (35.2)	294 (61.4)	495 (71.8)	146 (56.6)	349 (81.0)
>500000RMB/year	456 (50.8)	271 (64.8)	185 (38.6)	194 (28.2)	112 (43.4)	82 (19.0)
Smoking, n (%)						
No	657 (72.9)	188 (44.8)	469 (97.5)	521 (75.4)	97 (37.3)	424 (98.4)
Yes	244 (27.1)	232 (55.2)	12 (2.5)	170 (24.6)	163 (62.7)	7 (1.6)
Alcohol consumption, n (%)						
No	663 (73.6)	215 (51.2)	448 (93.1)	486 (70.3)	80 (30.8)	406 (94.2)
Yes	238 (26.4)	205 (48.8)	33 (6.9)	205 (29.7)	180 (69.2)	25 (5.8)
Self-reported respiratory diseases, n (%)	14 (1.5)	8 (1.9)	6 (1.3)	27 (3.9)	8 (3.1)	19 (4.4)

Self-reported respiratory diseases include tracheitis, bronchitis, pneumonia, asthma, Chronic obstructive pulmonary disease, etc.
DLCC, Diverse Life-Course Cohort; N, number; SD, standard deviation. Underweight was defined as BMI < 18.5 kg/m^2, 18.5 ≤ BMI < 24 as normal weight, 24 ≤ BMI < 28 as overweight, and BMI ≥ 28 as obesity. BMI body mass index, kg/m^2.

3.3. Stratified analyses and sensitivity analyses

The associations between ambient PM and forced expiratory volume parameters stratified by BMI category and age group are presented in Figures 2, 3. In the BMI category-stratified analysis, the adverse associations between forced expiratory volume parameters and ambient PM seemed predominant in overweight and obese populations, while the difference were not significant. In the age group-stratified analysis, the impact of PM on pulmonary function increased with age and greater associations between ambient PM and FVC in the age groups of 30–40 years old and those over 50 years old were observed both in men and women, however there was only an interaction between age and ambient PM on FVC among men that was not present among women in Hebei Province. Similarly, adverse association of PM on FEV_1 increased with age and the effect was more pronounced in the age groups of over 50 years old. The positive association between PM and FEV_1/FVC ratio increased with age in the age group of 20–50 years, and declined in group aged over 50 years. While, there was no interaction between age and ambient PM on FEV_1 and FEV_1/FVC ratio.

TABLE 2 Pulmonary function characteristics of study population in different provinces in DLCC (n=1,592).

Variable	Guangdong				Hebei				p-value for province
	Total (n =901)	Men (n =420)	Women (n =481)	p-value for gender	Total (n =691)	Men (n =260)	Women (n =431)	p-value for gender	
VC, mean ± SD, (L)	3.8 ± 0.8	4.4 ± 0.6	3.2 ± 0.5	<0.0001	4.0 ± 0.9	4.8 ± 0.7	3.4 ± 0.5	<0.0001	<0.0001
IC, mean ± SD, (L)	2.4 ± 0.7	2.7 ± 0.70	2.1 ± 0.5	<0.0001	2.6 ± 0.7	3.1 ± 0.7	2.2 ± 0.5	<0.0001	<0.0001
FEV_1, mean ± SD, (L)	3.0 ± 0.6	3.4 ± 0.5	2.6 ± 0.4	<0.0001	3.1 ± 0.7	3.7 ± 0.6	2.7 ± 0.4	<0.0001	0.0054
FVC, mean ± SD, (L)	3.7 ± 0.8	4.3 ± 0.6	3.1 ± 0.5	<0.0001	3.9 ± 0.9	4.7 ± 0.7	3.4 ± 0.5	<0.0001	<0.0001
FEV_1/FVC, mean ± SD, (%)	81.4 ± 7.1	80.0 ± 7.2	82.6 ± 6.9	<0.0001	79.5 ± 7.3	77.5 ± 7.3	80.7 ± 7.0	<0.0001	<0.0001
FEV_1%predicted, mean ± SD, (%)	101.4 ± 11.8	100.5 ± 12.1	102.3 ± 11.5	0.0183	104.6 ± 12.7	103.0 ± 12.3	105.6 ± 12.8	0.0086	<0.0001
FVC %predicted, mean ± SD, (%)	101.0 ± 12.3	100.1 ± 12.3	101.8 ± 12.2	0.0442	106.7 ± 13.1	105.9 ± 13.1	107.2 ± 13.0	0.1885	<0.0001
FEV_1/FVC%predicted, mean ± SD, (%)	100.4 ± 8.0	100.2 ± 8.4	100.7 ± 7.7	0.3608	98.1 ± 8.3	97.2 ± 8.5	98.6 ± 8.1	0.0350	<0.0001

VC, vital capacity; IC, inspiratory capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; N, number; SD, standard deviation.

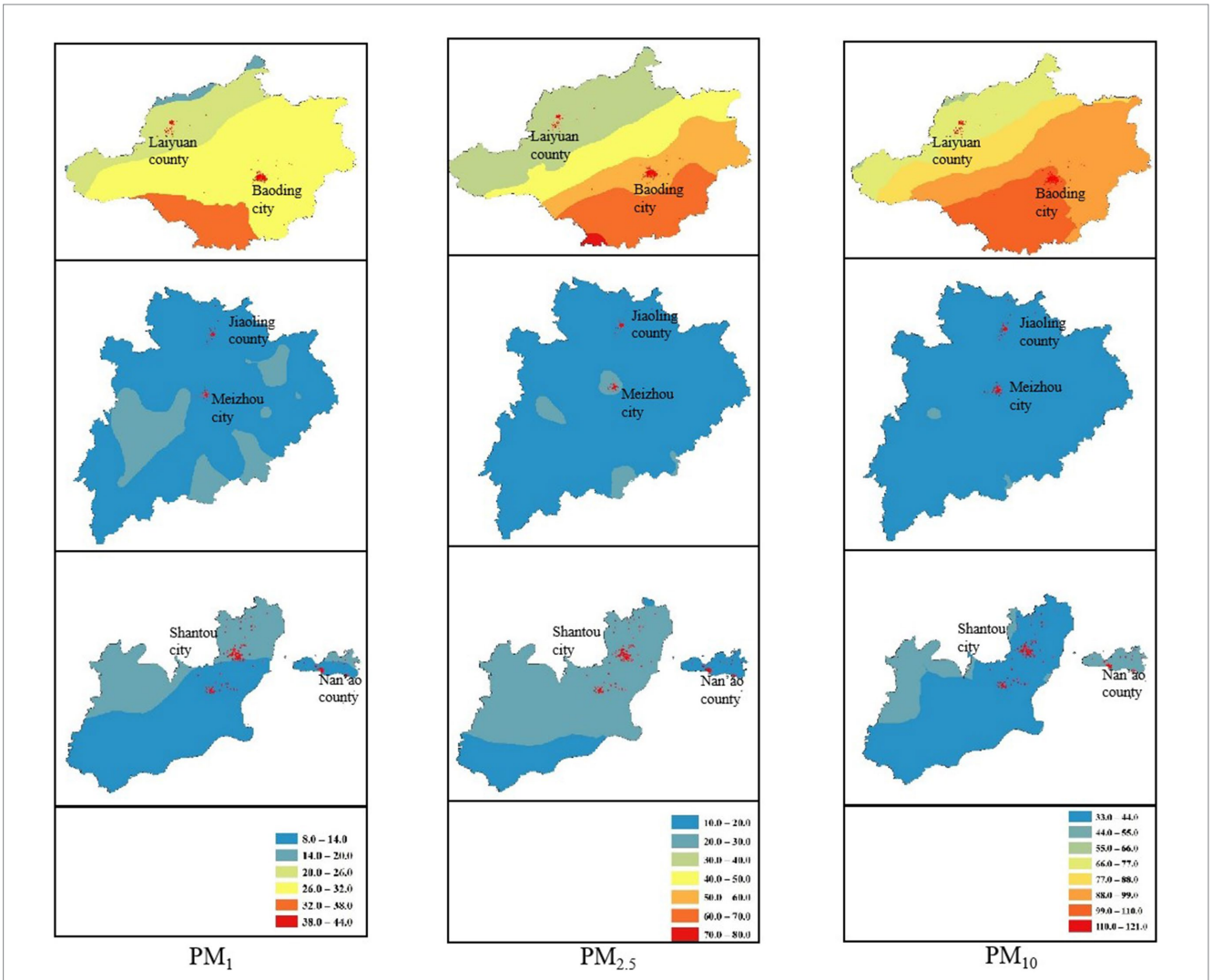

FIGURE 1
Locations of participant's residence and 3-year average of PM_1, $PM_{2.5}$, and PM_{10} concentrations from 2018 to 2020 in Shantou and Meizhou, Gaungdon Province and Baoding Hebei, Province.

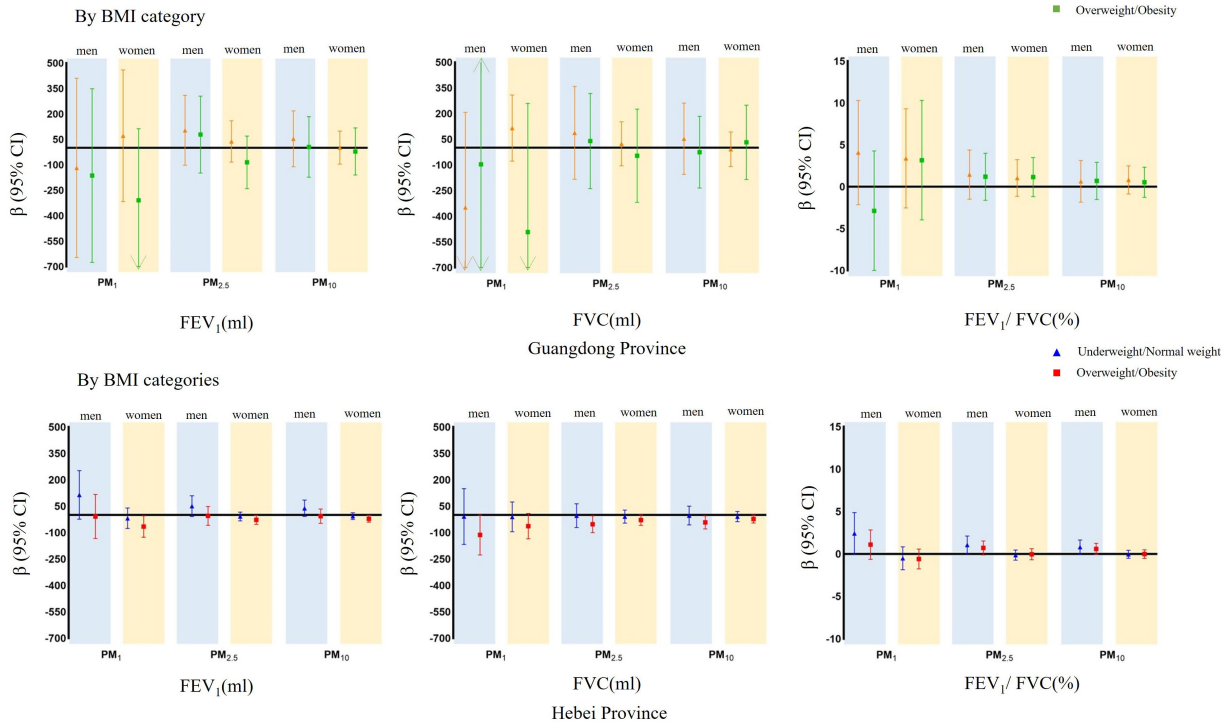

FIGURE 2
Mean differences with 95% confidence intervals in the pulmonary function parameters every 5μg/m^3 increase of PM_1, $PM_{2.5}$, and PM_{10} concentrations, stratified analyzed BMI categories in Guangdong and Hebei Provinces. The blue shadow represents men and the yellow shadow represents women.

The results of sensitivity analyses are presented in Figure 4. No changes occurred to the associations of PM_1, $PM_{2.5}$, or PM_{10} with forced expiratory volume parameters when we analyzed data among participants without self-reported respiratory diseases.

4. Discussion

The DLCC was a large-scale prospective study to explore the long-term effects of ambient air pollutants or other risk factors on population health of all ages. In the baseline survey of the CHB cohort (Visit 2 of the DLCC), we discovered that the 3-year average concentrations of ambient PM in Baoding city were much higher than those in Laiyuan county and two times higher than those in Meizhou and Shantou. Previous studies have illustrated that the spatial distributions of ambient PM vary greatly at different pollution levels across China (35) and we also observed this phenomenon. In Shantou and Meizhou, not only was the level of ambient PM low, but the correlations between ambient PM types was weaker. Due to high vegetation coverage and/or proximity to the ocean, the structure of ambient PM types was simple. In contrast, in Baoding, there were high concentrations of PM_1, $PM_{2.5}$, and PM_{10}, which were strongly correlated. A gradient increase in ambient PM was observed from the mountains (northwest Baoding) to the urban areas (southeast Baoding). Similar trends showed that the potential sources of ambient PM may be the same. Coal consumption and well-developed traffic have brought ambient particulate matter pollution to Baoding City.

Based on our study, we discovered negative effects of long-term ambient PM exposure on FVC and positive effects on FEV_1/FVC among men and adverse associations between ambient PM and FEV_1, FVC among women at high levels of PM. Stable effects were shown in sensitivity analyses. Moreover, higher estimated effects were observed for PM_1, than for $PM_{2.5}$ and PM_{10}. Particle size determines how deep particles can penetrate into the lung compartments. $PM_{2.5\text{-}10}$(particulate matter with diameters between 2.5 and 10 μm)is mainly deposited in the upper airways and can be cleared by the mucociliary system. $PM_{2.5}$ deposits in the tracheobronchial region, whereas PM_1 can reach the lung periphery, i.e., the alveolar region (U.S. Environmental Protection Agency) (36). The deeper PM is deposited, the slower it is removed, and the more likely it is to cause cell damage (37). $PM_{2.5}$ has the ability to penetrate deeper into the respiratory tract than PM_{10}, where $PM_{2.5}$ can more easily penetrate the air-blood barrier; while, greater health risks may be associated with PM_1 exposure, because it can access the gas-exchange region of the lungs (38, 39). In addition, smaller PM has a higher surface area to volume ratio, which having greater potential for deleterious biological interactions with respiratory tissues and risks for adverse health outcomes (40). Moreover, the effects of PM on pulmonary function may be related to induced airway inflammation, alveolar inflammation and lung tissue damage (40, 41). Therefore, finer PM is more strongly associated with reduced pulmonary function.

In our study, associations of ambient PM with pulmonary function differed among men and women in different regions, and it was suggested that when investigating risk factors for pulmonary function, regions and sex should be classified. Our study findings about the association of high concentration of $PM_{2.5}$ and PM_{10} with FEV_1 and FVC were similar to those of previous large-scale epidemiological studies (18–20, 42, 43). In contrast, most studies showed that $PM_{2.5}$

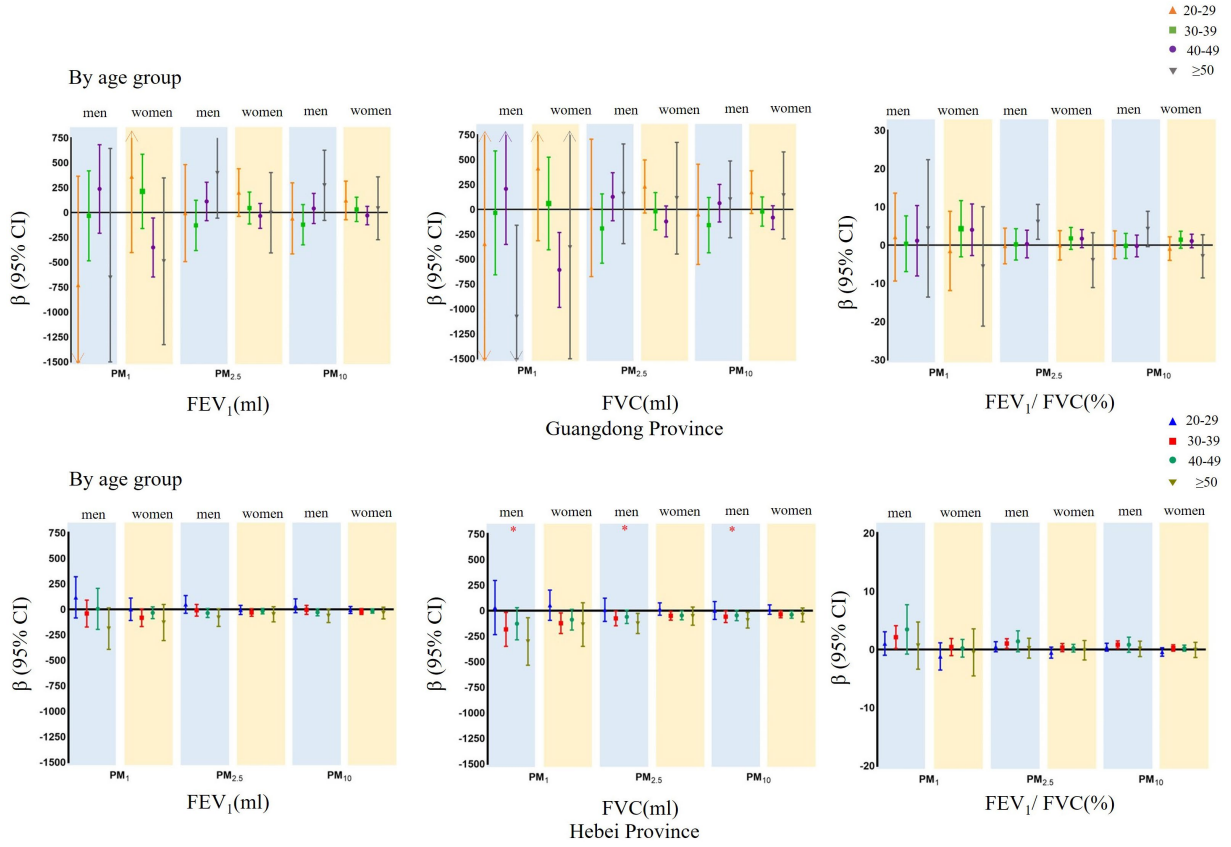

FIGURE 3
Mean differences with 95% confidence intervals in the pulmonary function parameters every 5μg/m^3 increase of PM_1, $PM_{2.5}$, and PM_{10} concentrations, stratified analyzed by age group in Guangdong and Hebei Provinces. The blue shadow represents men and the yellow shadow represents women. *P for interaction terms with statistically significance between air pollutants and modifiers.

and PM_{10} was related to decreased FEV_1/ FVC, while we failed to find the negative associations among women and found positive associations between ambient PM and FEV_1/ FVC among men. This may be ascribable to the differences in the concentration of $PM_{2.5}$ and PM_{10}, climatic conditions, geographical conditions and population susceptibility. Studies that found a larger effect in the extent of ambient PM on FVC than FEV_1 did not find a significant association with FEV_1/FVC (20). Although the effect of PM associated with pulmonary function decline differed between men and women, restrictive effects of ambient PM were observed. Restrictive pattern pulmonary function is generally characterized by a reduced FVC and/or FEV_1, but a stable or higher FEV_1/FVC (44). In a cross-sectional study in Shanghai, restrictive ventilation patterns of $PM_{2.5}$ were also observed (45). We discovered that the association between $PM_{2.5}$ and FVC was greater among men than among women in our study, and both were greater than that in Shanghai. The $PM_{2.5}$ concentration in western Shanghai between 2013 and 2014 was similar to that in Baoding city from 2018 to 2020, while, compared with 2013, ambient PM decreased by more than 40% in 2018 in Hebei Province (21). Thus, long-term exposure to ambient PM at higher concentrations is probably associated with more serious restrictive lung impairment and ambient PM-related restrictive ventilatory dysfunction suggests the presence of pulmonary fibrosis in Hebei Province. In addition, restrictive ventilation patterns were not only associated with respiratory diseases but also with cardiovascular disease (CVD) and mortality (46, 47). We should pay attention to restrictive pulmonary patterns in areas similar to Baoding city. For PM_1, a similar restrictive effect was shown in general population, while the magnitude of the association was larger than that for $PM_{2.5}$ and PM_{10}.

In BMI category-stratified analysis, the overweight population was affected more by ambient PM in the ESCAPE study and the CPH study (18, 43, 45). However, we failed to find a significantly different association between ambient PM and large airway function in different BMI categories and we only observed a different trend, possibly because breathlessness and grunting may occur in overweight and obese people and they may take steps to control weight. In age group-stratified analysis, we found that the impact of PM on FVC increased with age and FVC was susceptible to ambient PM among men aged 30–39 years and over 50 years. As was reported, age over 40 years is a risk factor for COPD (48) and the pulmonary function of adults reaches a peak at approximately 25 years and then began to decline (33). The aging-related decline in pulmonary function may be expedited by ambient PM. A previous report showed that the smoking rate among men in Hebei Province was high (49). In our study, we also found that unhealthy lifestyle habits such as smoking and drinking are common among men in Hebei Province. Such unhealthy lifestyle habits together with long-term exposure to ambient PM were likely to accelerate restrictive ventilatory dysfunction with increasing age among men in Hebei Province. Older men in Hebei Province should focus on respiratory health. However, the interaction between BMI categories, age groups

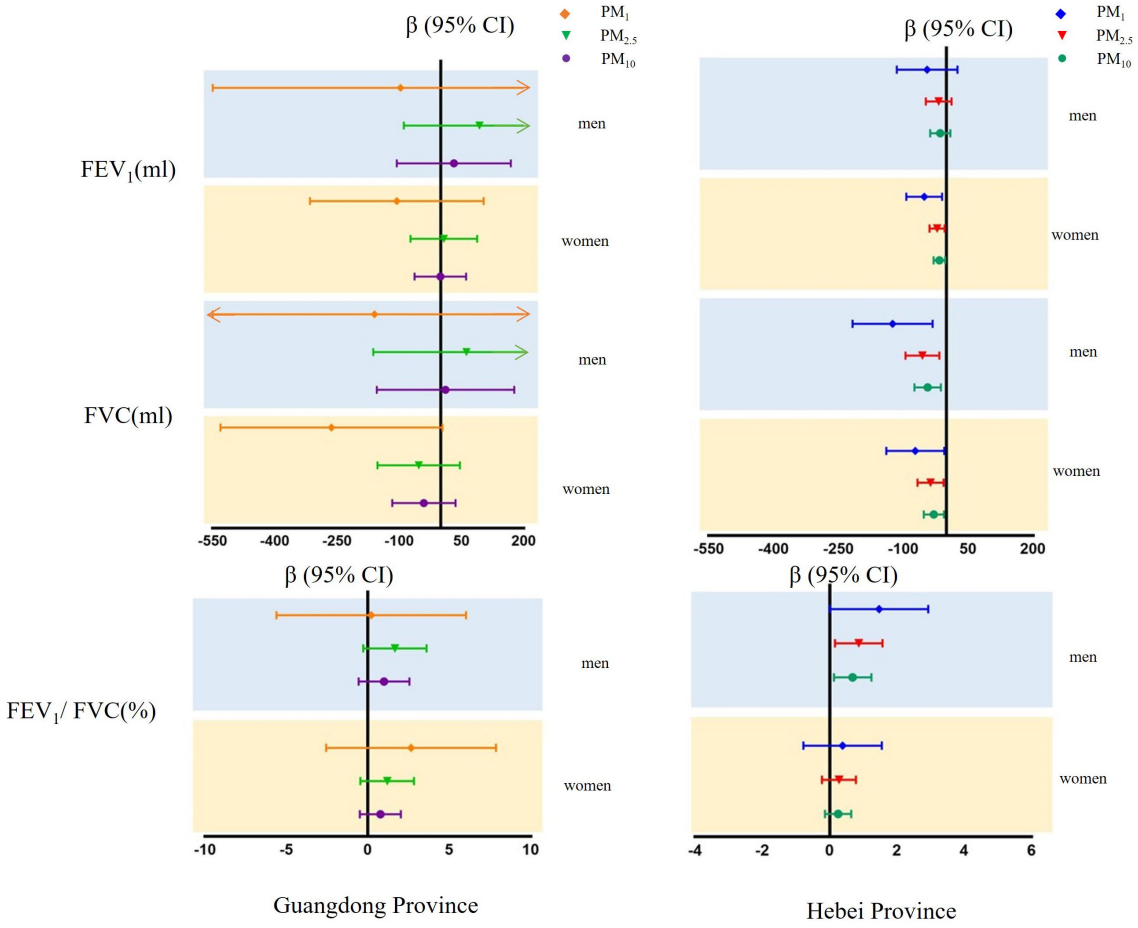

FIGURE 4
Mean differences with 95% confidence intervals in the pulmonary function parameters every 5μg/m^3 increase of PM_1, $PM_{2.5}$, and PM_{10} concentrations, sensitivity analyzed in participants without self-respiratory disease in Guangdong and Hebei Provinces. The blue shadow represents men and the yellow shadow represents.

and ambient PM on large airway function needs to be further studied by expanding the sample size. Presently, ambient PM pollution in Baoding city is still very serious. The Baoding government needs to take stricter measures to control air pollution. Ambient PM seems to have a greater restrictive effect on men, especially older men. Stricter smoke control measures need to be taken to prevent ambient PM from aggravating restrictive ventilatory dysfunction as men age. In addition to screening for ventilatory dysfunction, it is necessary to include pulmonary function examinations in the routine physical examination of people aged 40 and above. In this way, the incidence of chronic obstructive pulmonary disease, restrictive pulmonary disease and CVD can be reduced among older adults. For patients with ventilatory dysfunction, regular follow-ups with close attention to cardiopulmonary status should be carried out in areas with high concentrations of ambient PM.

5. Strengths and limitations

Our study has several strengths. Different natural ambient PM patterns were selected to conduct this comparative studies in South China and North China. We are also the first to conduct research on the relationship between ambient PM and lung function on Nan'ao Island. Shantou and Meizhou are typical areas with low ambient PM concentrations for decades, and ambient PM concentration in Baoding city has remained consistently high for several decades. Although we only evaluated ambient PM concentrations for 3 years, it can represent a long-term stable exposure. Our results can better reflect the association between different long-term ambient PM patterns and lung function. Besides, the ambient PM concentration in Laiyuan county was far lower than that in Baoding city, and clean controls were obtained to conduct comparative studies in the same areas. We could better observe the relationship between ambient PM and pulmonary function in Baoding. Nonetheless, this study also has the following limitations. First, there were few air monitoring stations in rural areas and we assigned PM concentration estimates for each participant based only on their geocoded current addresses; thus, exposure misclassification errors were inevitable. Nevertheless, we estimated the residential concentrations by using models with good performance in external cross validation. Second, because indoor ambient PM data were not available, we only included ambient PM data. Third, because it was time consuming to obtain pulmonary function measurement, we were unable to obtain more samples during this study. Finally, a questionnaire was used to collect self-reported demographic information and lifestyle characteristics, and thus, recall bias might have occurred.

6. Conclusion

In conclusion, long-term exposure to different levels of ambient PM was associated with large airway function differently. High concentrations of PM_1, $PM_{2.5}$, and PM_{10} were closely associated with decreased FVC and increased FEV_1/ FVC among men and reduced FEV_1 and FVC among women, greater effects were observed for PM_1, followed by $PM_{2.5}$ and PM_{10}. The restrictive effects of ambient PM on men and older adults should be of greater concern.

Collaboration

The collaborators are: Guangdong Provincial People's Hospital, Hebei University, China-Japan Friendship Hospital, Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, National Clinical Research Center for Respiratory Diseases.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data underlying this article will be shared on reasonable request to the corresponding author. Requests to access these datasets should be directed to guangliang_shan@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Bioethical Committee of Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences (055–2020). The patients/participants provided their written informed consent to participate in this study.

Author contributions

GS and QL contributed to the study conception and design and performed the data analysis. All authors contributed to the material preparation, data collection, and data interpretation. The first draft of the manuscript was written by QL and all authors commented on previous versions of the manuscript. All authors read and have approved the submitted version. All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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Conflict of interest

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

Publisher's note

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The dynamic relationship among economic development, air pollution, and health production in China: the DNSBM efficiency model

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China's economy has grown rapidly in response to the adoption of a high-energy, high-emissions development model, which has led to varying degrees of air pollution; moreover, the corresponding health damage has become a major concern for the public. Studies of the interrelationships between the economy, air pollution, and health often use empirical methods such as regression analysis, to explore the impacts of economic growth and air pollution, human health or air pollution on human health in isolation, and they rarely explore the interactions between the economy, air pollution, and health in terms of efficiency (i.e., the maximum output per unit of input resources that can be produced). Thus, this study constructed a Dynamic Network SBM efficiency model that unifies the production of economic development, air pollution, and health into a single framework. The article reports the findings of a comprehensive study of economic development, air pollution, and health management data for 30 Chinese provinces from 2015 to 2020. The results show that: 1) the overall efficiency (0.693) of China's two stages from economic production input to healthy output from 2015 to 2020 is low, and there is much room for improvement; 2) the efficiency of economic development (0.729) is higher than the efficiency of health production (0.657), indicating that the health production stage needs to be strengthened; 3) during the study period, China's PM2.5, SO_2, and NO_x control efficiency was low, at 0.786, 0.710, and 0.718, respectively, indicating that more effective measures are needed to improve environmental efficiency; and 4) there are significant differences in economic, environmental, and health efficiency across regions. China's developed eastern provinces are more efficient in terms of economic development, health production, and air pollution control. In contrast, the central and western provinces, which are relatively backward in their economic development, are less efficient. This means that each province should implement sound policies based on its own assessment to promote sustainable economic development while enhancing air pollution mitigation and health promotion.

KEYWORDS

economic development, air pollution, healthy production, efficiency analysis, DNSBM model

1 Introduction

After China's reform and opening up in 1978, its economy grew rapidly and became the world's second-largest economy in 2010. Although China has experienced rapid economic development, this progress has mainly been at the expense of excessive energy consumption, which has caused many environmental pollution issues (Xiong and Xu, 2021). Especially, air pollution has become one of the most serious environmental problems in China, which has created inevitable health losses and huge economic costs (Liu and Dong, 2021a). As a result, this work aims to investigate how to ensure minimal air pollution while maximising economic and health benefits.

Studies of the relationship between air pollution and health have focused on environmental health epidemiology and environmental toxicology (Brunekreef and Holgate, 2002; Lee et al., 2014; Kelly and Fussell, 2015; Ghorani-Azam et al., 2016; Dhital and Rupakheti, 2019; Dominski et al., 2021). However, these studies did not construct empirical health economics models to explore the socioeconomic factors involved in environmental health problems. In addition, other scholars have begun to examine the intersections among economic development, air pollution, and public health (Wang, 2010; Drabo, 2011; Sueyoshi and Yuan, 2015; Li et al., 2016; Chen et al., 2019; Feng et al., 2019; Gong et al., 2019; Kubatko and Kubatko, 2019; Fu et al., 2020; Mujtaba and Shahzad, 2021; Hussain et al., 2022; Zhang et al., 2023). Still, research on the economy–environment connection is usually conducted separately from health studies, and few approaches have combined economy, the environment, and health and analyzed their relationship in depth. The few studies on economic-environmental health usually use empirical methods such as regression analysis, but these methods do not adequately consider the efficiency issues between resource inputs and output. Therefore, it is necessary to adopt efficiency analysis methods to better reveal the efficiency relationships between the economy, environment, and health, consequently providing a more reliable basis for achieving sustainable development.

Based on the above considerations, this paper constructs a Dynamic Network SBM (DNSBM) efficiency model that unifies economic development, air pollution, and health into a single framework. It comprehensively evaluates the efficiency of economic development, air pollution control, and health production in 30 Chinese provinces from 2015 to 2020, which provides a policy rationale for balancing the relationship between economic growth, air pollution, and health promotion.

2 Literature review

Consulting the relevant literature, we found that most scholarly studies of economic development, air pollution, and human health are conducted from one of four angles.

2.1 Economic development and air pollution

Economic activity closely correlates with air pollution, particularly in developing nations. In 1955, Kuznets put forth the Environmental Kuznets Curve (EKC) theory, which states that it is possible that there exists an inverted U-shaped relationship between air pollution and economic growth. At the start of economic development, environmental quality declines continuously as *per capita* income rises, but once income reaches a tipping point, increased revenues promote environmental improvement (Kuznets, 1955). Based on this, most scholars in China and abroad have experimentally tested the EKC hypothesis to investigate the link between economic growth and environmental deterioration. Omri et al. (2015) indicated a bidirectional causal relationship between carbon emissions and economic development and identified the existence of an EKC for carbon emissions. Hanif (2018) confirmed the EKC theory for low- and middle-income sub-Saharan African countries. Halliru et al. (2020) reviewed the EKC hypothesis for ECOWAS. In China, researchers have primarily studied the inverted U-shaped curve and the link between economic growth and certain pollutants (SO_2, NO_x, wastewater emissions) and greenhouse gases (CO_2; Liu et al., 2015; Kang et al., 2016; Wang et al., 2016; Wang et al., 2017; Diao et al., 2018).

Meanwhile, environmental quality has an influence on economic development, in addition to economic development having an impact on environmental quality. For example, Khoshnevis, Yazdi, and Khanalizadeh (2017) demonstrated that air pollution adversely affects labor productivity and reduces industrial production and output, thus affecting economic growth. In addition, studies have fully confirmed that technological innovation in the process of economic development is a force that cannot be ignored in mitigating environmental pollution. Antweiler et al. (2001) point out that economic growth brought about by capital accumulation increases environmental pollution, while economic growth achieved by technological progress reduces environmental pollution. Erdoğan (2019) offers a similar idea: that economic growth without technological innovation may lead to an increase in national carbon emissions. Fernández Fernández et al. (2018) further emphasized technological innovation as a driver of sustainable economic development that allows economic growth to be reconciled with reduced environmental degradation. Similarly, Zhao et al. (2021) argue that technological innovation indirectly curbs CO_2 emissions by regulating the relationship between financial risk and CO_2 emissions. It is worth noting that innovation can also be influenced by economic factors. Zakaria and Bibi (2019) emphasized that financial growth can help increase the level of technological innovation and improve the efficiency of energy use, thereby improving environmental quality. Finally, Zhou and Du (2021) confirmed that the development of green finance under strict environmental regulatory policies acts as an incentive for technological innovation.

2.2 Economic development and human health

Many studies have proven a clear correlation between economic growth and improved human health. Preston (1985) determined that the correlation between *per capita* income and longevity is cross-sectional; he showed that increases in national income led to significant increases in life expectancy in developing countries.

Asiedu et al. (2015) noted that increases in *per capita* income improved health outcomes, and the effect was stronger at higher income levels. Well (2007) confirmed that economic growth could improve health outcomes by boosting a society's standard of living, modifying the public health environment, or promoting medical technology improvements. Using data from 1991 to 2015, Bul and Moracha (2020) demonstrated that economic growth can significantly improve health in sub-Saharan Africa. Akintunde et al. (2019) analyzed the socioeconomic determinants of health in Nigeria, the largest economy in West Africa, and found that shocks to *per capita* income had a positive effect on life expectancy. Cole (2019) explored the influence of economic growth on health using data from 134 developing nations between 1970 and 2015, and found that economic growth effectively improves health outcomes. Better health, in turn, enhances the accumulation of human capital, labor productivity, and, as a result, economic outcomes (Mayer, 2001; Alderman and Behrman, 2006; Akram et al., 2008; Mary, 2018).

2.3 Air pollution and human health

Air pollution has long been studied and shown to threaten human health severely. Dominici et al. (2002) showed that air pollution significantly increased mortality among the population. In particular, Anderson (2020) explored the relationship between the duration of pollution exposure and mortality in different age groups. He found that when the time of pollution exposure doubled among people over the age of 75 years, their mortality increased by 3.6%–6.8%. Brook et al. (2010) further demonstrated that the risk of non-accidental mortality rises with chronic PM2.5 exposure. At the same time, maternity and infants are more vulnerable to air pollution compared to other age groups (Hackley et al., 2007; Thornburg et al., 2022; Wang et al., 2023). Owili et al. (2017) made a similar observation regarding the significant influence of PM2.5 on maternal mortality. Emetere and Oladimeji (2022) further demonstrated that in Nigeria that maternal deaths are mainly caused by air pollution. Burnett et al. (2018) confirmed that the degree of harm to infant survival from air pollution may vary at different levels. Other studies have concluded that air pollution may be linked to other diseases and symptoms; for example, Cao et al. (2011) found that air pollution levels were significantly correlated with cardiopulmonary disease and lung cancer mortality. Chen et al. (2012) discovered that there was a 0.75% and 0.83% increase in overall cardiovascular and respiratory mortality for every 10 g/m^3 rise in the 2-day moving average of SO_2. Vlaanderen et al. (2017) discovered that prehypertension was linked to brief airborne pollution exposure. Finally, considering the severe impact of air pollution on public health, growing public attitudes toward the environment have prompted governments to consider whether they are willing to pay for air quality improvements (Yu et al., 2015).

2.4 Economic development, air pollution, and human health

In recent years, some researchers have begun investigating the intersections among economic development, air pollution, and human health. For instance, based on the correlations among personal income, air pollution, and life expectancy, Pope et al. (2015) proposed that clean air should be considered an "economic benefit" to national health. Siddique and Kiani (2020) discovered that air pollution reduces life expectancy and increases infant mortality in middle-income countries using panel data from 1990 to 2016. This shows that low- and middle-income countries are more vulnerable to the hazards of air pollution than are middle- and high-income countries. Wang et al. (2022) used panel data for 2012 to 2016 and multivariate ordered logit models to show that increasing economic levels make public health more vulnerable to air pollution, and that economic growth is becoming less effective at minimizing the adverse effects of air pollution on public health. Katrakilidis et al. (2016) explored panel data from 1960 to 2012 using Kuznets-type models and verified that economic development, environmental quality, and public health are mutually influential and interrelated. Urhie et al. (2020) employed data from Nigeria between 1980 and 2017 and a moderated mediation model to demonstrate that economic growth affects public health through air pollution.

Although there is a growing corpus of literature on economic development, air pollution, and human health, most of these studies have concentrated on the link between two variables, rather than all three. Moreover, the dynamic research on these three variables from an efficiency standpoint needs to be enhanced. The few studies examining the links among the economy, air pollution, and health have used empirical methods, such as regression analysis, and the analytic results do not adequately account for the decision unit's internal structure and the dynamic impacts between periods. To address the gap in this research, this paper constructs a DNSBM to comprehensively assess the efficiency of economic development, health production, and air pollution control within the same framework, and proposes improvement strategies.

3 Materials and methods

3.1 DNSBM model introduction

Two major methodological difficulties emerge for the simultaneous assessment of economic, environmental and health efficiency. The first is the need for a method that can integrate the interrelationship between economic development, environmental protection and health promotion into a unified framework. The second difficulty is that the method must be able to analyse and manage any undesirable outputs that occur in different phases. Several previous studies have attempted to address these difficulties.

First of all, to solve the problem of efficiency assessment, Charnes et al. (1978) developed the first DEA model (CCR), which has been widely used. It is a nonparametric method that constructs optimal production bounds for a decision unit by solving a linear programming problem for all decision units. In so doing, the production efficiency of each decision unit is obtained by comparing the distance from each decision unit to the optimal production boundary.

Second, one major drawback of the DEA model is that it cannot handle the presence of undesirable outputs. Consequently, researchers have developed expanded DEA models to convert

inputs into desirable and undesirable outputs for superior efficiency assessment (Zhou et al., 2006; Zhou et al., 2007). In these models, economic achievements can be measured by reducing inputs or increasing desirable outputs, and reductions in environmental pollution can be reflected by reducing undesirable outputs. Previous studies using these DEA models have successfully integrated economic growth and environmental protection into a unified framework but were unable to include analyses of the internal structure of the production system and generally neglected health promotion.

Third, Network Data Envelopment Analysis (NDEA), which was proposed by Färe et al. (2010), has achieved better results in capturing the internal structure of production systems. Specifically, NDEA model state that the production process is made up of many sub-production technologies, referred to as sub-decision units (Sub-DMU). These production techniques are used to discuss the effects of inputs and outputs on the production process, and the "black box" is eventually opened by traditional DEA or SBM models to find the optimal solution. Following in the footsteps of Färe et al. (2010), Tone and Tsutsui (2009) further proposed a weighted slack-based measures NDEA model. In other words, the NDEA model is analyzed using the connection between the various departments of the decision-making unit. To find the best solution using the SBM model, each department is treated as a Sub-DMU. The NDEA model corrects the traditional DEA's failure to analyze the efficiency of each phase, but does not take intertemporal continuation into account. The activity's effect is insufficient for determining long-term efficiency. Thus, to simultaneously assess the efficiency of various phases and periods, Färe et al. (2007) used the carryover to put connected variables into a dynamic model.

Finally, Based on previous results, Tone and Tsutsui (2014) proposed a weighted slack-based measures (Dynamic Network SBM) DEA model that considers each department of a decision unit as a sub-decision unit and each carryover activity as a link, as the basis for dynamic DEA model analysis; they then used the SBM model to find the optimal solution. Therefore, the Dynamic Network SBM (DNSBM) model is an appropriate approach for economic, environmental and health efficiency assessments owing to the model's ability to integrate the three interrelated phases of economic development, environmental protection and health promotion into a unified framework.

3.2 DNSBM model setting

First, the DNSBM model that we use is a method for evaluating relative efficiency. Then, we deal with N $DMU_s\,(j=1,\ldots,n)$ consisting of k divisions $(k=1,\ldots,K)$ over T time periods $(t=1,\ldots,T)$. Next, we assume that m_k and r_k are division k's respective input and output numbers. The link from division k to division h is indicated by (k,h) and the set of links by L. Finally, the observed data are as follows.

3.2.1 Inputs and outputs

The division k input i resource for DMU_j in period t is: $x^t_{ijk}\in R_+\,(i=1,K,m_k;\,j=1,K,n;\,K=1,\ldots K,K;\,t=1,K,T)$. The division K output i resource for DMU_j in period t is: $y^t_{rjk}\in R_+\,(r=1,K,r_k;\,j=1,K,n;\,K=1,\ldots K,K;\,t=1,K,T)$. If some of the outputs are undesirable, we treat them as division k inputs.

3.2.2 Links

The link between DMU_j intermediate products from division k to division h in period t is $Z^t_{j(kh)t}\in R_+\,(j=1,K,n;\,l=1;k;L_{hk};t=1;K;T)$, where L_{hk} is the number of items in connections from k to h; *Linkin* is the number of "as input" links from division k; and $Linout_k$ is the number of "as output" links from division k.

3.2.3 Carry-overs

The carryover of DMU_j from period t to period t+1 at division k is $Z^{t,t+1}_{jkl}\in R_+\,(j=1,K,n;l=1,K,L_k;k=1,K,K;t=1,K,T-1)$, where L_k is the total number of items in the division k carryover, and $ngood_k$ and $nbad_k$, respectively, are the number of desirables (good) and undesirables (bad) for each division k.

3.2.4 Objective function

The overall efficiency is evaluated using the following program:

$$\theta^*_o=min\frac{\sum_{t=1}^{T}W^t\left[\sum_{k=1}^{K}W^k\left[1-\frac{1}{m_k+linkin_k+nbad_k}\left(\sum_{i=1}^{m_k}\frac{S^{t-}_{iok}}{x^t_{iok}}+\sum_{k_l=1}^{nbad_k}\frac{S^{(t,t+1)}_{ok_lbad}}{Z^{(t,t+1)}_{ok_lbad}}+\sum_{(k,h)_l=1}^{Linkin_k}\frac{S^t_{o(k,h)_lin}}{Z^t_{o(k,h)_lin}}\right)\right]\right]}{\sum_{t=1}^{T}W^t\left[\sum_{k=1}^{K}W^k\left[1+\frac{1}{r_k+linkout_k+ngood_k}\left(\sum_{i=1}^{r_k}\frac{S^{t+}_{iok}}{y^t_{iok}}+\sum_{k_l=1}^{ngood_k}\frac{S^{(t,t+1)}_{ok_lgood}}{Z^{(t,t+1)}_{ok_lgood}}+\sum_{(k,h)_l=1}^{Linkout_k}\frac{S^t_{o(k,h)_lout}}{Z^t_{o(k,h)_lout}}\right)\right]\right]} \tag{1}$$

In Formula (1), θ^*_o represents the overall efficiency value. When $\theta^*_o=1$, it means that the decision making unit is relatively effiective. When $\theta^*_o<1$, it means that the decision making unit is invalid; With $\sum_{t=1}^{T}W^t=1,\sum_{k=1}^{K}W^k=1,W^t\geq 0\,(\forall t),W^k\geq 0\,(\forall k)$, where $W^t\,(t=1,K,T)$ is the weight to period t, and $W^k\,(k=1,K,K)$ is the weight to division k.

The constraints are as follows:

$$\begin{aligned}
x^t_{ok}&=X^t_k\lambda^t_k+S^{t-}_{ko}\,(k=1,K,K;t=1,K,T)\\
y^t_{ok}&=Y^t_k\lambda^t_k-S^{t+}_{ko}\,(k=1,K,K;t=1,K,T)\\
e\lambda^t_k&=1\,(k=1,K,K;t=1,K,T)\\
\lambda^t_k&\gg 0,S^{t+}_{ko}\gg 0,S^{t-}_{ko}\gg 0\,(\forall k,\forall t)\\
Z^t_{(kh)free}\lambda^t_h&=Z^t_{(kh)free}\lambda^t_k\,(\forall\,(k,h)free,\forall t)\\
where\,Z^t_{(kh)free}&=\left(Z^t_{(kh)free},K,Z^t_{n(kh)free}\right)\in R^{L_{(kh)free}\times n}\\
Z^{(t,t+1)}_{o(k_l)free}&=\sum_{j=1}^{n}Z^{(t,t+1)}_{jk_lfree}\lambda^t_{jk}+S^{(t,t+1)}_{ok_lfree};\,(k_l=1,k,nfreek;\\
&\quad k=1,K,K;t=1,K,T)
\end{aligned} \tag{2}$$

where $X^t_k=(X^t_{1k},K,X^t_{nk})\in R^{m_k\times n\times T}$ an $Y^t_k=(y^t_{1k},K,y^t_{nk})\in R^{r_k\times n\times T}$ are input and output matrices, and S^{t-}_{ko} and S^{t+}_{ko} are input/output slacks, respectively.

3.2.5 Term (period) and divisional efficiencies

The term (period) efficiency is defined by:

$$\tau^{t^*}_o=min\frac{\sum_{k=1}^{K}W^k\left[1-\frac{1}{m_k+linkin_k+nbad_k}\left(\sum_{i=1}^{m_k}\frac{S^{t-}_{iok}}{x^t_{iok}}+\sum_{(k,h)=1}^{linkin_k}\frac{S^t_{o(k,h)_lin}}{Z^t_{o(k,h)_lin}}+\sum_{k_l=1}^{nbad_k}\frac{S^{(t,(t+1))}_{ok_lbad}}{Z^{(t,(t+1))}_{ok_lbad}}\right)\right]}{\sum_{k=1}^{K}W^k\left[1+\frac{1}{r_k+linkout_k+ngood_k}\left(\sum_{i=1}^{r_k}\frac{S^{t+}_{iok}}{y^t_{iok}}+\sum_{(k,h)_l=1}^{linuot_k}\frac{S^t_{o(k,h)_lout}}{Z^t_{o(k,h)_lout}}+\sum_{k_l=1}^{ngood_k}\frac{S^{(t,(t+1))}_{ok_lgood}}{Z^{(t,(t+1))}_{ok_lgood}}\right)\right]}$$
$$(\boldsymbol{t=1,K,T}) \tag{3}$$

In Formula (3), $\tau^{t^*}_o$ represents the term (period) efficiency value. When $\tau^{t^*}_o=1$, it means that the decision making unit is relatively

effiective. When $\tau_o^{t^*} < 1$, it means that the decision making unit is invalid.

Divisional efficiency is defined by:

$$\delta_{ok}^{*} = \frac{\sum_{t=1}^{T} W^{k}\left[1 - \frac{1}{m_k+linkin_k+nbad_k}\left(\sum_{i=1}^{m_k}\frac{S_{iok}^{t-}}{x_{iok}^{t}} + \sum_{(k,h)=1}^{linkin_k}\frac{S_{o(k,h)_1 in}^{t}}{Z_{o(k,h)_1 in}^{t}} + \sum_{k_1=1}^{nbad_k}\frac{S_{ok_1 bad}^{(t,(t+1))}}{Z_{ok_1 bad}^{(t,(t+1))}}\right)\right]}{\sum_{t=1}^{T} W^{t}\left[1 + \frac{1}{r_k+linkout_k+ngood_k}\left(\sum_{i=1}^{r_k}\frac{S_{iok}^{t+}}{y_{iok}^{t}} + \sum_{(k,h)_1=1}^{linuot_k}\frac{S_{o(k,h)_1 out}^{t}}{Z_{o(k,h)_1 out}^{t}} + \sum_{k_1=1}^{ngood_k}\frac{S_{ok_1 good}^{(t,(t+1))}}{Z_{ok_1 good}^{(t,(t+1))}}\right)\right]}$$
$$(k = 1, K, K) \tag{4}$$

In Formula (4), δ_{ok}^{*} represents the divisional efficiency value. When $\delta_{ok}^{*} = 1$, it means that the decision making unit is relatively effiective. When $\delta_{ok}^{*} < 1$, it means that the decision making unit is invalid.

Term (period)-divisional efficiency is defined by:

$$\rho_{ok}^{t} = \frac{1 - \frac{1}{m_k+linkin_k+nbad_k}\left(\sum_{i=1}^{m_k}\frac{S_{iok}^{t-}}{x_{iok}^{t}} + \sum_{(k,h)=1}^{linkin_k}\frac{S_{o(k,h)_1 in}^{t}}{Z_{o(k,h)_1 in}^{t}} + \sum_{k_1=1}^{nbad_k}\frac{S_{ok_1 bad}^{(t,(t+1))}}{Z_{ok_1 bad}^{(t,(t+1))}}\right)}{1 + \frac{1}{r_k+linkout_k+ngood_k}\left(\sum_{i=1}^{r_k}\frac{S_{iok}^{t+}}{y_{iok}^{t}} + \sum_{(k,h)_1=1}^{linuot_k}\frac{S_{o(k,h)_1 out}^{t}}{Z_{o(k,h)_1 out}^{t}} + \sum_{k_1=1}^{ngood_k}\frac{S_{ok_1 good}^{(t,(t+1))}}{Z_{ok_1 good}^{(t,(t+1))}}\right)}$$
$$(k = 1, K, K; t = 1, K, T) \tag{5}$$

In Formula (5), $\rho_{ok}^{t^*}$ represents the term (period)-divisional value. When $\rho_{ok}^{t^*} = 1$, it means that the decision making unit is relatively effiective. When $\rho_{ok}^{t^*} < 1$, it means that the decision making unit is invalid.

Furthermore, we used Hu's (Hu and Wang, 2006) approach to assess the undesirable output efficiency:

$$\text{PM2.5 efficiency: } \frac{Target\ Undesirable\ PM2.5\ input\ (i,t)}{Actual\ Undesirable\ PM2.5\ input\ (i,t)} \tag{6}$$

$$SO_2 \text{ efficiency: } \frac{Target\ Undesirable\ SO_2\ input\ (i,t)}{Actual\ Undesirable\ SO_2\ input\ (i,t)} \tag{7}$$

$$NO_x \text{ efficiency: } \frac{Target\ Undesirable\ NO_x\ input\ (i,t)}{Actual\ Undesirable\ NO_x\ input\ (i,t)} \tag{8}$$

$$\text{Improvement ratio of variable} = 1 - \text{efficiency of variable} \tag{9}$$

In the above equations, i represents area and t represents time. When the target air pollutant input is equal to the actual input level, air pollutant control efficiency is equal to 1, indicating overall high efficiency; on the other hand, when the target air pollutant input is lower than the actual input level, air pollutant control efficiency is lower than 1, indicating overall inefficiency.

3.3 Data and variables

3.3.1 Data source

This study evaluates 30 provinces in China (including autonomous regions and municipalities directly under the central government), excluding Hong Kong, Macao, Tibet, and Taiwan. These are omitted because the majority of the data is missing. We divide the provinces into regions based on geographical differences: eastern, central, and western (Figure 1). The eastern region includes Beijing, Tianjin, Hebei, Shanghai, Hainan, and other provinces; the central area is composed of Shanxi, Jilin, Heilongjiang, Anhui, Jiangxi, Henan, and other provinces; and the western area is made up of Inner Mongolia, Chongqing, Guangxi, and other provinces. In addition, the "China Population and Employment Statistical Yearbook," the "China Health and Health Yearbook," and the "China Statistical Yearbook" provide data on Chinese economic and social development from 2015 to 2020. The "China Environmental Protection Bureau Annual Report" and the "China Environmental Statistics Yearbook" provide data on Chinese air pollutants.

3.3.2 Variables selection

Economic development stage variables:

Regarding input indicators, with reference to previous studies (Li et al., 2019a; Li et al., 2019b; He et al., 2020; Li et al., 2020), we chose to use labor and energy consumption as input indicators. However, this paper cannot include fixed assets as input indicators due to limitations in data availability. Regarding output indicators, we selected the Gross Domestic Product (GDP) as the output indicator (Sueyoshi et al., 2021).

Link economic development stage and healthy production stage variables:

The links PM2.5, SO_2, and NO_x are from (Zhang et al., 2018a; Lin et al., 2021). The carry-over variable for multiple periods is government health expenditures, referring to (Zhang et al., 2022).

Health production stage variables:

Regarding input indicators, this paper restricts health inputs to those that act directly on health (i.e., inputs in healthcare). In line with the relevant literature (Kawaguchi et al., 2014; Flokou et al., 2017; Top et al., 2020), we selected the number of health technicians per 1,000 population and the number of beds per 1,000 population as input indicators. Regarding output indicators, it is clear from the literature (Evans et al., 2000; Afonso and Aubyn, 2005; Spinks and Hollingsworth, 2009; Rajaratnam et al., 2010; Rutherford et al., 2010) that the main output indicators of population health status are: average life expectancy, disability-adjusted life expectancy, maternal mortality, and infant mortality, among others. Due to the lag in the release of Chinese health statistics, there are many gaps in current data on average life expectancy and disability-adjusted life expectancy, which do not reflect the sustained level of healthy production. Thus, this paper selects the maternal mortality rate and perinatal mortality rate as output indicators. However, since the levels of maternal mortality and perinatal mortality do not represent whether the trend of health output efficiency is positive or not, this indicator of health output is in inverse form (i.e., a higher value of the indicator represents a lower level of health output; Hadad et al., 2013). Consequently, we borrowed from (Sayem et al., 2019) to take the inverse of the indicator and transform it into maternal survival rate and perinatal survival rate.

Based on the above analysis, Figure 2 depicts the framework of the DNSBM model's intertemporal efficiency measures and variables.

4 Empirical analysis

4.1 Statistical analysis of relevant variables

Figure 3 shows the statistical analysis of the related variables. Regarding indicators of economic development, labor force input grew significantly from 2015 to 2020; therefore, the 6-year trend is somewhat increasing. Further, average energy consumption did not rise dramatically, and the highest and lowest levels of energy

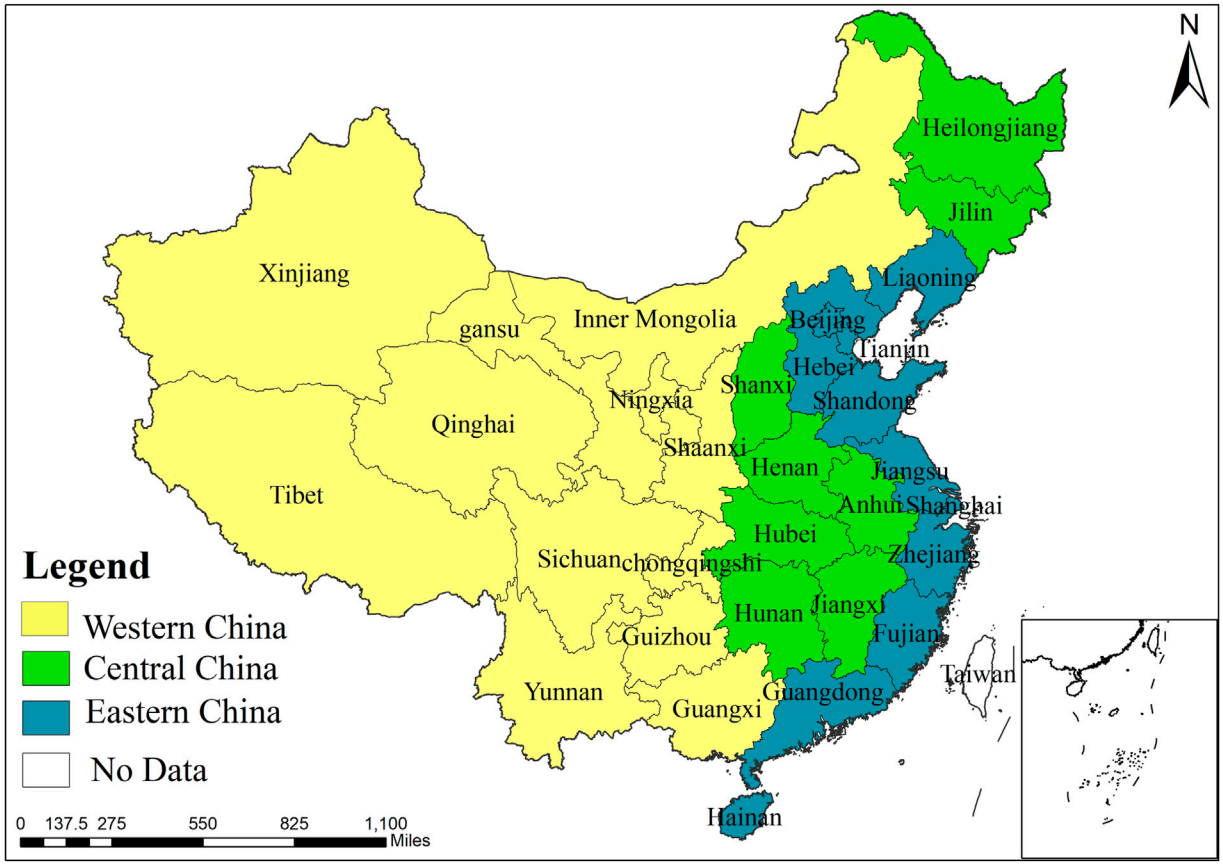

FIGURE 1
Distribution map of western, central, and eastern regions in China.

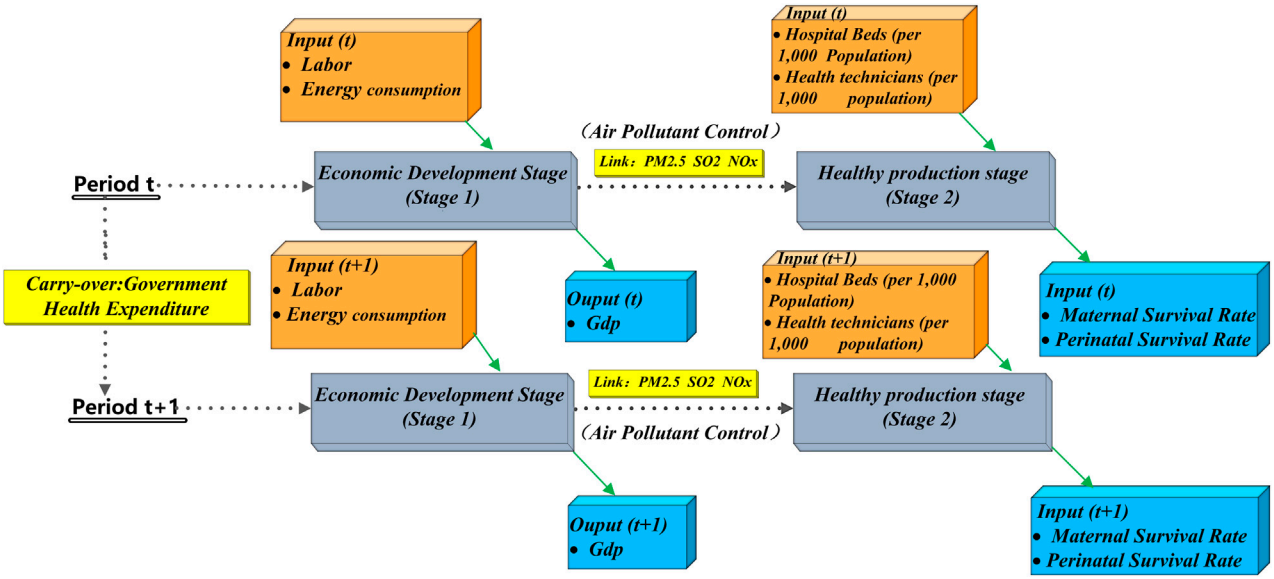

FIGURE 2
Dynamic and network SBM (DNSBM) model.

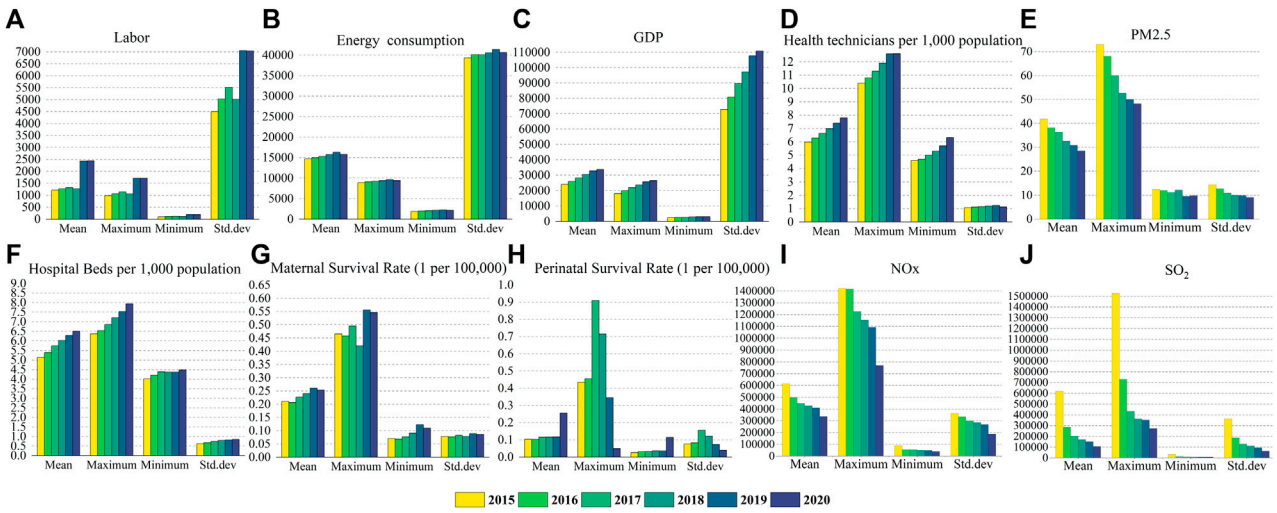

FIGURE 3
Statistical description of variables from 2015 to 2020. **(A)** Labor, **(B)** Energy consumption, **(C)** GDP, **(D)** Health technicians per 1,000 population, **(E)** PM2.5, **(F)** Hospital Beds per 1,000 population, **(G)** Maternal Survival Rate (1 per 100,000), **(H)** Perinatal Survival Rate (1 per 100,000), **(I)** NO_x, **(J)** SO_2.

consumption did not vary significantly. The highest GDP has steadily increased since 2015: the highest value climbed by 379.48 billion yuan from 2015 to 2020, while the lowest value increased modestly, from 230.332 billion yuan in 2015 to 262.48 billion yuan in 2020. However, the overall trend is still increasing slowly, from 241.7 billion yuan in 2015 to 300.6 billion yuan in 2020. This demonstrates that China's production capacity is improving, and the provinces' economic strength is gradually increasing.

Regarding indicators for health production, the average, highest, and lowest values of health technicians per 1,000 population and beds per 1,000 population exhibit consistent upward trends and significant overall increases. There is a fluctuating upward trend in the average perinatal survival rate, but the maximum value in 2018 was only 0.42, much lower than the other years, and it returned to 0.55 in 2020. The mean maternal survival rate (per 100,000 pregnancies) increased slightly, from 0.211 in 2015 to 0.254 in 2020; the maximum value decreased from 0.465 in 2015 to 0.495 in 2017, and then to 0.05 in 2020. This suggests that, while China's investment in health resources has increased year after year, it has yet to maximize health outcomes.

Regarding indicators for air pollutants, the average value of PM2.5 concentration decreased from 41.81 ug/m^3 in 2015 to 28.53 ug/m^3 in 2020. The average value of SO_2 emissions decreased from 619,527 tons in 2015 to 105,884 tons in 2020. NO_x emissions decreased from 615,250 tons in 2015 to 33,888 tons in 2020. The maximum values of PM2.5 concentration, SO_2 emissions, and NO_x emissions also show a decreasing trend. It is noteworthy that the difference between the maximum and minimum values of SO_2 emissions is the most significant of the pollutants. The above analysis shows that, in recent years, the Chinese government has been emphasizing the importance of air pollution control and investing a tremendous amount of funds in energy conservation and emission reduction, thus effectively mitigating the public health hazards of air quality deterioration.

4.2 Empirical results analysis

4.2.1 Analysis of economic development efficiency

We estimated the economic development efficiency of 30 provinces from 2015 to 2020 using the DNSBM model, including labor and energy consumption as input indicators and GDP as an output indicator. The results (Table 1; Figure 4A) show that Beijing, Shanghai, and Jiangsu had the highest average efficiency of economic development; provinces such as Tianjin, Zhejiang, and Fujian had an average efficiency of economic development of around 0.9, which was significantly higher than that of other provinces. Provinces such as Ningxia, Qinghai, Anhui, and Hubei had an economic development efficiency of 0.4–0.8. Xinjiang had the lowest average economic development efficiency of 0.34, followed by Gansu at 0.391, showing that the region requires further improvement.

There are also important regional differences. In the east (Figure 4B), the efficiency of economic development in Beijing, Shanghai, Jiangsu, and Guangdong was always equal to 1, suggesting that economic resources in these provinces are adequately employed. Hainan's efficiency was equal to 1 in all previous periods, but declined significantly to around 0.5 in 2020, showing that the high efficiency of economic resource usage in the first 5 years did not continue. Hebei's trend of changing economic development efficiency is similar to Liaoning's, where efficiency has declined for 6 years, with Liaoning reaching a low of 0.286 in 2020. Tianjin's and Shandong's economic development efficiency values were equal to 1 in 2015–2018 but dropped to around 0.7 in 2019–2020. In the central region (Figure 4C), Jiangxi had the highest economic development efficiency, with a stable efficiency value of 1 in 2015–2019, but it dropped sharply to about 0.4 in 2020. Hunan had the greatest swing, with an economic development efficiency of 1 in 2016–2018 that fell

TABLE 1 Economic development efficiency, by province and region, 2015–2020.

Region	DMU	2015	2016	2017	2018	2019	2020	2015–2020
Eastern	Beijing	1	1	1	1	1	1	1
	Guangdong	1	1	1	1	1	1	1
	Shanghai	1	1	1	1	1	1	1
	Jiangsu	1	1	1	1	1	1	1
	Hainan	1	1	1	1	1	0.530	0.922
	Tianjin	1	1	1	1	0.754	0.760	0.919
	Shandong	1	1	1	1	0.645	0.765	0.902
	Zhejiang	0.931	0.959	0.940	0.912	0.841	1.000	0.931
	Fujian	0.966	0.940	0.931	0.956	0.978	0.833	0.934
	Liaoning	0.859	0.604	0.624	0.618	0.368	0.286	0.560
	Hebei	0.768	0.706	0.670	0.689	0.361	0.359	0.592
Central	Jiangxi	1	1	1	1	1	0.465	0.911
	Hunan	0.932	1	1	1	0.682	0.495	0.852
	Hubei	0.885	0.920	0.914	0.909	0.790	0.562	0.830
	Jilin	0.880	0.842	0.812	0.767	0.387	0.285	0.662
	Shaanxi	0.789	0.707	0.720	0.803	0.515	0.455	0.665
	Anhui	0.816	0.790	0.772	0.815	0.668	0.521	0.730
	Henan	0.843	0.822	0.826	0.840	0.688	0.681	0.783
	Heilongjiang	0.768	0.665	0.620	0.630	0.333	0.257	0.546
Western	Yunnan	1	1	1	1	1	1	1
	Guangxi	0.863	0.768	0.757	0.785	0.465	0.305	0.657
	Shaanxi	0.789	0.707	0.720	0.803	0.515	0.455	0.665
	Chongqing	0.781	0.751	0.734	0.720	0.623	0.504	0.686
	Sichuan	0.745	0.756	0.904	0.812	0.574	0.570	0.727
	Inner Mongolia	0.689	0.613	0.443	0.477	0.351	0.310	0.481
	Qinghai	0.635	0.654	0.636	0.527	0.430	0.352	0.539
	Gansu	0.501	0.447	0.398	0.460	0.321	0.217	0.391
	Guizhou	0.499	0.524	0.544	0.609	0.354	0.223	0.459
	Ningxia	0.463	0.456	0.402	0.471	0.419	0.465	0.446
	Xinjiang	0.316	0.419	0.353	0.411	0.295	0.248	0.340
	Geometric mean	0.813	0.793	0.781	0.790	0.638	0.559	0.729
	Std. Dev.	0.198	0.203	0.221	0.205	0.266	0.276	0.199

to 0.495 in 2020. Jilin's and Heilongjiang's economic development efficiency values steadily declined over the last 6 years and are projected to decrease to around 0.25 by 2020. In the western region (Figure 4D), during the study period, the economic development efficiency of Yunnan reached 1. Except for Guangxi, Chongqing, Sichuan, and Shaanxi, most remaining provinces were below 0.6 in 2015–2020. For example, Xinjiang was below 0.4 in four out of 6 years studied. Gansu's efficiency was below 0.4 in three of the last 6 years, and it fell to a minimum of 0.217 in 2020.

4.2.2 Analysis of healthy production efficiency

We estimated the health production efficiency of 30 provinces from 2015 to 2020 by applying the DNSBM model, using health technicians per 1,000 population and beds per 1,000 population as input indicators and maternal survival rate and perinatal survival rate as output indicators.

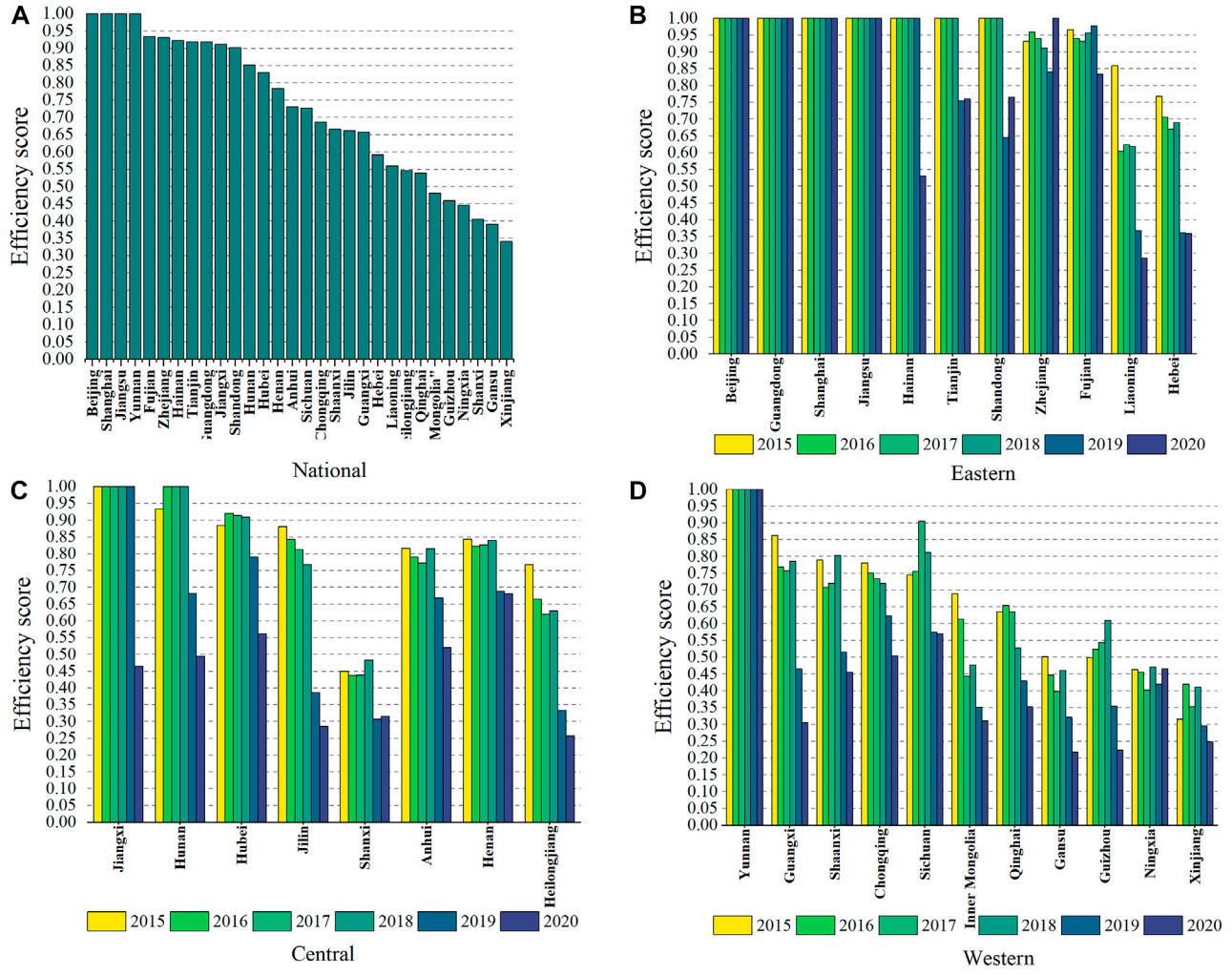

FIGURE 4
Economic development efficiency by province and region from 2015 to 2020. **(A)** Average economic development efficiency (geometric mean) in 30 provinces of China from 2015 to 2020. **(B)** Economic development efficiency in 11 provinces of the eastern region from 2015 to 2020. **(C)** Economic development efficiency in 8 provinces of the central region from 2015 to 2020. **(D)** Economic development efficiency in 11 provinces of the western region from 2015 to 2020.

The study results (Table 2; Figure 5A) show that only Beijing, Shanghai, Guangdong, and Jiangxi had an average efficiency of 1 in health production. This demonstrates that the healthcare services provided in these places are of outstanding quality and that the health production scale effect may be fulfilled. In contrast, health production efficiency in other provinces is generally poor; in different years, some provinces were severely inefficient, falling below 0.3. This indicates the region's failure to integrate economic development with healthy production and the need for significant improvements.

There are also important regional differences. In the eastern region (Figure 5B), health production efficiency was generally higher in the east than in the midwest. The fact that some provinces' health production efficiency was comparable to or even lower than that of the midwest should be emphasized. For example, Liaoning's health production efficiency has been consistent, at roughly 0.4 during the last 6 years. The health production in Hainan and Tianjin remained equal to 1 in the early period, but exhibited a slight fall in 2019–2020. Zhejiang is the most volatile province, with healthy production efficiency remaining around 0.6 in 2015–2016 but rising to 1 in 2020. In the central region (Figure 5C), Jiangxi has the most efficient health production. Shanxi, Heilongjiang, and Jilin have low health production efficiency, which remained between 0.4 and 0.5 for the past 6 years. In Henan, health production efficiency decreased over the first 5 years but peaked at 0.741 in 2020. In the western region (Figure 5D), Yunnan had the highest health production efficiency, reaching over 0.6; Xinjiang had the lowest value of 0.235. The efficiency of the remaining provinces, such as Inner Mongolia, Gansu, and Qinghai, was below 0.4. Ningxia was the most volatile, with healthy production efficiency falling below 0.4 in 2015–2018, but reaching a peak of around 0.7 in 2019–2020.

4.2.3 Analysis of overall efficiency

We additionally estimated the overall efficiency of the 30 provinces for the period 2015–2020 using the DNSBM model. Table 3 and Figure 6 display the calculated outcomes.

The findings reveal significant variation in the overall efficiency of the provinces. For example, the last 6 years have seen overall efficiency equal to 1 in Beijing, Shanghai, and Guangdong; these provinces have the highest resource utilization efficiency in the study. Zhejiang's overall

TABLE 2 Healthy production efficiency, by province and region, 2015–2020.

Region	DMU	2015	2016	2017	2018	2019	2020	2015–2020
Eastern	Beijing	1	1	1	1	1	1	1
	Shanghai	1	1	1	1	1	1	1
	Guangdong	1	1	1	1	1	1	1
	Hainan	1	1	1	1	1	0.973	0.996
	Tianjin	1	1	1	1	0.890	0.834	0.954
	Shandong	1	1	0.932	0.950	0.628	0.735	0.874
	Jiangsu	1	1	0.881	0.955	0.986	1.000	0.970
	Hebei	0.810	0.781	0.857	0.800	0.742	0.792	0.797
	Zhejiang	0.657	0.659	0.620	0.688	0.857	1.000	0.747
	Fujian	0.604	0.623	0.641	0.709	0.666	0.816	0.677
	Liaoning	0.477	0.473	0.383	0.431	0.421	0.514	0.450
Central	Jiangxi	1	1	1	1	1	1	1
	Anhui	0.727	0.734	0.759	0.781	0.812	0.791	0.767
	Henan	0.731	0.715	0.684	0.640	0.618	0.741	0.688
	Hubei	0.549	0.534	0.552	0.598	0.602	0.658	0.582
	Hunan	0.543	0.672	0.768	0.586	0.465	0.586	0.603
	Shanxi	0.451	0.381	0.414	0.408	0.427	0.496	0.430
	Heilongjiang	0.394	0.415	0.431	0.414	0.394	0.407	0.409
	Jilin	0.377	0.384	0.406	0.371	0.375	0.489	0.400
Western	Yunnan	0.641	1	0.738	0.818	0.917	0.823	0.823
	Sichuan	0.608	0.615	0.660	0.644	0.616	0.627	0.628
	Chongqing	0.579	0.576	0.536	0.590	0.512	0.625	0.570
	Guizhou	0.574	0.455	0.449	0.373	0.385	0.409	0.441
	Shaanxi	0.522	0.530	0.549	0.530	0.556	0.665	0.559
	Guangxi	0.426	0.484	0.423	0.437	0.396	0.651	0.470
	Inner Mongolia	0.467	0.420	0.420	0.420	0.437	0.406	0.428
	Gansu	0.384	0.357	0.336	0.320	0.311	0.438	0.358
	Ningxia	0.313	0.261	0.306	0.417	0.697	0.725	0.453
	Qinghai	0.344	0.326	0.315	0.458	0.453	0.495	0.399
	Xinjiang	0.262	0.203	0.170	0.225	0.244	0.303	0.235
	Geometric mean	0.648	0.653	0.641	0.652	0.647	0.700	0.657
	Std. Dev.	0.249	0.266	0.257	0.250	0.245	0.276	0.230

efficiency was less than 1 in 2015–2019 but rose to 1 in 2020; Jiangxi's and Hainan's overall efficiency values were 1 in 2015–2019 but fell to around 0.74 in 2020. Tianjin, Jiangsu, Yunnan, and Shandong performed well in terms of overall efficiency among the inefficient provinces; with the highest efficiency of less than 0.32 during the past 6 years, Xinjiang has the lowest performance. The efficiency of Liaoning, Jilin, and Guangxi was between 0.5 and 0.7, while that of Shanxi, Heilongjiang, Inner Mongolia, Guizhou, Qinghai, and Ningxia was around 0.4. As a result, these provinces must focus on overall efficiency improvement.

Over time, different trends in overall efficiency emerged among the provinces. For example, the overall efficiency of four provinces—Zhejiang, Fujian, Yunnan, and Ningxia—consistently climbed. Among them, Zhejiang experienced the largest increase, from 0.794 in 2015 to 1 in 2020, followed by Ningxia, from 0.388 in 2015 to 0.595 in 2020. Yet, the overall efficiency of the remaining 26 provinces decreased. Among them, Jiangxi and Liaoning had the largest decline, from 1 to 0.668, respectively, in 2015 to 0.732 and 0.4 in 2020. According to these results, we discovered

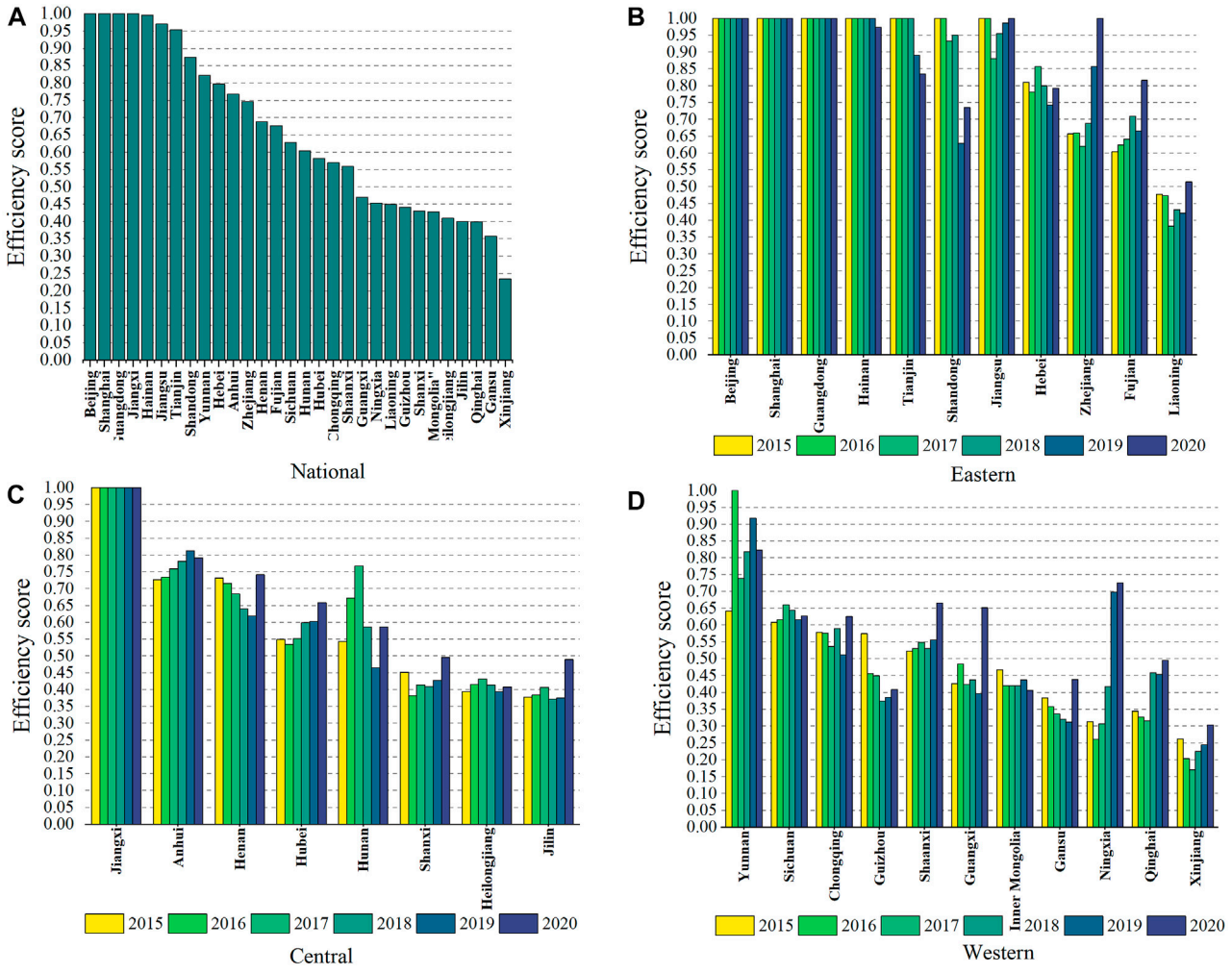

FIGURE 5
Healthy production efficiency by province and region from 2015 to 2020. **(A)** Average healthy production efficiency (geometric mean) in 30 provinces of China from 2015 to 2020. **(B)** Healthy production efficiency in 11 provinces of the eastern region from 2015 to 2020. **(C)** Healthy production efficiency in 8 provinces of the central region from 2015 to 2020. **(D)** Healthy production efficiency in 11 provinces of the western region from 2015 to 2020.

that there are more provinces with falling efficiency values than with growing efficiency values. This demonstrates that most provinces must perform better in terms of economic development and health production.

4.2.4 Comparative analysis of overall efficiency and two-stage efficiency

As shown in Figure 7A, economic development efficiency is the most crucial component of China's total efficiency performance, followed by health production efficiency. Figure 7B displays some trends in the data. Over the period 2015–2020, the decline in the efficiency of economic development led to a drop in overall efficiency, while the rise in the efficiency of health production was the main contributor to mitigating the decline in overall efficiency. Specifically, economic development efficiency exhibited negative growth in all years except 2017–2018. In contrast, health productivity efficiency showed positive growth in all years except 2016–2017 and 2018–2019, which showed negative growth.

The Kruskal–Wallis test was used to analyze the efficiency differences across the eastern, central, and western regions, and the *p*-values were compared with the confidence level, α, which was set at 0.01, 0.05, and 0.10. Table 4 provides detailed test results. Most of the *p*-values in the various phases from 2015 to 2020 are less than 0.05, and the validation findings are very significant, showing substantial variation in efficiency across the east, central, and west. Specifically, regarding overall efficiency (Figure 8A), the eastern region began from a relatively high base, and it extended its advantage over the central and western regions during the study period. This indicates that the east outperformed the west and central regions regarding economic development and health production. It is well known that unbalanced regional development has become a growing concern in China. However, the Chinese government has tried to promote the development of the central and western regions by introducing preferential policies and investing significant resources to solve this problem. Still, our calculations indicate that the midwest has continued to lag in terms of efficiency

TABLE 3 Overall efficiency, by province and region, 2015–2020.

Region	DMU	2015	2016	2017	2018	2019	2020	2015–2020
Eastern	Beijing	1	1	1	1	1	1	1
	Guangdong	1	1	1	1	1	1	1
	Shanghai	1	1	1	1	1	1	1
	Hainan	1	1	1	1	1	0.751	0.959
	Tianjin	1	1	1	1	0.822	0.797	0.937
	Shandong	1	1	0.966	0.975	0.637	0.750	0.888
	Jiangsu	1	1	0.941	0.977	0.993	1	0.985
	Hebei	0.789	0.743	0.764	0.745	0.551	0.575	0.695
	Zhejiang	0.794	0.809	0.780	0.800	0.849	1	0.839
	Fujian	0.785	0.781	0.786	0.832	0.822	0.824	0.805
	Liaoning	0.668	0.539	0.504	0.524	0.394	0.400	0.505
Central	Jiangxi	1	1	1	1	1	0.732	0.955
	Henan	0.787	0.769	0.755	0.740	0.653	0.711	0.736
	Anhui	0.771	0.762	0.766	0.798	0.740	0.656	0.749
	Hunan	0.738	0.836	0.884	0.793	0.573	0.540	0.727
	Hubei	0.717	0.727	0.733	0.753	0.696	0.610	0.706
	Jilin	0.629	0.613	0.609	0.569	0.381	0.387	0.531
	Heilongjiang	0.581	0.540	0.525	0.522	0.364	0.332	0.477
	Shanxi	0.450	0.409	0.427	0.445	0.367	0.406	0.417
Western	Yunnan	0.820	1	0.869	0.909	0.958	0.911	0.911
	Chongqing	0.680	0.664	0.635	0.655	0.567	0.565	0.628
	Sichuan	0.677	0.685	0.782	0.728	0.595	0.599	0.678
	Guangxi	0.645	0.626	0.590	0.611	0.431	0.478	0.564
	Shaanxi	0.655	0.618	0.635	0.667	0.536	0.560	0.612
	Inner Mongolia	0.578	0.516	0.431	0.449	0.394	0.358	0.454
	Guizhou	0.536	0.489	0.496	0.491	0.369	0.316	0.450
	Gansu	0.442	0.402	0.367	0.390	0.316	0.328	0.374
	Qinghai	0.490	0.49	0.475	0.493	0.442	0.424	0.469
	Ningxia	0.388	0.358	0.354	0.444	0.558	0.595	0.450
	Xinjiang	0.289	0.311	0.262	0.318	0.270	0.276	0.288
	Geometric mean	0.730	0.723	0.711	0.721	0.643	0.629	0.693
	Std. Dev.	0.208	0.226	0.229	0.219	0.247	0.235	0.212

levels. These gaps have widened in recent years and may continue to do so in the future. Furthermore, economic development efficiency (Figure 8B) decreased in all three regions. The east began with a relatively high standard among the three regions, suggesting that it performed more efficiently, using its economic output for economic development. According to the findings, the eastern region had better economic development efficiency in 2020, an advantage that appears to be expanding in the years ahead. Despite the fluctuating downward trend in health production efficiency in the three significant regions around 2017 (Figure 8C), it still improved at the end of the observation period compared to 2015. Finally, the eastern region's health production efficiency is higher than the national average; as evidence of the "central collapse"

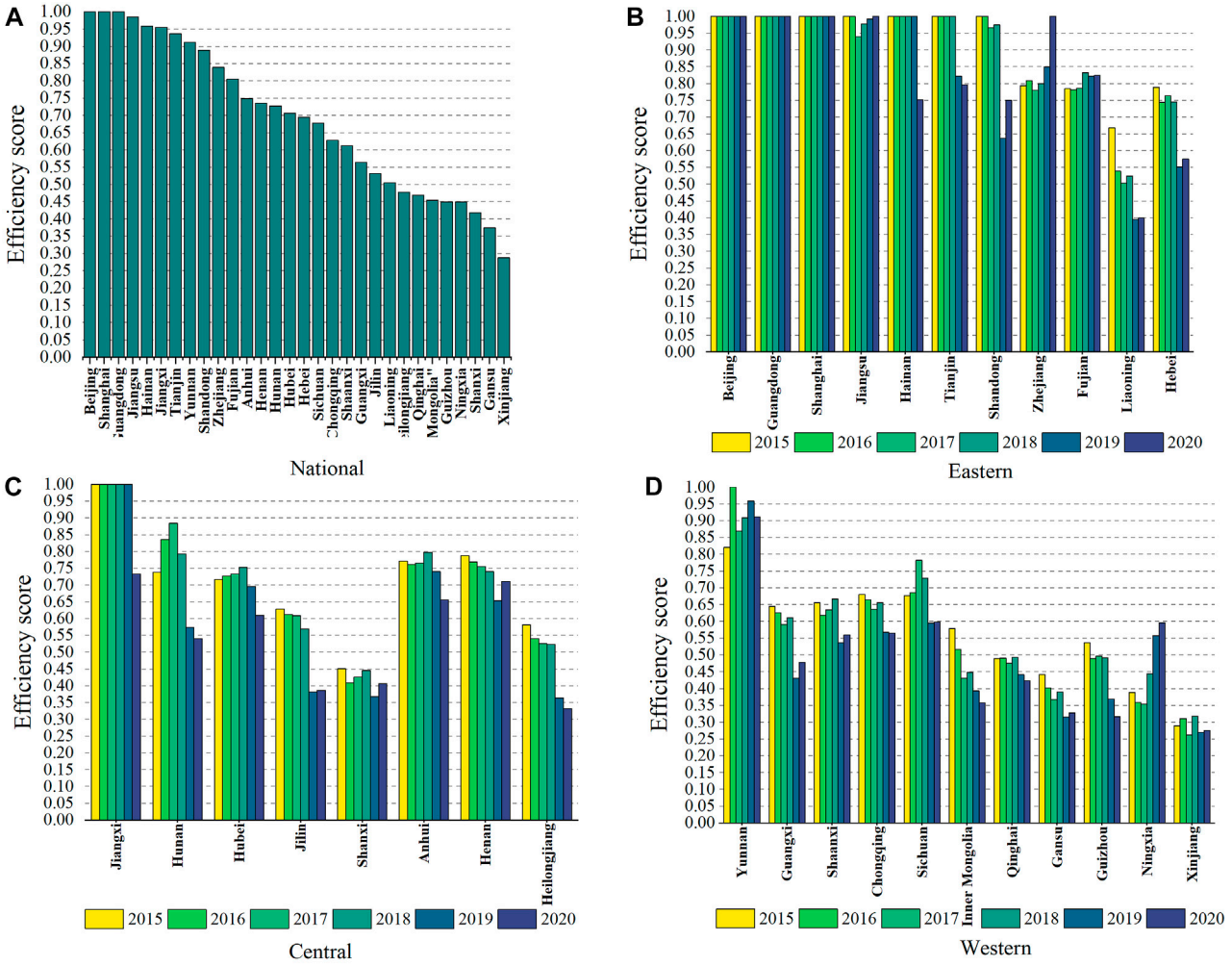

FIGURE 6
Overall efficiency by province and region from 2015 to 2020. **(A)** Average overall efficiency (geometric mean) in 30 provinces of China from 2015 to 2020. **(B)** Overall efficiency in 11 provinces of the eastern region from 2015 to 2020. **(C)** Overall efficiency in 8 provinces of the central region from 2015 to 2020. **(D)** Overall efficiency in 11 provinces of the western region from 2015 to 2020.

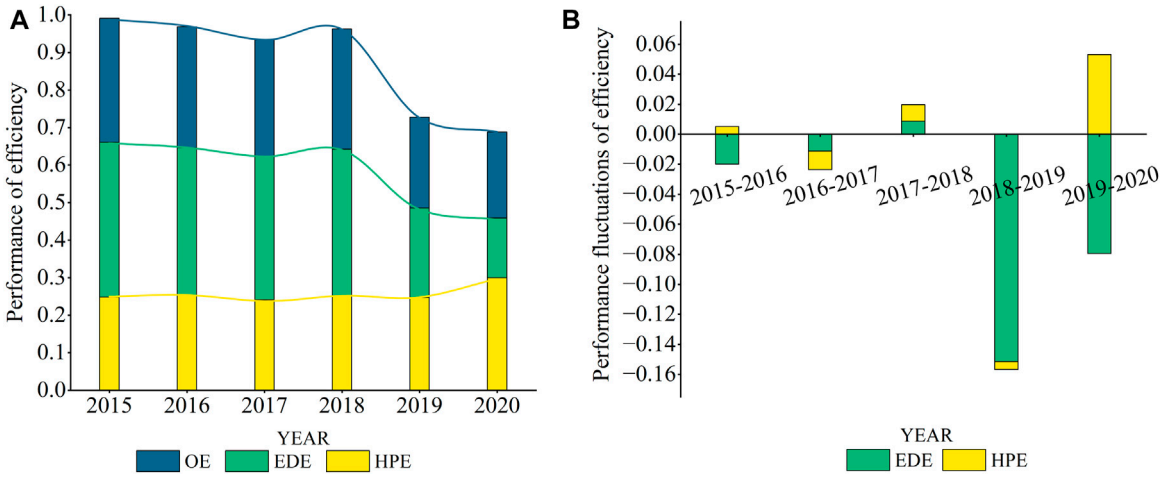

FIGURE 7
The performance of efficiency in China during the period of 2015–2020. **(A)** The performance of Overall Efficiency (OE), Economic Development Efficiency (EDE), and Healthy Production Efficiency (HPE) in China during the period of 2015–2020. **(B)** The performance fluctuation of Economic Development Efficiency (EDE), and Healthy Production Efficiency (HPE) in China during the period of 2015–2010.

TABLE 4 Kruskal–Wallis test of all-stage efficiencies for the eastern, central, and western regions, 2015–2020.

Stages	2015	2016	2017	2018	2019	2020	2015–2020
Economic development	14.334***	11.156**	10.788**	11.599**	8.347	9.521*	11.98**
Healthy production	13.946***	12.206**	12.173**	12.931**	10.52**	12.931**	12.789**
Overall phase	15.985***	12.706***	12.908**	14.177***	9.774*	12.521**	13.886***

Notes: *$p < 0.1$; **$p < 0.05$; ***$p < .001$.

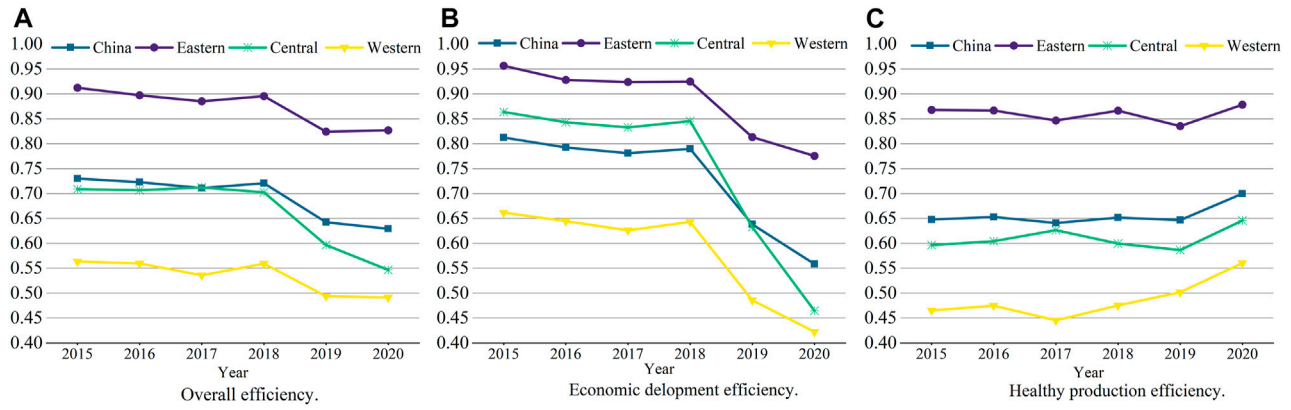

FIGURE 8
Comparison of different stage efficiency in the three regions. **(A)** Comparison of overall efficiency in China and three regions from 2015 to 2020. **(B)** Comparison of economic development efficiency in China and the three regions from 2015 to 2020. **(C)** Comparison of healthy production efficiency in China and the three regions from 2015 to 2020.

phenomenon, the values for the central and western areas are lower than the national average.

4.2.5 Analysis of air pollution control efficiency

This study also evaluated the air pollution control capacity of 30 Chinese provinces using the DNSBM model for 2015–2020. The results reveal that China's average PM2.5, SO_2, and NO_x control efficiency are 0.786, 0.710, and 0.718, respectively; these are relatively low and have considerable room for improvement. Specifically, regarding PM2.5 (Figure 9A), 13 provinces have a governance efficiency higher than 0.9, accounting for 43.3% of the total. The provinces with the lowest efficiency are Shanxi, Xinjiang, Gansu, and Ningxia, with governance efficiencies below 0.5. Regarding SO_2 (Figure 9B), ten provinces have a governance efficiency higher than 0.9, accounting for 33.3% of the total. The eight provinces with the lowest efficiency are Shanxi, Inner Mongolia, Gansu, Liaoning, Chongqing, Guizhou, Xinjiang, and Ningxia, with governance efficiencies below 0.5. Turning to NO_x (Figure 9C), ten provinces have a governance efficiency higher than 0.9, accounting for 33.3% of the total. The eight provinces with the lowest efficiency are Hebei, Shanxi, Inner Mongolia, Heilongjiang, Anhui, Liaoning, Xinjiang, and Ningxia, all with governance efficiencies below 0.5.

Considering these dramatic regional differences, China's potential to reduce air pollution is enormous. If these inefficient provinces are given the management capacity and cutting-edge technology possessed by the more efficient provinces, they should be able to achieve this goal. In addition, as shown in Table 5, most of the p-values for air pollutants from 2015 to 2020 are less than 0.05, and the validation findings are very significant, showing substantial variation in the air pollution control efficiency across the eastern, central, and western provinces. Figure 9 makes it clear that all of the high-efficiency provinces are in the developed eastern region. Five of the eight provinces that are inefficient are located in the west, while three are located in the center of the country. It is evident that regional economic development is positively connected with air pollution control. Thus, economic growth could be essential in improving the effectiveness of regional air pollution control in China.

Next, we applied the DNSBM model for each inefficient province to capture their air pollution reduction targets. However, when we examined the data we discovered that these provinces are struggling to meet the DNSBM model-calculated targets because of their significant differences from the efficient provinces regarding economic development, management capability, and technological level. As a result, the DNSBM model's air pollution reduction targets in this study are considered long-term goals, as they are not achievable in the short term for inefficient provinces. To further demonstrate the point, Table 6 shows the actual and target values for each province in China and the improvement in PM2.5 concentrations, SO_2 emissions, and NO_x emissions.

As seen in Table 6, Beijing, Shanghai, Jiangsu, Jiangxi, Guangdong, and Yunnan have zero air pollution reduction targets and are benchmarks for other inefficient Chinese

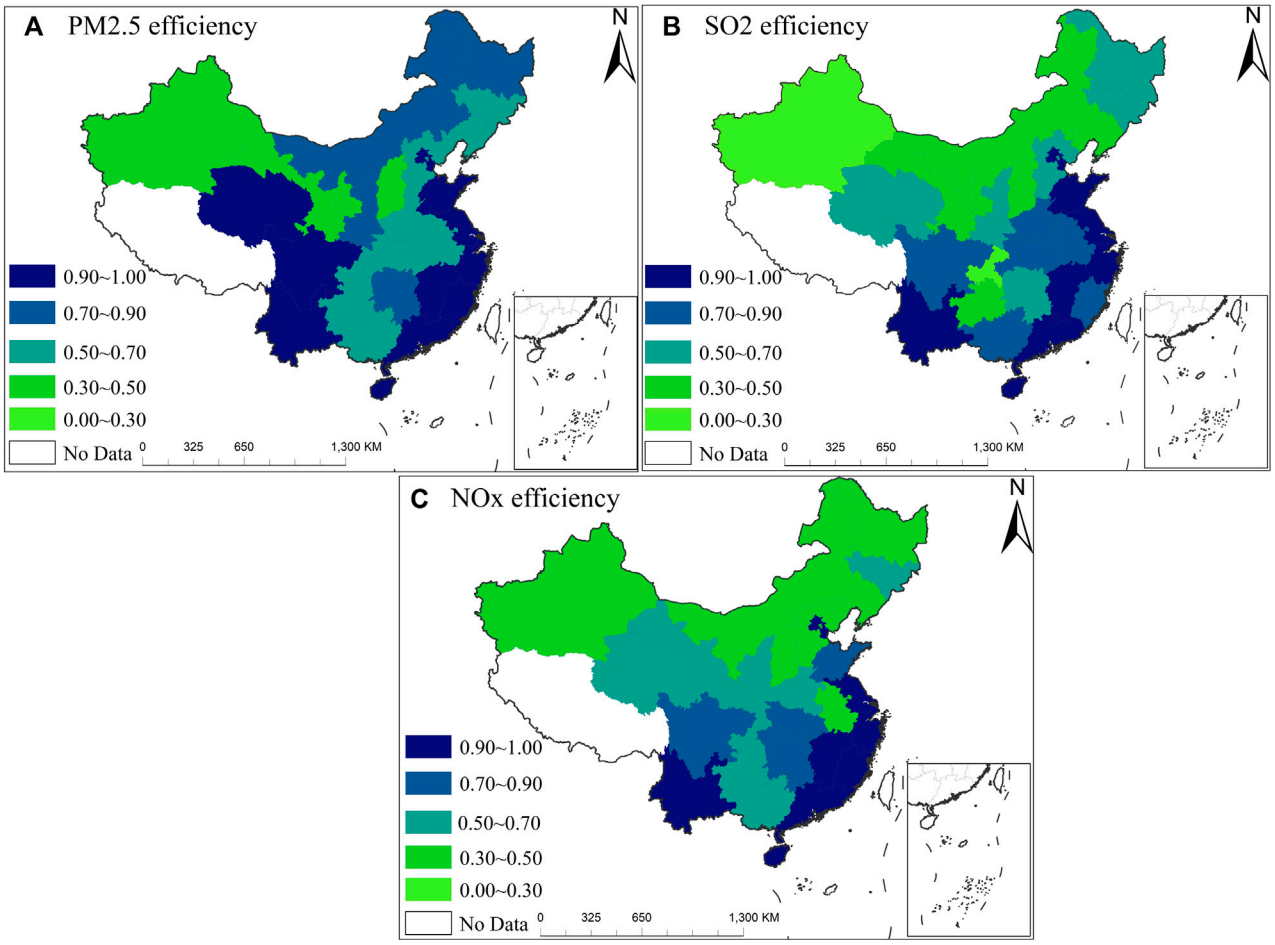

FIGURE 9
Regional disparities of air pollution efficiency in China. **(A)** Average control efficiency (geometric mean) of PM2.5 in China from 2015 to 2020. **(B)** Average control efficiency (geometric mean) of SO_2 in China from 2015 to 2020. **(C)** Average control efficiency (geometric mean) of NO_x in China from 2015 to 2020.

TABLE 5 Kruskal–Wallis test of air pollutant control efficiency for the eastern, central, and western regions, 2015–2020.

Air pollutant	2015	2016	2017	2018	2019	2020	2015–2020
PM2.5	8.841	7.256*	6.429**	10.546**	4.809*	2.823	7.236**
SO2	10.175**	3.709	5.96*	8.544*	7.776**	6.288*	9.176**
NOx	8.881**	6.764**	6.158**	8.128**	5.065*	4.815*	7.228**

Notes: *$p < 0.10$; **$p < 0.05$; ***$p < 0.01$.

provinces. For low-efficiency provinces to achieve high efficiency (e.g., Hubei, with PM2.5, SO_2, and NO_x control efficiencies of 0.694, 0.830, and 0.860, respectively), their PM2.5 concentrations should be reduced from 39.16 ug/m^3 to 27.18 ug/m^3 (30.59% improvement), SO_2 emissions from 212,946.50 tons to 176,847.42 tons (16.95% improvement), and NO_x emissions from 420,771.00 tons to 361,894.87 tons (13.99% improvement). Meanwhile, Hunan, with PM2.5, SO_2, and NO_x control efficiency values of 0.843, 0.695, and 0.894, respectively, should reduce PM2.5 concentrations from 36.17 ug/m^3 to 30.48 ug/m^3 (15.74% improvement), SO_2 emissions from 283,944.33 tons to 197,406.04 tons (30.48% improvement), and NO_x emissions from 414,936 tons to 371,080.54 tons (10.57% improvement). For these two higher-ranked provinces, these air pollution reduction goals are immediately realizable. Nevertheless, we also discovered that it is difficult to meet the targets for some less efficient regions in a single step or within a short period of time. For example, Xinjiang's PM2.5, SO_2, and NO_x control efficiencies are 0.394, 0.301, and 0.334, respectively, and it must reduce these values by 60.55%, 69.87%, and 66.61%, respectively. Thus, for these inefficient provinces, these goals cannot be achieved overnight or even within a short time, and should be considered long-term goals.

TABLE 6 Long-term air pollution reduction targets for 30 Chinese provinces, 2015–2020.

Provinces	PM2.5 concentration (ug/m^3)				SO_2 emissions (tons)				NOx emissions (tons)			
	Actual avg	Target avg	IS	SE	Actual avg	Target avg	IS	SE	Actual avg	Target avg	IS	SE
Beijing	44.85	44.85	0	1	16,510	16,510	0	1	11,4693.5	114,693.5	0	1
Tianjin	58.72	53.86	8.28%	0.917	47,474	45,309.28	4.56%	0.954	14,1292.67	127,835.58	9.52%	0.905
Hebei	46.57	32.61	29.98%	0.700	480,858.83	286,794.57	40.36%	0.596	1,131,395.5	480,408.26	57.54%	0.425
Shanxi	40.18	19.49	51.50%	0.485	438,134.17	154,793.69	64.67%	0.353	681,323.17	228,315.09	66.49%	0.335
Inner Mongolia	24.31	19.81	18.50%	0.815	528,042.67	166,884.79	68.40%	0.316	666,539.67	240,882.69	63.86%	0.361
Liaoning	37.10	25.53	31.18%	0.688	419,938.83	170,490.93	59.40%	0.406	719,311.17	289,212.26	59.79%	0.402
Jilin	32.64	17.55	46.23%	0.538	147,655.17	87,991.02	40.41%	0.596	290,308.00	152,834.53	47.35%	0.526
Heilongjiang	25.53	17.96	29.63%	0.704	213,818.83	130,556.23	38.94%	0.611	432,120.00	198,933.40	53.96%	0.460
Shanghai	37.84	37.84	0	1	45,618.33	45,618.33	0	1	184,842.83	184,842.83	0	1
Jiangsu	46.52	46.52	0	1	418,370.67	418,370.67	0	1	889,290.5	889,290.5	0	1
Zhejiang	30.65	30.60	0.17%	0.998	166,522.00	165,521.63	0.60%	0.994	438,793.83	436,427.92	0.54%	0.995
Anhui	43.02	27.00	37.25%	0.628	228,295.33	166,583.41	27.03%	0.730	605,136.00	298,045.78	50.75%	0.493
Fujian	23.91	23.28	2.64%	0.974	168,626.00	144,301.35	14.43%	0.856	307,619.33	307,077.62	0.02%	0.998
Jiangxi	31.41	31.41	0	1	313,731.67	313,731.67	0	1	412,366.83	412,366.83	0	1
Shandong	54.58	50.64	7.21%	0.928	581,298.67	536,500.86	7.71%	0.923	1,149,989.67	101,2525.75	11.95%	0.880
Henan	52.73	32.78	37.83%	0.622	327,389.67	244,922.58	25.19%	0.748	764,396.00	473,183.18	38.10%	0.619
Hubei	39.16	27.18	30.59%	0.694	212,946.5	176,847.42	16.95%	0.830	420,771	361,894.87	13.99%	0.860
Hunan	36.17	30.48	15.74%	0.843	283,944.33	197,406.04	30.48%	0.695	414,936.00	371,080.54	10.57%	0.894
Guangdong	28.01	28.01	0	1	251,574.67	251,574.67	0	1	763,848.33	763,848.33	0	1
Guangxi	30.84	18.73	39.28%	0.607	157,986.00	129,708.91	17.90%	0.821	358,761.5	217,189.54	39.46%	0.605
Hainan	17.89	17.89	0	1	12,696.33	12,664.02	0.25%	0.997	56,540.00	56,433.83	0.19%	0.998
Chongqing	34.47	23.48	31.88%	0.681	163,623.00	49,381.43	69.82%	0.302	210,400.83	142,172.38	32.43%	0.676
Sichuan	20.93	20.91	0.12%	0.999	298,613.33	223,657.89	25.10%	0.749	498,086.17	419,071.11	15.86%	0.841
Guizhou	28.46	18.91	33.56%	0.664	383,694.00	162,170.72	57.73%	0.423	303,766.33	196,671.46	35.26%	0.647
Yunnan	23.55	23.55	0	1	325,885.5	325,885.50	0	1	369,709.33	369,709.33	0	1
Shaanxi	32.94	25.87	21.47%	0.785	259,205.33	175,230.56	32.40%	0.676	385,182.33	264,863.02	31.24%	0.688

(Continued on following page)

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TABLE 6 (*Continued*) Long-term air pollution reduction targets for 30 Chinese provinces, 2015–2020.

Provinces	PM2.5 concentration (ug/m^3)				SO_2 emissions (tons)				NOx emissions (tons)			
	Actual avg	Target avg	IS	SE	Actual avg	Target avg	IS	SE	Actual avg	Target avg	IS	SE
Gansu	30.39	14.96	50.79%	0.492	197,144.33	91,794.32	53.44%	0.466	250,787.83	126,438.30	49.58%	0.504
Qinghai	11.19	11.16	0.26%	0.997	64,508.5	39,267.69	39.13%	0.609	87,630.50	60,218.02	31.28%	0.687
Ningxia	33.43	14.45	56.79%	0.432	171,577.00	59,848.64	65.12%	0.349	200,730.00	81,761.57	59.27%	0.407
Xinjiang	43.78	17.27	60.55%	0.394	364,361.83	109,793.04	69.87%	0.301	446,999.33	149,233.08	66.61%	0.334
Average	34.73	26.82	21.38%	0.786	256,334.85	170,003.73	29.00%	0.710	456,585.61	314,248.70	28.19%	0.718

Note: IS, indicates improvement space; SE, indicates efficiency score.

5 Discussion

In recent years, researchers from a variety of disciplines have started investigating the intersections among economic development, air pollution, and human health (Cao and Ramirez, 2020; Zhou and Li, 2021), but few studies have examined the combined effects of these factors from an efficiency standpoint. Thus, this study uses a DNSBM model to assess the efficiency of economic development, health production, and air pollution control in 30 Chinese provinces from 2015 to 2020. This approach avoids the shortcomings of static analysis, includes carryover effects over time, and accounts for regional differences. The study's findings provide government-targeted recommendations for promoting sustainable economic development while strengthening health promotion and mitigating air pollution. The principal findings are as follows.

First, at the national level, the overall efficiency value of the two stages, from economic production input to health output, in China from 2015 to 2020 is 0.693, suggesting much room for improvement. This result is mainly caused by the failure of coordinated and balanced economic development and healthy production, similar to the conclusions of other studies (Shi et al., 2021). Specifically, the average annual efficiency of economic development (0.729) is significantly higher than the average annual efficiency of health production (0.657). Thus, greater efforts are required to increase the effectiveness of healthcare resource utilization. Going further, the overall efficiency values exhibit a downward trend, which is primarily brought on by the decline in economic development efficiency. In contrast, the rise in the efficiency of health production is the main contributor to mitigating the overall efficiency decline. This indicates that improving the efficiency of health production, rather than the efficiency of economic development, should be the main priority when working to improve overall efficiency, which is similar to the findings of other studies (Wang and Feng, 2015). At the provincial level, the efficiency of economic development in Beijing, Guangdong, and Shanghai is equivalent to the efficiency of healthy production, each with a value of 1. In the other provinces, the efficiency of the economic development phase outweighs the efficiency of the health production phase. One possible reason is that, as China's economic reforms gained momentum and local governments competed for economic growth while being given more autonomy, the government prioritized economic development over public services such as healthcare (Audibert et al., 2013). Therefore, restricted public funding and rapidly rising healthcare costs have hampered the healthy development of healthcare services (Dong, 2009). On the other hand, due to insufficient medical and healthcare resource management in China, scarce health resources are not being allocated and utilized rationally. In other words, these health resources have yet to be invested to maximize health outcomes, resulting in a decline in health productivity and an increase in the population's health burden (Zhang et al., 2017). At the same time, people's bad health can contribute to their already precarious economic circumstances, limiting productivity, pushing them into poverty (Liu and Griffiths, 2011), and eventually hampering the country's long-term development.

Second, research shows that the regional differentiation of China's economic development and health production efficiency

is apparent, which is the same as the results of Zhang et al. (2018b). Specifically, the eastern regions of China, such as Beijing and Guangdong, have economic development and health production efficiency values higher than 0.9. China's eastern region is the most developed; greater input and output efficiency in the east is strongly supported by the region's higher level of economic development and superior endowment of health resources (Yan et al., 2021). Even though these areas still have some air pollution issues that affect residents' health, the beneficial impacts of higher economic levels and more healthcare resources on population health exceed the negative effects (Lu et al., 2020). As a result, these areas are almost certain to sustain a high degree of economic development and healthy output. The central and western areas' (e.g., Shanxi, Xinjiang, Gansu, and Ningxia provinces) economic development and health production efficiency are low, with values less than 0.4. On the one hand, the relatively weak industrial base and imperfect industrial structure in these areas means that they lack appropriate conditions for making full use of input variables, such as energy and labor, resulting in lower economic development efficiency in these regions. On the other hand, some of the industrial businesses eliminated from the eastern provinces have shifted to the central and western regions, resulting in increased energy consumption and pollutant emissions that pose major health risks to local populations (Xu and Wang, 2021). Furthermore, there is an unequal distribution of medical resources in China such that high-quality medical resources are increasingly clustered in the east (Zhang et al., 2021). Inadequate investment in high-quality medical equipment and health professionals has occurred in the central and western regions due to a lack of financial resources for health (Jiang et al., 2021), thus limiting the efficiency of health production in this area.

Finally, the study shows that, from 2015 to 2020, China's average PM2.5, SO_2, and NO_x control efficiency values are 0.786, 0.710, and 0.718, respectively; these are relatively low and have considerable room for improvement, similar to the conclusions of other studies (Wang et al., 2020). At the same time, the efficiency of air pollution control varies greatly among Chinese regions due to the disparities in economic development levels, which is consistent with the findings of Wang et al. (2019). The provinces with high efficiency (equal to 1) in PM2.5, SO_2, and NO_x control, such as Beijing, Guangdong, and Jiangsu, are in the economically developed eastern region, and they all achieved a zero air pollution reduction target, which is a benchmark for inefficient Chinese provinces. The provinces with the lowest efficiency (values less than 0.4) include Xinjiang, Gansu, Shanxi, and Ningxia; all are located in the central and western regions with more backward economic development, and all have air pollution reduction targets greater than 50%. This makes it necessary to focus on air pollution in these regions to achieve ideal air quality and a green ecological environment. Furthermore, the data on China's air pollution control show noticeable regional differences, with the eastern provinces typically having higher air pollution control efficiency than the central and western provinces, which is similar to the findings of Liu and Dong (2021b). It is significant to note that the enormous gap between these less efficient provinces and the more efficient ones in terms of economic development, management capacity, and technical level of air pollution treatment makes it difficult to achieve the air pollution reduction goals calculated with the DNSBM model in the short term. Therefore, the air pollution reduction targets calculated using the DNSBM model for the inefficient provinces mentioned above should instead be viewed as long-term targets.

6 Conclusion

With China's rapid economic development, the threats to public health from environmental pollution, ecological balance disruption, and air quality degradation have gradually become crucial elements limiting socioeconomic sustainability. However, most previous studies have concentrated on the link between environmental quality and economic growth, or the impact of air pollution on public health; few have engaged in comprehensive research on the links among these three variables. Thus, this study evaluates the dynamic association between economic development, air pollution, and health production from an efficiency perspective using the DNSBM model, and the following conclusions are offered.

First, at the national level, the average overall efficiency value is 0.693, which is low and has much room for improvement. Economic development efficiency (0.729) is higher than health productivity efficiency (0.657), which indicates that China worked effectively on economic development but not as well on health during 2015–2020. In terms of trends in efficiency, growth in health production efficiency has been the main contributor to overall efficiency gains over the study period, while the decline in economic development efficiency has been the main obstacle.

Second, at the provincial level, efficiency varies widely among the 30 provinces, and this difference is statistically significant. Regarding individual differences in economic development and health production efficiency, Beijing, Jiangxi, Shanghai, and Jiangsu have the highest efficiency values, over 0.9. In contrast, Xinjiang, Inner Mongolia, Gansu, and Qinghai have the lowest efficiency, with values less than 0.4. Regarding individual differences in overall efficiency, Beijing, Shanghai, and Guangdong have the highest efficiency, equal to 1, while Xinjiang has the lowest efficiency of less than 0.35. Moreover, the efficiency of the three regions demonstrated distinct spatial differences. The eastern region has the highest efficiency, followed by the central region, and the western region has the lowest.

Finally, in controlling air pollutants, from 2015 to 2020, China's average PM2.5, SO_2, and NO_x control efficiency values are 0.786, 0.710, and 0.718, respectively; these results are poor and could be greatly improved. Moreover, the different levels of economic development have led to large differences in the efficiency of air pollution control among regions in China. The air pollution control capacity of the developed eastern provinces (e.g., Beijing, Shanghai, and Guangdong) is generally higher than that of the more economically underdeveloped central and western regions (e.g., Xinjiang, Gansu, Shanxi, and Ningxia). In addition, the air pollution reduction targets achieved by applying the DNSBM model for inefficient provinces should be viewed as long-term rather than short-term targets due to a significant gap between the inefficient and highly efficient provinces regarding economic development, management capability, and pollution technology level.

The following recommendations for policy are based on the findings of this study.

First and foremost, the central government must adhere to the requirements of sustainable development, abandon previous dualistic development thinking, and enhance economic development efficiency while ensuring the excellent effect of healthy output. Second, the state should improve the economic and institutional environments, which influence healthcare system efficiency. Regarding the economic development environment, the scope of public health expenditures should be extended, as should the percentage of government spending and GDP, so that the growth rate keeps pace with, or even exceeds, economic growth. Regarding institutional environment development, the emphasis is on restraining investment preferences in production and boosting the weight of public services, particularly health system quality, in government evaluation. Finally, local governments should focus on improving the management and allocation of health resources, rationally distributing limited medical and health resources, and improving resource utilization rates, thereby improving residents' health and promoting the coordinated development of the economy and health production.

To address the significant efficiency differences among provinces and regions regarding economic development, the central government should strike a balance between different areas and speed up the execution of three major regional development initiatives. It should narrow the efficiency gap in their economic development by rationally allocating regional resource factors, industrial contacts, and complementary advantages. Regarding health production, the central government should continue to promote the "Rise of Central China" and "Western Development" initiatives and boost policy support and financial investment in the west and central healthcare systems. On the other hand, local governments should build an evaluation mechanism, with efficiency as an indicator, and establish mechanisms to support health resources in backward areas, such as health resource sharing and medical association construction. This would facilitate the distribution of health resources across regions and improve China's uneven health production development.

Based on the structure of energy consumption, meteorological characteristics, and the level of industrialization in each province, the central government ought to establish targeted policies and measures to mitigate air pollution. Second, local governments should capitalize on their comparative advantages and strengthen regional cooperation. For provinces with a high overall level of air pollutant treatment efficiency, such as Beijing and Shanghai, a "two-point synergistic approach" to treatment should be adopted. On the one hand, it should provide advanced air purification technology and business management experience and generously help reduce air pollution in the central and western provinces. On the other hand, it should coordinate scientific and technological resources, accelerate the development of energy and environmental technology, and play a significant role in improving the current coal-based energy structure. Most regions with low air pollutant management efficiency, such as Xinjiang and Gansu, should optimize and adjust their industrial structure as a core, gradually changing the energy consumption structure of coal, steel, and other high-energy-consumption and high-pollution resources. They should also establish green corridors and clean technology industrial parks in conjunction with China's "One Belt, One Road" initiative, cultivate and develop new energy and new materials, and eventually realize a circular economy and healthy development model. Finally, considering the wide disparities in efficiency levels between regions, particularly the central and western provinces, selecting the best benchmark province for learning based on each province's unique characteristics, setting more realistic air pollution reduction goals, and setting short-term and long-term goals separately will be instructive for advancing China's ongoing work on air pollution mitigation.

In conclusion, there are some limitations to our research. First, the indicators reported in this paper were chosen based on the literature and data availability, which may have introduced bias into the study results. Second, we only considered efficiency evaluations and did not conduct a specific analysis of the influencing factors, nor did we offer a discussion of other influences, such as population mobility and urban development. Thus, the selection of indicators and influencing factors will be studied in depth in the future.

Data availability statement

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

Author contributions

YY wrote the entire article. QT gave review suggestions on the entire writing process and went through all the sections. 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

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Association between air pollution and primary liver cancer in European and east Asian populations: a Mendelian randomization study

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Purpose: The incidence of primary liver cancer is increasing year by year, with environmental factors playing a non-negligible role. At present, many studies are still disputing whether air pollution is associated with primary liver cancer incidence, and it is difficult to draw causal inferences. Therefore, in this study, we used two-sample Mendelian randomization (MR) to assess the causal relationship between air pollution (including PM2.5, PM2.5–10, PM10, nitrogen dioxide and nitrogen oxides) and primary liver cancer risk and its related biomarkers (Alpha-fetoprotein, Osteopontin, Glypican-3 and Arginase-1).

Patients and methods: We used large-scale publicly available genome-wide association studies (GWAS) summary data to conduct MR analyses of European and East Asian populations. Inverse variance weighted (IVW) method was used as the main analysis method, and weighted median model, MR-Egger, simple model and weighted model methods were selected for quality control. Heterogeneity was checked by the Cochran's Q test. The MR-Egger regression and the MR-PRESSO global test detect pleiotropy. The sensitivity analysis was performed using the leave-one-out method.

Results: Between air pollution and primary liver cancer in either European (PM2.5: $p = 0.993$; PM2.5–10: $p = 0.833$; PM10: $p = 0.257$; nitrogen dioxide: $p = 0.215$; nitrogen oxides: $p = 0.614$) or East Asian (PM2.5: $p = 0.718$; PM2.5–10: $p = 0.362$; PM10: $p = 0.720$; nitrogen dioxide: $p = 0.101$; nitrogen oxides: $p = 0.760$) populations were found no statistical association. Notably, there was a causal relationship between nitrogen oxides and Arginase-1, a biomarker associated with hepatocellular differentiation, statistically significant associations remained after deletion for single nucleotide polymorphisms (SNPs) associated with alcohol intake frequency, Body mass index (BMI) and cancers (Beta: 4.46; 95%CI: 0.83–8.08; $p = 0.015$). There was no heterogeneity or pleiotropy in the results.

Conclusion: This MR study found no evidence to support a causality between air pollution and primary liver cancer in European and East Asian populations, but nitrogen oxides may affect hepatocellular differentiation.

KEYWORDS
air pollution, primary liver cancer, particulate matter, nitrogen oxides, biomarkers

1. Introduction

Primary liver cancer is a malignant tumor originating from liver cells or intrahepatic bile duct epithelial cells, which is composed of hepatocellular carcinoma, cholangiocarcinoma, and mixed carcinoma (1). The estimated global cancer incidence rate for primary liver cancer in 2018 was 9.3 per 100,000 person-years, with a corresponding mortality rate of 8.5, making it the sixth most common cancer and the fourth leading cause of cancer death globally (2, 3). Currently, the region with the highest rates and prevalence of primary liver cancer is East Asia. However, from 1978 to 2012, the incidence of primary liver cancer has also increased year-on-year in regions with low incidence rates, such as most European countries, India and the United States, placing a huge burden on individuals, families and society (4). Diagnosis of primary liver cancer relies on pathological biopsies, and the detection of tumor biomarkers also plays an important role in early screening, diagnosis, treatment assessment, recurrence and prognosis prediction of tumors (1). Alpha-fetoprotein (AFP), Osteopontin (OPN), Glypican-3 (GPC-3) and Arginase-1 (Arg-1) are common primary liver cancer related biomarkers. AFP, derived from fetal hepatocytes and yolk sacs, has been widely used as a useful cancer biomarker in the diagnosis of liver cancers (5). OPN is a highly modified, phosphorylated and glycosylated extracellular matrix protein that binds to integrins and is expressed in a variety of cells. When combined with AFP, the sensitivity of OPN in the diagnosis of liver cancers increases to 65% (6). GPC-3, a membrane-bound heparin sulfate proteoglycan belonging to the glycoprotein family, is over-expressed in up to 80% of patients with hepatocellular carcinoma and can distinguish liver cancer from other malignancies (7). Arg-1, an enzyme associated with the hydrolysis of arginine to ornithine and urea, is highly sensitive and specific for the detection of malignant hepatocytes and is considered a useful biomarker of hepatocellular differentiation (8, 9). Hepatitis B virus (HBV) infection is the most important driver of primary liver cancer, but with the increase of HBV vaccination coverage, HBV infection has been effectively controlled, and the increase in incidence and mortality from primary liver cancer may be more attributable to other factors such as smoking, alcohol consumption and dietary habits (10, 11). In addition, the impact of environmental factors cannot be ignored as industrialization and associated pollution from burning fossil fuels, or coal, oil and gas, and vehicle emissions increase.

As a long-standing and widespread industrial pollutant, air pollution poses a worrying health hazard. Air pollutants are usually classified as particulate matter (PM), or as gases such as nitrogen dioxide (NO_2), nitrogen oxides (NO_x), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3), etc. (12). PM2.5 is the most frequently inspected pollutant, followed by NO_2 and NO_x, with few studies focusing on other pollutants. From 1990 to 2015, the death rate attributable to PM2.5 increased from 3.5 to 4.2 million, accounting for 7.6 percent of the total global deaths (13). The high health hazard of PM2.5 is the main reason for its widespread concern. The International Agency for Research on Cancer (IARC) classifies air pollutants as Group I human carcinogens, and numerous studies have shown a positive association between air pollution and some cancers, such as lung, kidney and breast cancer (14–16).

There is no consensus on the association between air pollution and the risk of primary liver cancer. Although a study involving 20,221 participants in the United States found a positive association between PM2.5 and liver cancer mortality (HR was 1.18 by 5 $\mu g/m^3$ increase in PM2.5; 95% CI: 1.16–1.20) (17), among the 8 studies on PM2.5 and the risk of primary liver cancer, only three studies (Coleman et al., Pan et al. and Vo Pham et al.) showed significant association between PM2.5 and primary liver cancer risk, while the other five studies did not (18–22). However, in five studies on the association between NO_2 and liver cancer incidence, only So et al. found that an increase of NO_2 concentration of 10 $\mu g/m^3$ would affect the risk of liver cancer (HR = 1.17, 95%CI:1.02–1.35) (16, 20, 21). Therefore, to further explore whether there is an association between air pollution and the risk of primary liver cancer, we conducted a Mendelian randomization (MR) study using large-scale publicly available genome-wide association studies (GWAS) data with PM2.5, PM2.5–10, PM10, nitrogen dioxide and nitrogen oxides as exposures and primary liver cancer and its related biomarkers (Alpha-fetoprotein, Osteopontin, Glypican-3, and Arginase-1) as outcome to assess the causal relationship between air pollution and the risk of primary liver cancer.

2. Materials and methods

2.1. Study design

Our study is based on the Mendelian randomization design, which depends on three core assumptions that instrumental variants (1) are associated with the exposure, (2) are not associated with the outcome via a confounding pathway, and (3) do not affect the outcome directly, only possibly indirectly via the exposure. In this study, air pollution (PM2.5, PM2.5–10, PM10, nitrogen dioxide and nitrogen oxides) was used as the exposure factor, single nucleotide polymorphisms (SNPs) significantly related to air pollution were used as instrumental variables (IVs), and primary liver cancer and its related biomarkers (Alpha-fetoprotein, Osteopontin, Glypican-3, and Arginase-1) were the outcome variable. Here, we conducted a two-sample MR analysis to estimate the causal effects of air pollution and primary liver cancer. The flowchart of this Mendelian randomization study is presented in Supplementary Figure 1.

Abbreviations: PM, particulate matter; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; IVs, instrumental variables; MR, Mendelian randomization; GWAS, genome-wide association studies; IVW, inverse variance weighted; SNPs, single nucleotide polymorphisms; BMI, body mass index; AFP, alpha-fetoprotein; OPN, osteopontin; GPC-3, Glypican-3; Arg-1, Arginase-1; CI, confidence interval; HR, hazard ratio.

TABLE 1 Summary of the genome-wide association studies (GWAS) included in this two-sample MR study.

Exposures/ outcomes		Dataset	Sample size	Number of SNPs	Population	Consortium	Sex	Year
Particulate matter (PM)	PM2.5 um	ukb-b-10,817	423,796	9,851,867	European	MRC-IEU	Males and Females	2018
	PM2.5 um	ukb-e-24006_EAS	2,505	8,268,350	Asian (East Asia)	NA	Males and Females	2020
	PM2.5–10 um	ukb-b-12,963	423,796	9,851,867	European	MRC-IEU	Males and Females	2018
	PM2.5–10 um	ukb-e-24008_EAS	2,505	8,268,350	Asian (East Asia)	NA	Males and Females	2020
	PM10 um	ukb-b-589	455,314	9,851,867	European	MRC-IEU	Males and Females	2018
	PM10 um	ukb-e-24005_EAS	2,505	8,268,350	Asian (East Asia)	NA	Males and Females	2020
Nitrogen dioxide		ukb-b-2,618	456,380	9,851,867	European	MRC-IEU	Males and Females	2018
Nitrogen dioxide		ukb-e-24016_EAS	2,625	8,260,777	Asian (East Asia)	NA	Males and Females	2020
Nitrogen oxides		ukb-b-12,417	456,380	9,851,867	European	MRC-IEU	Males and Females	2018
Nitrogen oxides		ukb-e-24004_EAS	2,625	8,260,777	Asian (East Asia)	NA	Males and Females	2020
Primary liver cancer		finn-b-C3_LIVER_ INTRAHEPATIC_ BILE_DUCTS	218,752	16,380,466	European	NA	Males and Females	2021
Primary liver cancer		bbj-a-158	197,611	8,885,115	Asian (East Asia)	NA	Males and Females	2019
Alpha-fetoprotein		prot-a-53	3,301	10,534,735	European	NA	Males and Females	2018
Osteopontin		ebi-a-GCST90010244	1,322	18,221,494	European	NA	Males and Females	2020
Glypican-3		prot-c-4842_62_2	3,301	501,428	European	NA	Males and Females	2019
Arginase-1		ebi-a-GCST90010286	1,072	17,593,887	European	NA	Males and Females	2020

PM: Particulate matter; MR: Mendelian randomization; GWAS: Genome-wide association studies; SNPs: Single nucleotide polymorphisms; NA: No data.

2.2. Data sources

The data sources are detailed in Table 1. We selected air pollution (including PM2.5, PM2.5–10, PM10, nitrogen dioxide and nitrogen oxides) as exposures, with data on all air pollution obtained from UK Biobank, a large prospective study with more than half a million United Kingdom participants for which data on phenotypes, genetic details, and genome-wide genotyping have been published (23, 24). We used the GWAS summary databases of air pollution for populations in Europe and East Asia. In European populations, the PM2.5 (GWAS ID: ukb-b-10,817), PM2.5–10 (GWAS ID: ukb-b-12,963), PM10 (GWAS ID: ukb-b-589), nitrogen dioxide (GWAS ID: ukb-b-2,618) and nitrogen oxides (GWAS ID: ukb-b-12,417) GWAS summary datasets included 423,796, 423,796, 455,314, 456,380, 456,380 participants, respectively. Among East Asian populations, the PM2.5 (GWAS ID: ukb-e-24006_EAS), PM2.5–10 (GWAS ID: ukb-e-24008_EAS), PM10 (GWAS ID: ukb-e-24005_EAS), nitrogen dioxide (GWAS ID: ukb-e-24016_EAS) and nitrogen oxides (GWAS ID: ukb-e-24004_EAS) GWAS summary datasets included 2,505, 2,505, 2,505, 2,625, 2,625 participants, respectively. Air pollution-related indicators were measured by land use regression (LUR) models (25).

We used primary liver cancer and its related biomarkers (Alpha-fetoprotein, Osteopontin, Glypican-3 and Arginase-1) as the outcome, and all GWAS data for primary liver cancer were obtained from FinnGen (European population) and Biobank Japan (East Asian population). The four biomarkers (only European population) Alpha-fetoprotein, Osteopontin, Glypican-3 and Arginase-1 were derived from the prot-a-53 (26), ebi-a-GCST90010244 (27), prot-c-4842_62_2 (28) and ebi-a-GCST90010286 (27) GWAS summary data. FinnGen is a large public-private research project that combines imputed genotype data generated from newly collected and legacy samples from the Finnish biobank and digital health record data from the Finnish Health Registry[1] to provide new insights into disease genetics. As of August 2020, samples from 412,000 people have been collected and 224,737 have been analyzed, with 500,000 participants expected by the end of 20,232 (29, 30). Biobank Japan is a large patient-based biobank consisting of 200,000 patients. As a basic biobank for common disease gene research, the project has conducted genome-wide association studies for various diseases and identified many genetic variants associated with disease susceptibility and drug response. All publications are in this project from the project web site[2] and open to the public (31). GWAS summary dataset of primary liver cancer in European populations (GWAS ID: finn-b-C3_LIVER_INTRAHEPATIC_BILE_DUCTS) contained 218,752 individuals (including 304 cases and 218,448controls). GWAS summary dataset of primary liver cancer in East Asian populations (GWAS ID: bbj-a-158) contained 197,611 individuals (including 1,866 cases and 195,745controls). Primary liver cancer cases were identified according to clinical diagnosis and conformed to the International Classification of Diseases, 8th Revision and 10th Revision codes.

2.3. Selection of instrumental variables

As shown in Supplementary Figure 1, in order to satisfy assumption 1, $p < 5 \times 10^{-8}$ was used as the genome-wide significance threshold for exposure, but only PM2.5 (European, ukb-b-10,817),

1 https://www.FinnGen.fi\/en

2 https://biobankjp.org//work\/public.html

PM10 (European, ukb-b-589), nitrogen dioxide (European, ukb-b-2,618) and nitrogen oxides (European, ukb-b-12,417) were able to pick out enough SNPs. Previous studies have shown that linear regression of each genetic variant on the risk factor with $p < 5 \times 10^{-6}$ as the screening criterion results in a low probability of weak instrumental variable bias in the MR Analysis (32, 33), so we lowered the genome-wide significance threshold of the remaining exposure (ukb-b-12,963, ukb-e-24006_EAS, ukb-e-24008_EAS, ukb-e-24005_EAS, ukb-e-24016_EAS and ukb-e-24004_EAS) to $p < 5 \times 10^{-6}$ to select enough SNPs as IVs associated with this significance level.

In order to remove SNPs with linkage disequilibrium (LD), $r^2 < 0.001$ and kb > 10,000 was set when extracting IVs. If the selected SNP was not collected in the resulting GWAS, the proxy SNP in linkage disequilibrium ($r^2 > 0.8$) was used. Palindromic SNPs were then removed to ensure that the effect of these SNPs on exposure corresponded to the same allele as the effect on outcome. Finally, we calculated the R^2 ($R^2 = 2 \diamondsuit EAF \diamondsuit (1-EAF) \diamondsuit \beta^2$) (34) and F-statistic ($F = \beta^2/SE^2$) (35) for each SNP. R^2 is the percentage of iron status variability explained by each SNP and F statistic to assess the presence of a weak IV bias. The F-statistic of each SNP we selected was > 10, suggesting that the genetic instruments selected strongly predicted the exposure (36). For specific SNP information and corresponding R^2 and F-statistic, shown in Supplementary Tables 1–7.

2.4. Mendelian randomization analysis

To assess the causal relationship between air pollution and primary liver cancer and its related biomarkers, we used the inverse variance weighted (IVW) method to predict the genetic predictive value of the exposure factor for the outcome variable with an effect value of β. IVW can obtain an estimate of causal effect based on a single genetic IV through Wald ratio, and then select a fixed effect model to perform a meta-analysis of multiple estimates of causal effect based on a single

TABLE 2 Mendelian randomization (MR) analysis of air pollution (particulate matter, nitrogen dioxide and nitrogen oxides, exposure) with primary liver cancer outcome in European population.

Exposures	Methods	Beta	*p*	Number of SNPs	R^2	*F*	*P* (Cochran's Q heterogeneity test)	*P* (MR-Egger intercept test)	*P* (MR-PRESSO global test)
PM2.5	IVW	−0.014	0.993	8	0.069%	292.604	0.078	0.411	0.326
	Weighted median	0.285	0.846						
	MR-Egger	1.315	0.596						
	Simple mode	0.191	0.955						
	Weighted mode	0.435	0.770						
PM2.5–10	IVW	0.313	0.833	23	0.130%	534.813	0.057	0.720	0.081
	Weighted median	1.250	0.422						
	MR-Egger	0.879	0.691						
	Simple mode	−1.000	0.776						
	Weighted mode	0.990	0.522						
PM10	IVW	−1.698	0.257	22	0.159%	810.361	0.593	0.609	0.578
	Weighted median	−3.305	0.107						
	MR-Egger	0.173	0.965						
	Simple mode	−4.763	0.182						
	Weighted mode	−4.506	0.171						
Nitrogen dioxide	IVW	6.478	0.215	4	0.032%	158.579	0.079	0.888	0.219
	Weighted median	3.917	0.458						
	MR-Egger	−3.456	0.966						
	Simple mode	2.864	0.641						
	Weighted mode	3.270	0.594						
Nitrogen oxides	IVW	3.337	0.614	8	0.060%	283.730	0.204	0.198	0.271
	Weighted median	1.283	0.720						
	MR-Egger	28.909	0.180						
	Simple mode	4.573	0.786						
	Weighted mode	4.237	0.730						

PM, Particulate matter; MR, Mendelian randomization; IVW, Inverse variance weighted; SNPs, Single nucleotide polymorphisms.
R^2: the percentage of iron status variability explained by each SNP; *F* statistic to assess the presence of a weak instrumental variable bias.

gene IV, which can provide a reliable estimate of causal effect and is widely used in MR Analysis (32, 37). In order to further improve the reliability and accuracy of the study results, weighted median model, MR-Egger, simple model and weighted model methods were further used to verify the causal relationship between exposure factors and results, and were verified in both European and Asian populations (38). Biomarkers were only analyzed in European populations due to lack of GWAS data in East Asian populations.

2.5. Sensitivity analysis

First of all, we used leave-one-out method to test the sensitivity of the remaining SNPs after deleting SNPs one by one. If the results changed significantly, it indicated that the removed SNPs might be directly related to the results, which violated assumption 3 (39). Then, for the IVW method, Cochran's Q test was used to evaluate the heterogeneity, and $p > 0.05$ indicated that there was no significant heterogeneity in the selected IVs (40). Finally, we need to perform pleiotropic tests using MR-Egger regression and MR-PRESSO global testing to ensure that IV does not influence the risk of primary liver cancer through other confounding factors or other biological pathways unrelated to air pollution exposure. The MR Egger regression effect model allows for causal estimation of pleiotropic effect corrections, evaluating instrumental intensity under the direct effect assumption independently of the null causality assumption, and MR-PRESSO enables a systematic assessment of the role of pleiotropy (41). The statistical threshold for IVs without pleiotropy was $p > 0.05$.

2.6. Statistical analysis

All analyses were performed using the packages "TwoSampleMR" (42) and "MR-PRESSO" (41) in R version 4.2.2. The threshold of statistical significance for evidence is $p < 0.05$.

TABLE 3 Mendelian randomization (MR) analysis of air pollution (particulate matter, nitrogen dioxide and nitrogen oxides, exposure) with primary liver cancer outcome in Asian population (East Asia).

Exposures	Methods	Beta	*p*	Number of SNPs	R^2	*F*	*P* (Cochran's Q heterogeneity test)	*P* (MR-Egger intercept test)	*P* (MR-PRESSO global test)
PM2.5	IVW	0.074	0.718	4	3.527%	87.086	0.057	0.714	0.133
	Weighted median	−0.050	0.769						
	MR-Egger	0.300	0.660						
	Simple mode	−0.086	0.706						
	Weighted mode	−0.097	0.622						
PM2.5–10	IVW	−0.131	0.362	3	3.371%	72.691	0.740	0.675	NA
	Weighted median	−0.116	0.490						
	MR-Egger	0.070	0.885						
	Simple mode	−0.040	0.865						
	Weighted mode	−0.063	0.783						
PM10	IVW	−0.026	0.720	5	4.933%	112.709	0.512	0.936	0.984
	Weighted median	−0.033	0.701						
	MR-Egger	−0.037	0.814						
	Simple mode	−0.037	0.783						
	Weighted mode	−0.033	0.735						
Nitrogen dioxide	IVW	−0.186	0.101	6	5.536%	126.644	0.308	0.337	0.368
	Weighted median	−0.194	0.171						
	MR-Egger	0.569	0.463						
	Simple mode	−0.204	0.385						
	Weighted mode	−0.218	0.351						
Nitrogen oxides	IVW	0.038	0.760	4	4.014%	95.452	0.613	0.412	0.652
	Weighted median	−0.014	0.921						
	MR-Egger	−2.936	0.417						
	Simple mode	−0.040	0.857						
	Weighted mode	−0.038	0.853						

PM, Particulate matter; MR: Mendelian randomization; IVW, Inverse variance weighted; SNPs, Single nucleotide polymorphisms.
R^2: the percentage of iron status variability explained by each SNP; *F* statistic to assess the presence of a weak instrumental variable bias.

3. Results

3.1. Air pollution and primary liver cancer

The MR results are shown in Table 2 (European population) and Table 3 (Asian population), as well as in Figure 1 (Scatter plots, European population), Figure 2 (Scatter plots, Asian population), Figure 3 (Forest plots, European population) and Figure 4 (Forest plots, Asian population).

To assess the causal effect of air pollution (including PM2.5, PM2.5–10, PM10, nitrogen dioxide, and nitrogen oxides) on primary liver cancer, we first performed MR Analysis in a European population. 8, 23, 22, 4, and 8 SNPs for PM2.5, PM2.5–10, PM10, nitrogen dioxide, and nitrogen oxides were identified after removal of chained unbalanced IVs (Supplementary Table 1). Using IVW, weighted median model, MR-Egger, simple model and weighted model methods, we found no evidence of a causal relationship between air pollution and primary liver cancer risk (IVW method, PM2.5: $p = 0.993$; PM2.5–10: $p = 0.833$; PM10: $p = 0.257$; nitrogen dioxide: $p = 0.215$; nitrogen oxides: $p = 0.614$), and there was no evidence of significant heterogeneity or horizontal pleiotropy (Table 2). The scatter plots of the causal relationships between air pollution and the risk of primary liver cancer are shown in Figure 1. Leave-one-out analyses (Figure 3) showed that removing each SNP in turn had little effect on the results, suggesting that no single SNP had a significant effect on the overall causal effect estimates.

The MR analysis was repeated in the East Asian population to enhance the confidence of the above results. 4, 3, 5, 6, and 4 SNPs for PM2.5, PM2.5–10, PM10, nitrogen dioxide, and nitrogen oxides were identified after removal of chained unbalanced IVs (Supplementary Table 2). Consistent with the findings in the European population, we found no causal relationship between air pollution and primary liver cancer risk in the East Asian population using the above five methods (IVW method, PM2.5: $p = 0.718$; PM2.5–10: $p = 0.362$; PM10: $p = 0.720$; nitrogen dioxide: $p = 0.101$; nitrogen oxides: $p = 0.760$), and no significant heterogeneity and pleiotropy were found (Table 3). The scatter plots are shown in Figure 2. Leave-one-out analyses also did not identify abnormal SNPs (Figure 4).

3.2. Air pollution and biomarkers

The MR results are shown in Table 4, as well as in Supplementary Figures 2–5 (Scatter plots), and Supplementary Figures 6–9 (Forest plots).

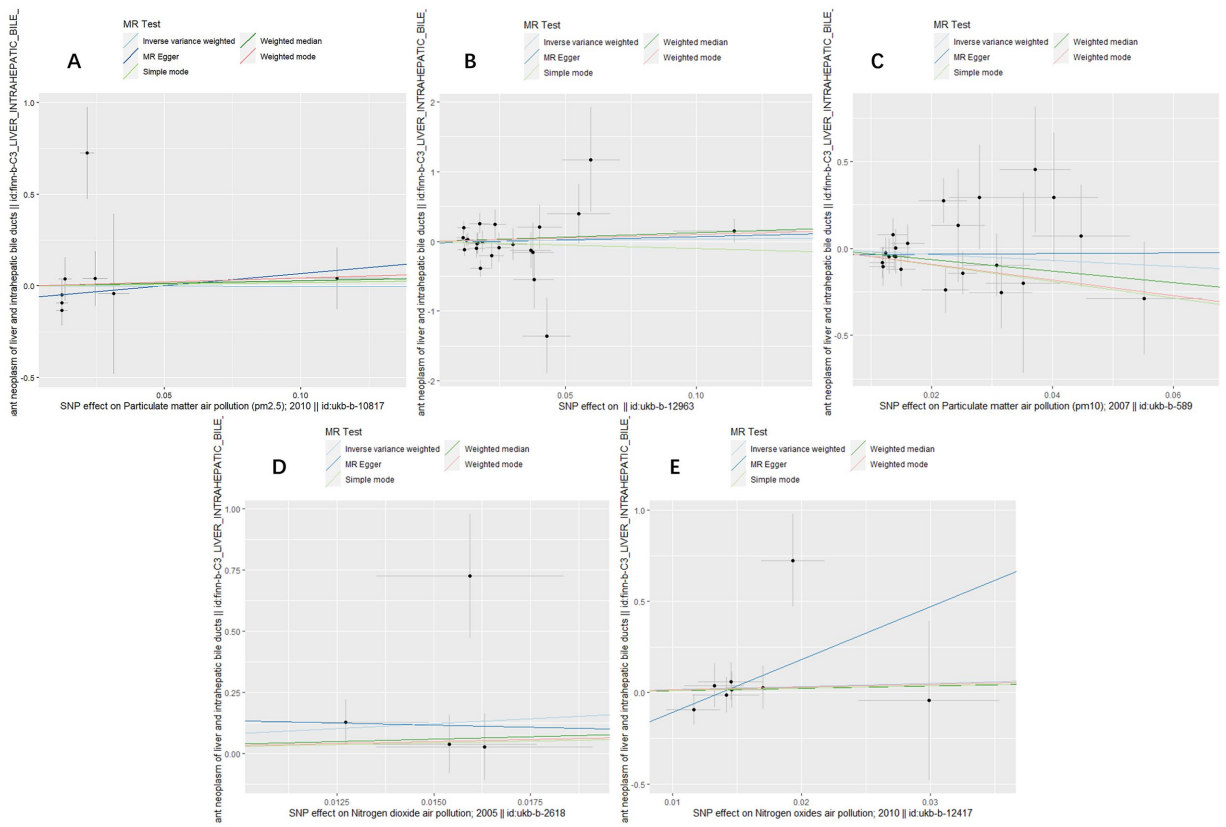

FIGURE 1
Scatter plots for causal single nucleotide polymorphism (SNP) effect of air pollution (particulate matter, nitrogen dioxide and nitrogen oxides) on primary liver cancer in European population. Each black point representing each SNP on the exposure (horizontal-axis) and on the outcome (vertical-axis) is plotted with error bars corresponding to each standard error (SE). The slope of each line corresponds to the combined estimate using each method of the inverse variance weighted (light blue line), the MR-Egger (blue line), the simple mode (light green line), the weighted median (green line), and the weighted mode (pink line). **(A)** PM2.5; **(B)** PM2.5–10; **(C)** PM10; **(D)** Nitrogen dioxide; **(E)** Nitrogen oxides.

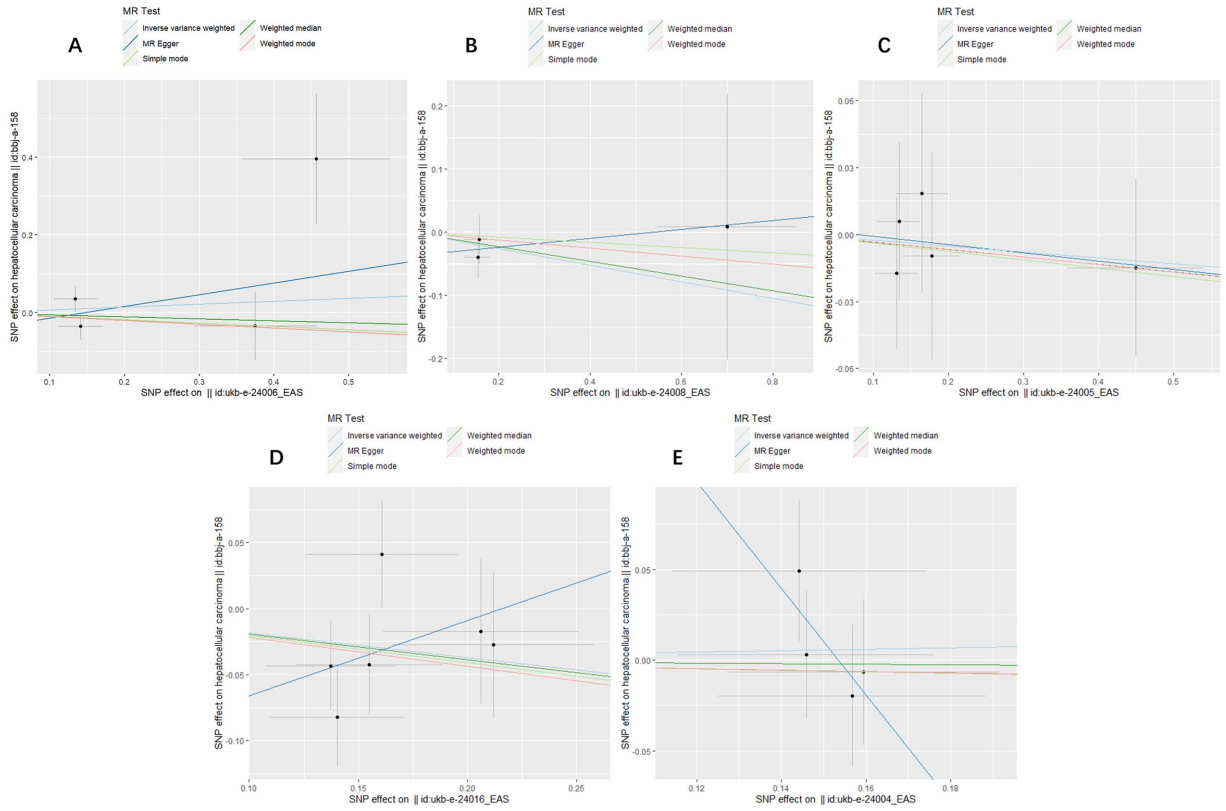

FIGURE 2
Scatter plots for causal SNP effect of air pollution (particulate matter, nitrogen dioxide and nitrogen oxides) on primary liver cancer in Asian population. Each black point representing each SNP on the exposure (horizontal-axis) and on the outcome (vertical-axis) is plotted with error bars corresponding to each standard error (SE). The slope of each line corresponds to the combined estimate using each method of the inverse variance weighted (light blue line), the MR-Egger (blue line), the simple mode (light green line), the weighted median (green line), and the weighted mode (pink line). **(A)** PM2.5; **(B)** PM2.5–10; **(C)** PM10; **(D)** Nitrogen dioxide; **(E)** Nitrogen oxides.

In order to further verify the causal relationship between air pollution and primary liver cancer, we selected four biomarkers (Alpha-fetoprotein, Osteopontin, Glypican-3 and Arginase-1) which are closely related to primary liver cancer as the outcome and conducted MR Analysis again. Consistent with the above results, we did not find any causal association between air pollution and Alpha-fetoprotein (PM2.5: $p = 0.370$; PM2.5–10: $p = 0.405$; PM10: $p = 0.842$; nitrogen dioxide: $p = 0.585$; nitrogen oxides: $p = 0.652$), Osteopontin (PM2.5: $p = 0.695$; PM2.5–10: $p = 0.780$; PM10: $p = 0.517$; nitrogen dioxide: $p = 0.615$; nitrogen oxides: $p = 0.271$) and Glypican-3 (PM2.5: $p = 0.228$; PM2.5–10: $p = 0.058$; PM10: $p = 0.814$; nitrogen dioxide: $p = 0.388$; nitrogen oxides: $p = 0.405$) through IVW method. The results showed no heterogeneity or pleiotropy (Table 4).

It is worth mentioning that we initially extracted 8 SNPs (rs1217106, rs12203592, rs1318845, rs6749467, rs72808024, rs7514956, rs77205736, and rs77255816) that were strongly associated with nitrogen oxides as instrumental variables and found a significant association between nitrogen oxides and Arginase-1 using IVW method (Beta: 3.56; 95%CI: 0.63–6.49; $p = 0.017$). Subsequently, we searched these 8 SNPs for possible confounding related to primary liver cancer through the PhenoScanner database (http://www.Phenoscanner.medschl.Cam.ac.uk/ accessed on March 12, 2023) one by one, and found 3 SNPs (rs1217106, rs12203592 and rs77205736) related to alcohol intake frequency, cancers (breast cancer, nonmelanoma skin cancer, cutaneous squamous cell carcinoma, and basal cell carcinoma) and Body mass index (BMI). After deleting them, we analyzed again and found that the results were still statistically significant (Beta: 4.46; 95%CI: 0.83–8.08; $p = 0.015$), and there was no heterogeneity or pleiotropy. The specific SNP information, corresponding R^2 and F-statistic are shown in Supplementary Tables 3–7.

4. Discussion

This study is the first to evaluate the causal relationship between air pollution (including PM2.5, PM2.5–10, PM10, nitrogen dioxide and nitrogen oxides) and primary liver cancer using MR methods. We found no genetic evidence of an association between air pollution and primary liver cancer risk in either the European or East Asian populations. However, in a further MR analysis of air pollution and biomarkers associated with primary liver cancer (Alpha-fetoprotein, Osteopontin, Glypican-3 and Arginase-1), we found a significant association between nitrogen oxides and biomarker Arginase-1 related to hepatocellular differentiation (Beta: 3.56; 95%CI: 0.63–6.49; $p = 0.017$), which remained statistically significant after adjustment (Beta: 4.46; 95%CI: 0.83–8.08; $p = 0.015$) for possible confounding alcohol intake frequency, body mass index (BMI) and cancers (breast

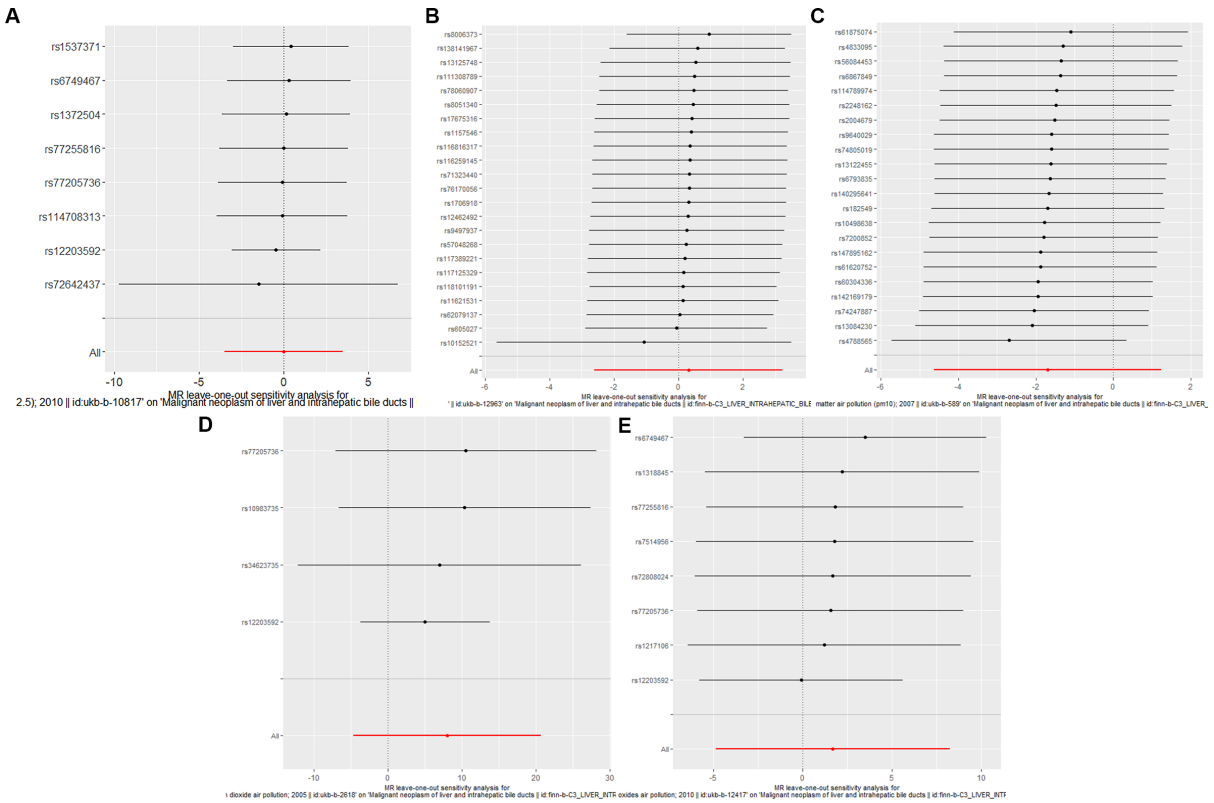

FIGURE 3
Forest plots of Leave-one-out analyses for causal SNP effect of air pollution (particulate matter, nitrogen dioxide and nitrogen oxides) on primary liver cancer in European population. The error bars indicate the 95% confidence interval (CI). **(A)** PM2.5; **(B)** PM2.5–10; **(C)** PM10; **(D)** Nitrogen dioxide; **(E)** Nitrogen oxides.

cancer, nonmelanoma skin cancer, cutaneous squamous cell carcinoma, and basal cell carcinoma).

Our findings further confirm several population-based cohort studies. Marie Pedersen et al. (20) pooled data from 174,770 participants in four cohorts [Diet, Cancer and Health study (43), Vorarlberg Health Monitoring and Promotion Program (44), European Prospective Investigation into Cancer and Nutrition (EPIC)-Varese (45) and EPIC-Turin (46)] from European Study of Cohorts for Air Pollution Effects (ESCAPE) in Denmark, Austria, and Italy to examine the association between air pollution (including PM2.5, PM2.5–10, PM10, nitrogen dioxide and nitrogen oxides) and the risk of primary liver cancer, and land-use regression models were used to measure PM2.5, PM2.5–10, PM10, nitrogen dioxide and nitrogen oxides. During an average follow-up period of 17 years, 279 patients with liver cancer were diagnosed, and the meta-analysis found that PM2.5, PM2.5–10, PM10, nitrogen dioxide and nitrogen oxides were all associated with an increased incidence of primary liver cancer, with Hazard ratios (HRs) greater than 1 for all exposures, but none of the associations were statistically significant. After adjusting for age, sex, smoking, drinking, high-risk occupations and other confounding factors that might be associated with primary liver cancer, no statistical association was found between air pollution and primary liver cancer. Unlike our findings, another prospective cohort study in Taiwan (19) followed 23,820 participants without a history of liver cancer for an average of 16.9 years suggested that every 0.73 $\mu g/m^3$ increase in PM 2.5 increased the risk of hepatocellular carcinoma incidence by 22% in Penghu Islets (HR = 1.22, 95%CI: 1.02–1.47). However, PM2.5 levels in Taiwan and the Main Island of Taiwan (per 1 and 13.1 $\mu g/m^3$) were not statistically associated with the risk of liver cancer. The reasons for the two conclusions may be related to the different levels of air pollution in different areas or the different susceptibility of people in different areas to air pollution, and genetic factors may also play a role. Therefore, we selected SNPs strongly associated with air pollution as instrumental variables, used two-sample Mendelian randomization to conduct causal analysis on air pollution and primary liver cancer at the genetic level, and verified them separately on European and East Asian populations, so as to improve the reliability and credibility of our research conclusions. Our study demonstrates the lack of statistical causality between air pollution and primary liver cancer, reduces the possibility of their clinical relevance, refutes the role of air pollution in the etiology of primary liver cancer, and complements and updates the methodology of several cohort studies that have reached similar conclusions as our study.

Alpha-fetoprotein (AFP), Osteopontin (OPN) and Glypican-3 (GPC-3) are commonly used as tumor markers for primary liver cancer. AFP, a glycoprotein derived from embryonic endodermal cells, is an important cytokine closely related to the malignant growth of tumors, which can promote the malignant transformation of hepatocytes and the occurrence and development of liver cancer and up to 70% of patients with liver cancer have elevated serum AFP levels (47). AFP has been reported to be 52% sensitive to tumors larger than 3 cm in diameter in hepatocellular carcinoma patients, and is the most

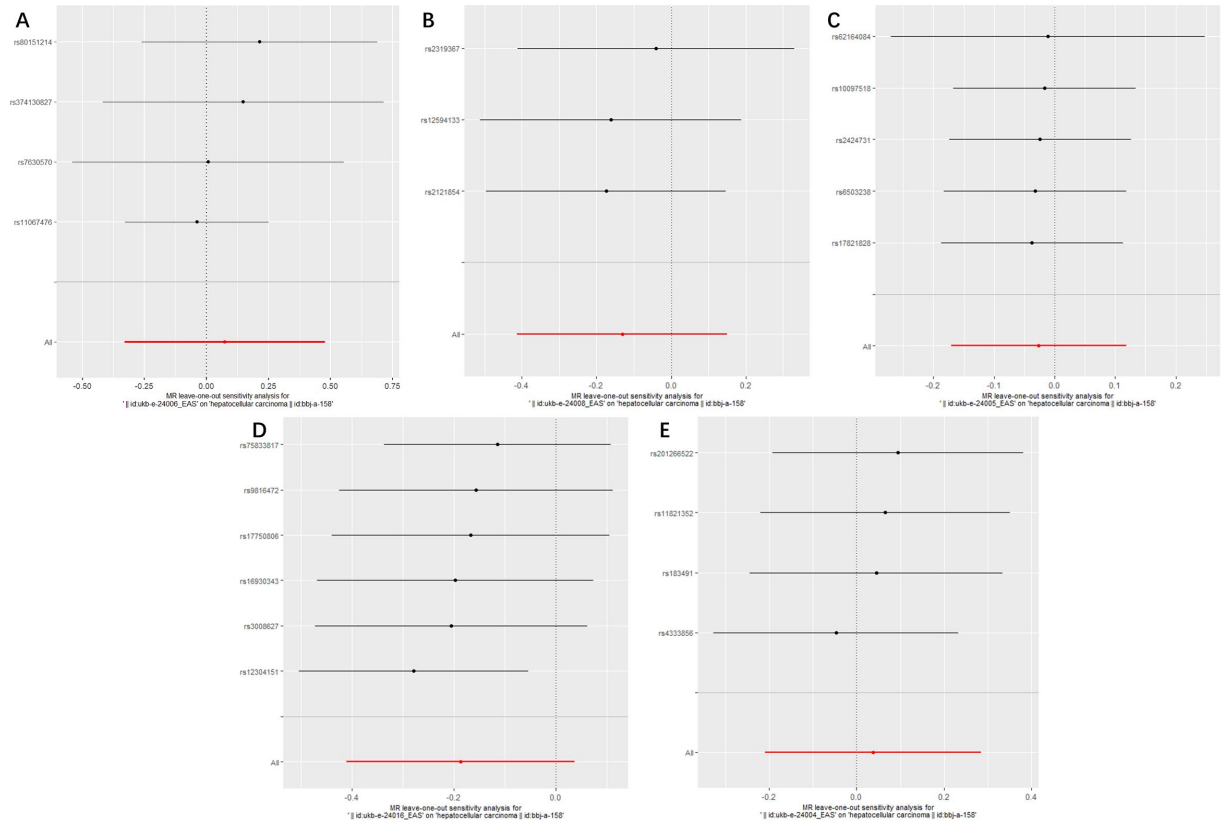

FIGURE 4
Forest plots of Leave-one-out analyses for causal SNP effect of air pollution (particulate matter, nitrogen dioxide and nitrogen oxides) on primary liver cancer in Asian population. The error bars indicate the 95% confidence interval (CI). **(A)** PM2.5; **(B)** PM2.5–10; **(C)** PM10; **(D)** Nitrogen dioxide; **(E)** Nitrogen oxides.

widely used tumor marker in clinical practice (48). OPN, a highly modified extracellular matrix protein, is found in 0% of serum in healthy people and increases in hepatitis, cirrhosis and liver cancer patients. OPN even outperforms AFP in distinguishing cirrhosis from liver cancer. When OPN and AFP are combined in the diagnosis of hepatocellular carcinoma, the sensitivity can increase to 65% (6, 49). GPC-3 is a hepatocellular carcinoma related biomarker with a specificity of up to 97%, which can detect hepatocellular carcinoma at an earlier stage than AFP and one study showed that serum GPC-3 levels in 50% of patients with early hepatocellular carcinoma were >300 ng/L, despite their serum AFP levels <100 μg/L (50). MR Analysis of air pollution and primary liver cancer related tumor markers AFP, OPN and GPC-3 found no causal association, further confirming our previous conclusion that there was no statistical association between air pollution and primary liver cancer risk.

Arginase-1 (Arg-1), an enzyme that catalyzes the hydrolysis of arginine to ornithine and urea in the urea cycle, is mainly expressed in the cytoplasm of hepatocytes and is not expressed in bile duct epithelial cells, Kupffer cells, or vascular endothelial cells, and thus can be used in the differential diagnosis between hepatocellular carcinoma and other potentially confounding malignancies. Arg-1 is reported to be a highly specific biomarker for hepatocellular differentiation, with sensitivities of 100, 96.2 and 85.7% in highly differentiated, moderately differentiated and poorly differentiated hepatocellular carcinoma, respectively (51, 52). Our results found a significant association between nitrogen oxides and Arginase-1, a biomarker highly associated with hepatocellular differentiation, which remained statistically significant after adjusting for possible confounding factors such as alcohol intake frequency, body mass index (BMI) and cancers (breast cancer, nonmelanoma skin cancer, cutaneous squamous cell carcinoma, and basal cell carcinoma; Beta: 4.46; 95%CI: 0.83–8.08; $p = 0.015$). Currently, there is a lack of relevant research on the effects of nitrogen oxides on Arg-1, but it has been shown that nitric oxide can affect liver cell differentiation by affecting the tumor microenvironment. On the one hand, nitric oxide can play a role in tumor differentiation, growth progression and metastasis by modulating the expression of multiple inflammatory factors. On the other hand, it can affect and regulate anabolism and catabolism, including sugar, fatty acid and amino acid metabolism, to affect the tumor microenvironment, and which plays a very important role in the hepatocellular differentiation and the conversion of normal cells into tumor cells, and even determines to some extent the direction and type of differentiation of liver cancer (53–56). To some extent, this may explain our results that nitrogen oxides air pollution may affect hepatocellular differentiation by altering the hepatocyte microenvironment, but further *in vivo* and *in vitro* experiments are needed to confirm this hypothesis.

There were several limitations to our study. To begin with, although we conducted the MR Analysis on the causal relationship between air pollution and primary liver cancer in both European and East Asian populations, due to the limitation of data, we only analyzed the European population when we analyzed the tumor markers (Alpha-fetoprotein, Osteopontin, Glypican-3 and Arginase-1) of liver

TABLE 4 Mendelian randomization (MR) analysis of air pollution (particulate matter, nitrogen dioxide and nitrogen oxides, exposure) with biomarkers in primary liver cancer in European population (IVW method).

Exposures	Outcomes (biomarkers)	Beta (95%CI)	*p*	Number of SNPs	R^2	*F*	*P* (Cochran's Q heterogeneity test)	*P* (MR-Egger intercept test)	*P* (MR-PRESSO global test)
PM2.5	Alpha-fetoprotein	−0.64 (−2.05, 0.76)	0.370	7	0.059%	257.485	0.871	0.287	0.884
	Osteopontin	−0.35 (−2.10, 1.40)	0.695	8	0.069%	292.604	0.684	0.177	0.671
	Glypican-3	−2.12 (−5.58,1.33)	0.228	4	0.038%	166.694	0.691	0.464	0.725
	Arginase-1	1.39 (−0.49, 3.29)	0.147	8	0.069%	292.604	0.631	0.360	0.663
PM2.5–10	Alpha-fetoprotein	−0.50 (−1.82, 0.80)	0.405	21	0.117%	482.903	0.106	0.464	0.091
	Osteopontin	0.20 (−1.26, 1.68)	0.780	23	0.129%	531.943	0.155	0.214	0.187
	Glypican-3	−3.30 (−6.59, 0.02)	0.058	6	0.033%	136.070	0.575	0.790	0.592
	Arginase-1	−0.41 (−1.80, 0.97)	0.559	23	0.129%	531.943	0.794	0.890	0.810
PM10	Alpha-fetoprotein	0.08 (−0.77, 0.95)	0.842	22	0.159%	810.360	0.506	0.955	0.515
	Osteopontin	0.49 (−0.99, 1.98)	0.517	22	0.159%	810.360	0.882	0.656	0.887
	Glypican-3	−0.39 (−3.69, 2.90)	0.814	6	0.052%	271.045	0.125	0.579	0.180
	Arginase-1	1.78 (−0.08, 3.64)	0.061	22	0.159%	810.360	0.136	0.070	0.127
Nitrogen dioxide	Alpha-fetoprotein	0.51 (−1.33, 2.36)	0.585	5	0.039%	191.857	0.343	0.530	0.391
	Osteopontin	0.86 (−2.50, 4.24)	0.615	5	0.039%	191.857	0.856	0.708	0.855
	Glypican-3	−1.47 (−4.70, 1.75)	0.388	5	0.039%	191.857	0.625	0.398	0.654
	Arginase-1	−0.44 (−4.10, 3.21)	0.812	5	0.039%	191.857	0.432	0.195	0.494
Nitrogen oxides	Alpha-fetoprotein	0.33 (−1.11, 1.78)	0.652	8	0.060%	283.730	0.394	0.527	0.430
	Osteopontin	−1.52 (−4.24, 1.19)	0.271	8	0.060%	283.730	0.833	0.286	0.819
	Glypican-3	−1.56(−5.26, 2.12)	0.405	4	0.033%	160.302	0.682	0.458	0.702
	Arginase-1	4.46 (0.83, 8.08)	0.015	5	0.033%	155.317	0.453	0.366	0.502

PM, Particulate matter; MR, Mendelian randomization; IVW, Inverse variance weighted; SNPs, Single nucleotide polymorphisms; CI, Confidence Interval.
R^2: the percentage of iron status variability explained by each SNP; *F* statistic to assess the presence of a weak instrumental variable bias; Genetic predictive value of the exposure factor for the outcome variable with an effect value of Beta.

cancer, and whether this relationship is also present in other populations needs more verification. Additionally, our results in East Asian populations were based on a 5×10^{-6} significance level, as there were not enough SNPs associated with a 5×10^{-8} genome-wide significance threshold, and this may require an expanded sample size to further validate our conclusions.

5. Conclusion

In conclusion, our results suggested that there is no causal association between air pollution (including PM2.5, PM2.5–10, PM10, nitrogen dioxide, and nitrogen oxides) and primary liver cancer. However, there was a statistical association between nitrogen oxides and Arg-1, further experimental and mechanistic studies are needed to verify the validity of the findings obtained in this study.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://gwas.mrcieu.ac.uk/datasets/.

Author contributions

MS and MG: designing, carrying out the study, analyzing the data, and writing the article. ML, TW, and TZ: carrying out the study, and revising. JQ: designing, revising, and financial support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the study 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.2023.1212301/full#supplementary-material

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Does air pollution exposure affect semen quality? Evidence from a systematic review and meta-analysis of 93,996 Chinese men

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Background: Air pollution may impair male fertility, but it remains controversial whether air pollution affects semen quality until now.

Objectives: We undertake a meta-analysis to explore potential impacts of six pollutants exposure during the entire window (0–90 days prior to ejaculation) and critical windows (0–9, 10–14, and 70–90 days prior to ejaculation) on semen quality.

Methods: Seven databases were retrieved for original studies on the effects of six pollutants exposure for 90 days prior to ejaculation on semen quality. The search process does not limit the language and search date. We only included original studies that reported regression coefficients (β) with 95% confidence intervals (CIs). The β and 95% CIs were pooled using the DerSimonian-Laird random effect models.

Results: $PM_{2.5}$ exposure was related with decreased total sperm number (10–14 lag days) and total motility (10–14, 70–90, and 0–90 lag days). PM_{10} exposure was related with reduced total sperm number (70–90 and 0–90 lag days) and total motility (0–90 lag days). NO_2 exposure was related with reduced total sperm number (70–90 and 0–90 lag days). SO_2 exposure was related with declined total motility (0–9, 10–14, 0–90 lag days) and total sperm number (0–90 lag days).

Conclusion: Air pollution affects semen quality making it necessary to limit exposure to air pollution for Chinese men. When implementing protective measures, it is necessary to consider the key period of sperm development.

KEYWORDS

semen analysis, air pollution, particulate matter, meta-analysis, systematic review

Introduction

8–12% of reproductive-age couples are infertile in the world and its prevalence may be increasing (1). Male factors cause 40–50% of infertile couples (2). Total sperm number, sperm concentration, progressive and total motility are commonly adopted to evaluate male reproductive potential. Sperm quality of sperm donors in China's Henan Province showed a

decreasing trend from 2009 to b2019 (3). Although the exact cause remains unclear, air pollution might be a hazard factor for declining semen quality (4).

Particulate matter (PM) pollution included PM ≤ 10 μm (PM_{10}) as well as PM ≤2.5 μm ($PM_{2.5}$). Gaseous pollutants included sulfur dioxide (SO_2), carbon monoxide (CO), nitrogen dioxide (NO_2), and ozone (O_3). Due to different economic growth levels and economic development patterns, air pollution varies greatly from place to place (5–9). Air pollution was serious in China due to rapid industrialization (10–13). Air pollution could cause respiratory symptoms (14–16), cardiovascular disease (17–20), kidney disease (21–23), adverse prenatal outcomes (24), and impaired neurodevelopment (25, 26). It remains controversial whether air pollution exposure during the whole sperm development window has an influence on sperm quality (27–47). A meta-analysis of relevant research data is needed.

The growth period of mature sperm is approximately 90 days, including three critical windows: 0–9 days prior to ejaculation (epididymal storage), 10–14 days prior to ejaculation (development of sperm motility), and 70–90 days prior to ejaculation (spermatogenesis) (48). There are fewer studies on which stage of sperm development is most vulnerable to air pollution, but the findings remain controversial (27, 29, 33, 34, 36–40, 42–44, 47). A meta-analysis of relevant research data is needed.

Although there are five systematic review and meta-analyses on whether semen quality is affected by air contaminants (49–53), the measured indicators of the four systematic review and meta-analyses were the mean differences and the exposure periods were not 90 days (49–52). The four systematic review and meta-analyses compare semen quality between men exposed to high levels of air pollution and men exposed to low levels of air pollution and were not standardized when merging the effects of air pollution from different studies (49–52). The main distinction between the reported four meta-analyses and the present work is that we have studied the association air pollution exposure during the whole 90 day period as well as the three critical windows of sperm development. A systematic review and meta-analysis by Xu et al. reported the effect of air pollution exposure during lag 0–90 days or 0–12 weeks on semen quality based on exposure-response relationships but did not report the effect of air pollution exposure during the three critical windows of sperm development (53). The included articles did not include those published in Chinese and those published recently in 2023, and subgroup or sensitivity analyses were also not performed (53). There is still no systematic review on whether semen quality is affected by air pollution exposure during the three critical windows of sperm development.

Therefore, the first meta-analysis was done for analyzing the relation of air pollution exposure during the whole and three critical windows of sperm development and sperm quality in China.

Methods

The present meta-analysis was performed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (54) as well as PRISMA 2020 checklist had been provided in Supplementary Materials A. This meta-analysis was registered on the PROSPERO website (No. CRD42022374712). Literature search.

We retrieved the Cochrane Library, EMBASE, Web of Science, PubMed, VIP, China National Knowledge Infrastructure (CNKI) as well as Wanfang databases for articles. The search process does not limit the language and search date. Only epidemiological observational studies published in Chinese or English would be included. The applied search words and detailed search strategies are shown in Supplementary Table S1; Supplementary Materials B, respectively. Searches were performed independently by RL and JY Disagreement was resolved by a third author (JL)

Outcomes

Outcomes included total sperm number, sperm concentration, total and progressive motility.

Inclusion and exclusion criteria

Inclusion criteria were: (a) reporting the effect of at least one air pollutant exposure during the whole window and/or critical stages of sperm development on sperm quality; (b) cross-sectional or cohort studies; (c) reporting regression coefficients (β) and 95% confidence intervals (CIs); (d) Chinese males; and (e) English and Chinese articles. The measured indicators of case-control studies were the means and standard deviations (SDs) rather than β and 95% CIs.

The following exclusion criteria were adopted: (a) animal studies, case reports, commentaries, reviews, protocols, editorials, conference abstracts, letters, or book chapters; (b) case-control studies; (c) studies in countries other than China; (d) reported shorter or longer exposure period; (e) focused on indoor air pollution; and (f) multivariate logistic regression.

Study selection

Two authors (RL and JY) conducted the literature selection independently. If any disagreement arose during the selection process, it would be resolved by discussing with the third author (JL).

Data extraction

Using a standardized form, the following information was extracted independently from eligible publications by two authors (RL and JY): publication year, first author, design of study, region, setting, research period, study subjects, size of the sample, pollutants exposure measurement, outcome, exposure period, statistical model, adjusted confounding factors, adjusted β with their corresponding 95% CIs. Through discussion with the third author (JL), any disagreement in the data extraction was resolved. The missing information of the original study was requested by contacting the corresponding author.

Quality assessment

Quality assessments of eligible publications were executed independently by two researchers (QW and LW). If there was any

inconsistent opinion, it would be resolved by discussing with the third researcher (YD). The Newcastle-Ottawa Scale (NOS) checklist was adopted for evaluating the quality of retrospective as well as prospective cohort studies (55). The Joanna Briggs Institute (JBI) critical appraisal checklist was adopted for evaluating the quality of cross-sectional studies (56). Based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) guidelines (57), the certainty of evidence was started with moderate and further downgraded based on the following items: publication bias, directness, study limitations, consistency, and precision (58, 59), and upgraded for dose-response gradient, strong effect size as well as plausible confounding effect (60).

Data analyses

> If the articles did not give interquartile range (IQR) values or original incremental units of pollutant exposure, we would contact the authors by email. For parts per billion (ppb) units, the following equations were used to convert to μg/m^3: 1 ppb = 48/22.4 μg/m^3 (O_3); 1 ppb = 46/22.4 μg/m^3 (NO_2). It was assumed that the standard ratio of 24 h average, 8 h max, and 1 h max was 8:15:20, which was widely used for O_3 conversion (61–63). To improve comparability, we converted all estimates to 24-h average. The standardized increment was 10 μg/m^3 in this study, otherwise it would be converted using the following formula (64, 65):

$$\beta_{(\text{standardized})} = \beta_{(\text{original})} \times \text{Increment}\,(10) / \text{Increment}\,(\text{original})$$

Statistical analyses were conducted with Stata v12.1 (Stata Corp., United States). The β and 95% CIs were combined using the DerSimonian-Laird random effect models. Chi-squared test and I^2 statistics were used to quantify the heterogeneity. Heterogeneity existed when $p < 0.05$ or $I^2 > 50\%$ (66). In order to find sources of heterogeneity, we conducted sub-group analyses based on design of the study (cross-sectional and cohort), location (northern and southern China), and exposure assessment approaches (estimating models or monitoring station). Egger's test as well as funnel plots were adopted for assessing publication bias. Stability of the findings was judged with the help of sensitivity analysis. $p < 0.05$ was statistical significance.

Results

Study characteristics

As depicted in Figure 1, 3,952 publications were retrieved from the seven databases, and 34 articles remained after duplicate literature, abstracts and titles exclusion. After reading the full article, 14 articles were further excluded and detailed exclusion reasons were given in Supplementary Table S2. The remaining 21 eligible publications were eventually included in this meta-analysis. Missing data of original articles were requested by contacting the authors *via* email or WeChat. Studies with missing information were excluded if multiple contacts with the corresponding author remained unanswered. Table 1 illustrates the primary characteristics of the eligible publications. Table 2 demonstrates the original incremental units, outcomes, statistical models used and adjusted confounding factors of all the eligible studies. If the increment unit of the original study was not

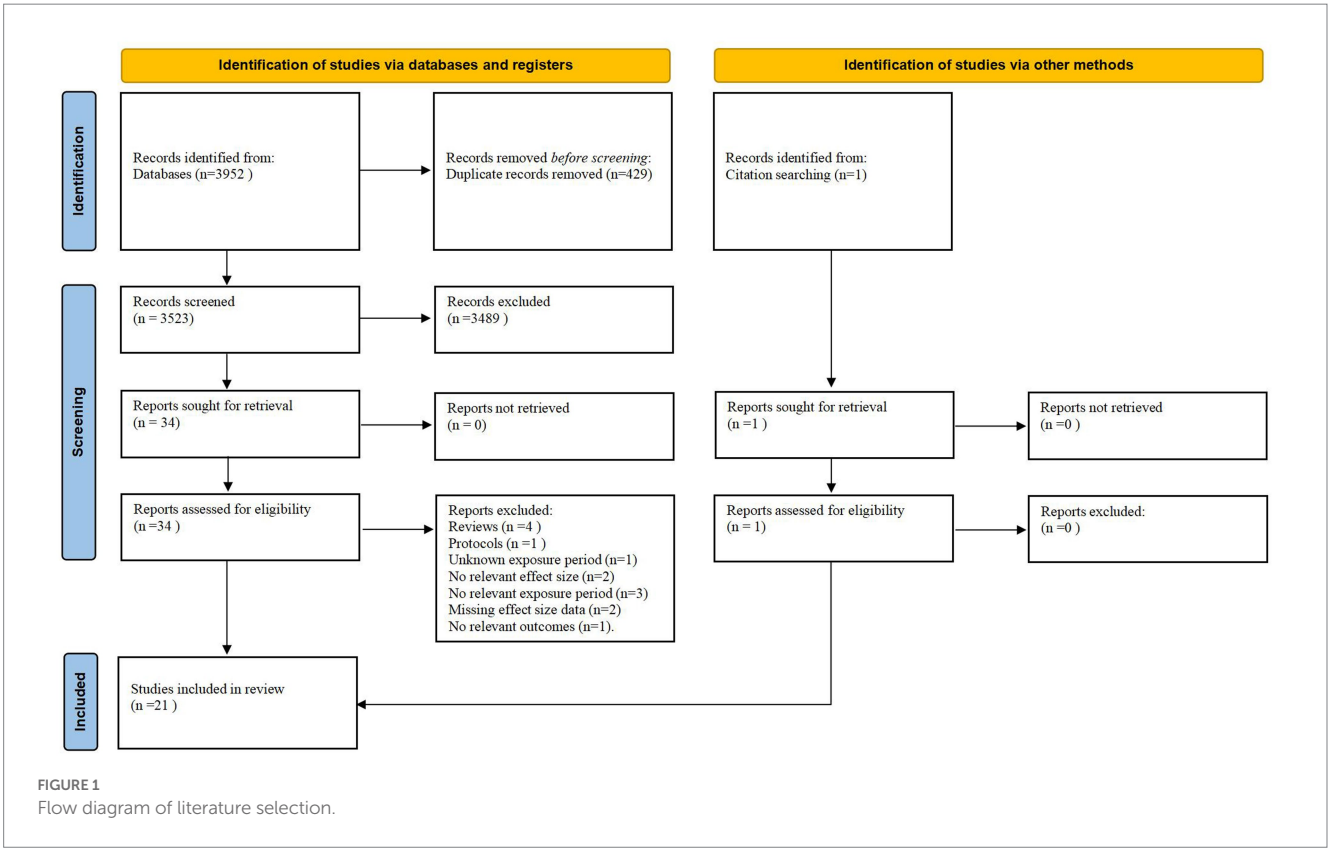

FIGURE 1
Flow diagram of literature selection.

TABLE 1 Characteristics of the included studies in this meta-analysis.

Author publication year	Study design	Location	Setting	Study period	Subjects	Sample size	Exposure measurement	Quality[a,b]
Dai et al. (2022)	Cohort	East China	Urban	2014–2019	Male partners of infertile couples	1,494 men	Air monitoring station	6 (NOS)
Guan et al. (2020)	Cohort	East China	Urban and rural	2015–2017	Male partners of infertile couples	1955 men with 2073 semen samples	Inverse distance weighting model	7 (NOS)
Huang et al. (2019)	Cohort	Central China	Urban	2014–2015	Male partners of infertile Couples	1,081 with 1,278 semen samples	Air monitoring station	7 (NOS)
Huang et al. (2020)	Cohort	South China	Urban	2018–2019	Sperm donors	1,168 men with 3,797 semen samples	Inverse distance weighting model	8 (NOS)
Lao et al. (2018)	Cross-sectional	East China	Urban and rural	2001–2014	Men from the general population	6,475 men	Hybrid spatiotemporal model	8 (JBI)
Liu et al. (2017)	Cohort	Central China	Urban	2013–2015	Male partners of infertile couples	1759 men with 2,184 semen samples	Inverse distance weighting model	8 (NOS)
Ma et al. (2022)	Cohort	Central China	Urban and rural	2015–2020	Male partners of infertile couples	15,112 men with 28,267 semen samples	Inverse distance weighting model	8 (NOS)
Ma et al. (2023)	Cohort	Central China	Urban and rural	2015–2020	Male partners of infertile couples	15,112 men with 28,267 semen samples	Inverse distance weighting model	8 (NOS)
Qiu et al. (2020)	Cohort	Southwest China	Urban	2013–2018	Sperm donors	686 men with 4,841 semen samples	Air monitoring station	7 (NOS)
Tian et al. (2017)	Cohort	Central China	Urban	2013–2015	Male partners of infertile couples	1780 men	Air monitoring station	7 (NOS)
Wang et al. (2018)	Cross-sectional	Central China	Urban	2013–2015	Male partners of infertile couples	1827 men	Air monitoring station	7 (JBI)
Wang et al. (2020)	Cross-sectional	Central China	Urban and rural	2013–2015	Male partners of infertile couples	1852 men	Air monitoring station	7 (JBI)
Wu et al. (2017)	Cohort	Central China	Urban	2013–2015	Male partners of infertile couples	1759 men with 2,184 semen samples	Inverse distance weighting model	8 (NOS)
Wu et al. (2022)	Cohort	East China	Urban	2014–2016	Fertile men from NUM-LIFE study	1,554 men	Inverse distance weighting model	8 (NOS)
Yu et al. (2022)	Cohort	South China	Urban	2019	Sperm donors	1,310 men with 4,912 semen samples	Land-use random forest model	8 (NOS)
Zhang et al. (2019)	Cohort	North China	Urban	2015–2018	Sperm donors	1,116 men with 8,945 semen samples	Air monitoring station	7 (NOS)
Zhang et al. (2023)	Cohort	East China	Urban	2019–2021	Sperm donors	1,515 men	Inverse distance weighting model	8 (NOS)
Zhao et al. (2022)	Cohort	East China	Urban and rural	2013–2019	Male partners of infertile couples	33,876 men	Air monitoring station	7 (NOS)
Zhou et al. (2014)	Cohort	Southwest China	Urban and rural	2007–2013	Healthy fertile men	1,346 men	Air monitoring station	8 (NOS)
Zhou et al. (2018)	Cohort	Southwest China	Urban	2014–2015	General college students	796 men	Air monitoring station	7 (NOS)
Zhou et al. (2021)	Cross-sectional	North China	Urban and rural	2018–2019	Male partners of infertile couples	423 men	Ordinary Kringing model	8 (JBI)

[a]The Newcastle-Ottawa Scale (NOS) checklist was adopted for evaluating the quality of retrospective as well as prospective cohort studies and the maximum score is 9.
[b]The Joanna Briggs Institute (JBI) critical appraisal checklist was adopted for evaluating the quality of cross-sectional studies and the maximum score is 8. NUM-LIFE, Nanjing Medical University Longitudinal Investigation of Fertility and the Environment; NOS, Newcastle-Ottawa Scale; JBI, Joanna Briggs Institute.

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TABLE 2 Pollutants, outcomes, and statistical information of the 19 included studies.

Author publication year	Outcome	Exposure period (day)	Pollutants (Original incremental unit)	Statistical mode	Adjusted confounding factors
Dai et al. (2022)	Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ (IQR) PM_{10} (IQR)	Multivariate linear regression models	Age, abstinence days, education level, occupation, average ambient temperature, seasons, and gaseous air pollutants
Guan et al. (2020)	Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ (IQR) PM_{10} (IQR)	Multivariate linear regression models	Age, abstinence days, semen volume
Huang et al. (2019)	Sperm concentration Total sperm count Total motility	90	$PM_{2.5}$ (IQR)	Multivariate linear mixed models	Age, BMI, race, education, smoking, alcohol consumption, abstinence period, and season
Huang et al. (2020)	Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ ($\mu g/m^3$) PM_{10} ($\mu g/m^3$) SO_2 ($\mu g/m^3$) NO_2 ($\mu g/m^3$) CO (mg/m^3)	Linear mixed-effect models	Age, BMI, percent body fat, ethnic, marital status, childbearing history, career, smoking, alcohol consumption, abstinence period, season, a natural cubic spline function of time, a natural cubic spline function of temperature during exposure period
Lao et al. (2018)	Sperm concentration Progressive motility Total motility Percentage of normal morphology	90	$PM_{2.5}$ (5 $\mu g/m^3$)	Multivariate linear regression models	Age, education level, smoking status, alcohol drinking, exercise and occupational exposure to asbestos and organic solvent, body mass index, systolic blood pressure, fasting blood glucose and total cholesterol levels, season, year of medical examination
Liu et al. (2017)	Sperm concentration Total sperm count Progressive motility Total motility Total motile sperm count	90	SO_2 (IQR) NO_2 (IQR) CO (IQR) O_3 (IQR)	Multiple linear regression analysis	Age, BMI, race, education, smoking amount, alcohol consumption, and abstinence period, temperature, season
Ma et al. (2022)	Sperm concentration Total sperm count Progressive motility Total motility Progressively motile sperm count Total motile sperm count	90	$PM_{2.5}$ (IQR) PM_{10} (IQR)	Linear mixed-effects models	Age, BMI, smoking, drinking, occupation, abstinence period, month (at the date of semen collection) and temperature (average temperature of contemporary period)
Ma et al. (2023)	Sperm concentration Total sperm count Progressive motility Total motility Progressively motile sperm count Total motile sperm count	90	SO_2 (IQR) NO_2 (IQR) CO (IQR) O_3 (IQR)	Linear mixed-effects models	Age, BMI, smoking, drinking, occupation, abstinence period, month (at the date of semen collection) and temperature (average temperature of contemporary period)
Qiu et al. (2020)	Semen volume Sperm concentration Progressive motility	90	$PM_{2.5}$ ($\mu g/m^3$) PM_{10} ($\mu g/m^3$) SO_2 ($\mu g/m^3$) NO_2 ($\mu g/m^3$) CO (mg/m^3) O_3 (1ppb)	Linear mixed-effects models	Abstinence days, age, BMI, education level, year of sample collection, relative humidity (current day, 90-day preceding), temperature (current day, 90-day preceding)
Tian et al. (2017)	Sperm concentration Total sperm count	90	O_3 ($\mu g/m^3$)	Multivariate linear mixed models	Age, BMI, education level, smoking status, seasons of semen collection, abstinence days, average temperature, average relative humidity

(Continued)

TABLE 2 (Continued)

Author publication year	Outcome	Exposure period (day)	Pollutants (Original incremental unit)	Statistical mode	Adjusted confounding factors
Wang et al. (2018)	Semen volume Sperm concentration Total sperm count Progressive motility Total motility	90	PM_{10} (10 μg/m^3)	Multiple linear regression analysis	Age, BMI, education level, smoking status, abstinence days, seasons of semen collection, average temperature, average relative humidity
Wang et al. (2020)	Sperm concentration Total sperm count Progressive motility	90	SO_2 (IQR) NO_2 (IQR)	Multivariate linear regression models	BMI, education level, smoking, age, and abstinence period, temperature, humidity, season, and PM2.5
Wu et al., (2017)	Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ (IQR) PM_{10} (IQR)	Multivariate linear regression models	Age, BMI, ethnic, education, smoking, alcohol consumption, abstinence period, season and temperature
Wu et al. (2022)	Semen volume Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ (10 μg/m^3)	Multivariate linear regression models	Age, BMI, ethnicity, education, smoking status, drinking status, family income, abstinence period, season, and temperature
Yu et al. (2022)	Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ (IQR) PM_{10} (IQR)	Linear mixed-effect models	Age. BMI, percent body fat, education, ethnic, martial status, childbearing history, career, smoking, drinking, abstinence period, month, a natural cubic spline function of temperature during exposure period
Zhang et al. (2019)	Sperm concentration Progressive motility	90	$PM_{2.5}$ (μg/m^3) PM_{10} (μg/m^3) SO_2 (μg/m^3) NO_2 (μg/m^3) CO (mg/m^3) O_3 (μg/m^3)	Linear mixed-effect models	Age, abstinence duration, month, average temperature
Zhang et al. (2023)	Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ (μg/m^3) PM_{10} (μg/m^3) SO_2 (μg/m^3) NO_2 (μg/m^3) CO (μg/m^3) O_3 (μg/m^3)	Multivariate linear regression models	Age, ethnicity, season of semen collection, abstinence period and temperature.
Zhao et al. (2022)	Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ (IQR) PM_{10} (IQR)	Linear mixed-effect models	Ethnicity, age, educational level, body mass index, smoking, alcohol consumption, season of semen collection, abstinence period, temperature, relative humidity, and gaseous pollutants
Zhou et al. (2014)	Semen volume Sperm concentration Progressive motility Total motility Percentage of normal morphology	90	PM_{10} (μg/m^3) SO_2 (μg/m^3) NO_2 (μg/m^3)	Multiple linear regression analysis	Age, education, smoking, BMI, alcohol use, abstinence time period and season
Zhou et al. (2018)	Semen volume Sperm concentration Total sperm count Progressive motility Percentage of normal morphology	90	$PM_{2.5}$ (μg/m^3) PM_{10} (μg/m^3)	Multiple linear regression analysis	Age, smoking, alcohol use, BMI and abstinence time

(Continued)

TABLE 2 (Continued)

Author publication year	Outcome	Exposure period (day)	Pollutants (Original incremental unit)	Statistical mode	Adjusted confounding factors
Zhou et al. (2021)	Sperm concentration Total sperm count Progressive motility Total motility	90	$PM_{2.5}$ (μg/m^3) PM_{10} (μg/m^3) SO_2 (μg/m^3) NO_2 (μg/m^3) CO (mg/m^3) O_3 (μg/m^3)	Multiple linear regression models	Abstinence, age, BMI, socioeconomic status, smoking status, alcohol consumption, psychological stress, exposures to heat, metals or solvents, average ambient air temperature, multi-time windows and multi-pollutants

$PM_{2.5}$, particulate matter with the diameter ≤ 2.5 μm; PM_{10}, particulate matter with diameter ≤ 10 μm; SO_2, sulfur dioxide; NO_2, nitrogen dioxide; CO, carbon monoxide; O_3, ozone; BMI, body mass index; IQR, inter-quartile rages (IQR).

10 μg/m^3, effect sizes were converted. The credibility of the evidence was categorized as very low or low (Supplementary Table S3).

Air pollutants and sperm quality

Six air pollutants exposure during the whole window did not affect sperm concentration (Supplementary Table S4; Figure 2). PM_{10}, SO_2, and NO_2 exposure during the whole window were related with decreased total sperm number, while such association was not found for $PM_{2.5}$, CO, and O_3 exposure (Supplementary Table S4; Figure 2). $PM_{2.5}$, PM_{10} as well as SO_2 exposure during the entire window were negatively related with total motility, while such association was not found for other pollutants.

In order to find sources of heterogeneity, we conducted sub-group analyses based on design of the study (cohort and cross-sectional), location (northern China and southern China), and exposure assessment approaches (monitoring station or estimating models). The majority of sub-group results were consistent with the pooled results (Supplementary Table S5; Figure 3).

During 0–9 lag days, only SO_2 exposure was related with declined total motility (Supplementary Table S5; Figure 3). During 10–14 lag days, $PM_{2.5}$ exposure was adversely related with total sperm number and total motility, SO_2 with total motility (Supplementary Table S5; Figure 3). During 70–90 lag days, PM_{10} and NO_2 exposure were adversely related with total sperm number, $PM_{2.5}$ with total motility (Supplementary Table S5; Figure 3).

Sensitivity analysis

In the sensitivity analyses for six pollutants exposure during the whole window and sperm quality, pooled effect sizes did not change significantly by omitting one study from each analysis, thus indicating that our findings were stable (Supplementary Table S4; Supplementary Figure S1). However, when the study of Wu et al. (40) was omitted from sensitivity analyses of $PM_{2.5}$ exposure and progressive motility, a significant association disappeared ($p = 0.081$; Supplementary Table S4; Supplementary Figure S1A). When the study of (34) was omitted from sensitivity analyses of PM_{10} exposure and sperm concentration, a significant association disappeared ($p = 0.119$; Supplementary Table S4; Supplementary Figure S1B). When the study by Ma et al. (33) was omitted from the sensitivity analysis of O_3 exposure and total motility, a significant association disappeared ($p = 0.104$; Supplementary Table S4; Supplementary Figure S1F).

In the sensitivity analyses of six pollutants exposure during critical windows and sperm quality, the pooled effect sizes did not change significantly by omitting one study from each analysis, thus indicating that our findings were stable. However, when the study of Ma et al. (33) was omitted from the sensitivity analyses of O_3 (70–90 lag days) exposure and total motility, a significant association disappeared ($p = 0.197$) with heterogeneity decreasing from 51 to 0% (Supplementary Table S5).

Discussion

Summary of study results

China has a population of more than 1.4 billion and covers a land area of approximately 9.6 million km^2. Due to the vast territory of China, it varies greatly in climate conditions, landforms, geography, population density, and economic development level in different regions. Based on economic development levels and climatic conditions, China is generally grouped into seven geographic regions (67–69). Detailed geographic location is presented in Supplementary Figure S2. China is roughly classified as southern and northern China (70–72). Distribution of southern and northern China is shown in Figure 4. As a result of the limited sample size, we performed sub-group analysis by location (northern China and southern China). Air quality is closely related with climatic conditions and economic development levels. Air quality is better in western China than in eastern China (67). Economic development levels in western and eastern regions result in different chemical compositions of pollutants (73, 74). In the eastern and central regions, industry and traffic are the primary causes of air pollution (75). Biomass burning and soil dust are the primary reasons of air pollution in the western region. Different sources of air pollution in different regions result in different toxicity, concentrations, and chemical compositions. This may explain, to some extent, the inconsistent results.

Different individual exposure assessment approaches can partially explain the controversial results. Lao et al. estimated individual exposure levels of $PM_{2.5}$ using a high-resolution (1 × 1 km) spatiotemporal model (31). Zhou et al. (44) adopted the ordinary Kriging model to measure individual exposure concentrations. Some studies used the land-use random forest model (41) or inverse distance weighting model (28, 29, 32, 34, 39, 40) to assess the actual individual exposure levels. Some other studies used the averaged levels of the city-wide or the nearest monitoring station to assess actual individual pollutant exposure concentrations (27, 30, 35–38, 42, 43, 45, 46).

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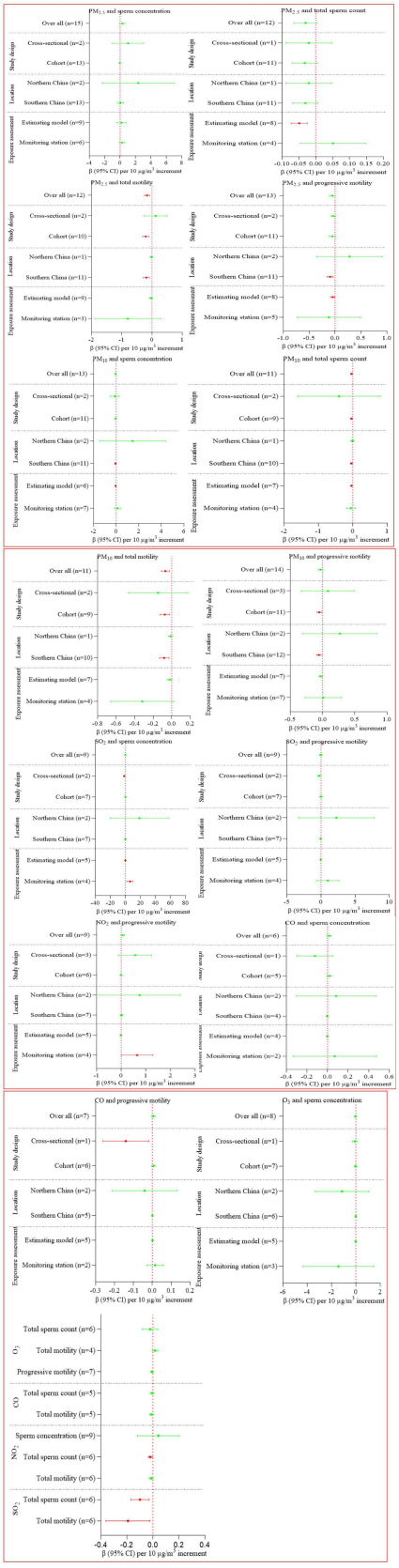

FIGURE 2
Regression coefficients and 95% confidence intervals for the relation between six pollutants exposure during the whole window and sperm quality.

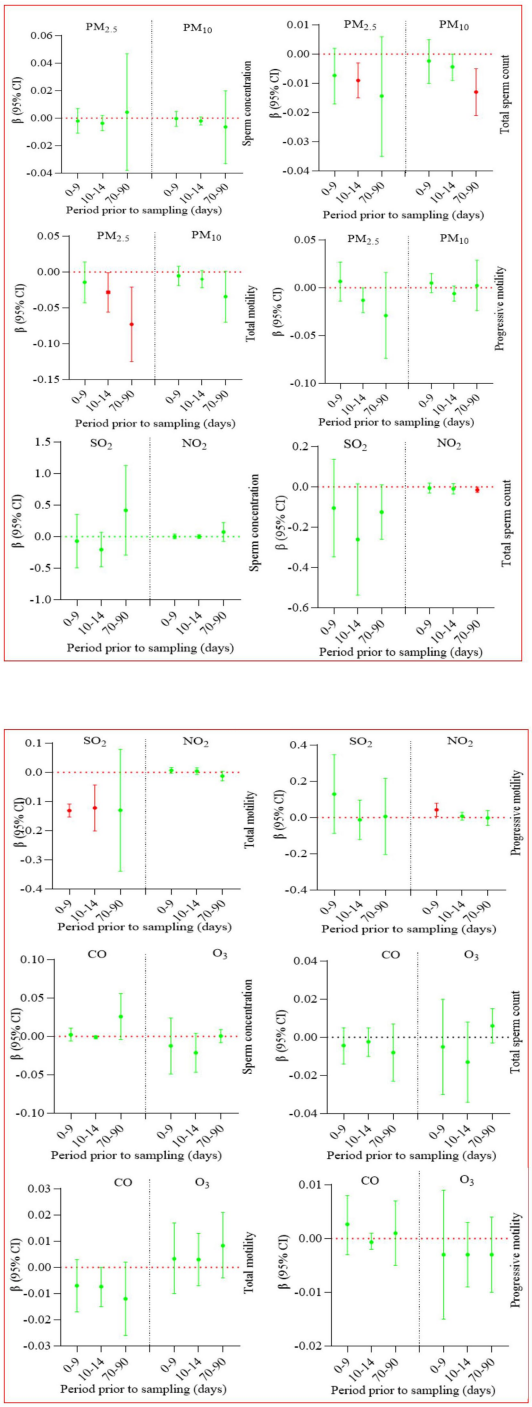

FIGURE 3
Regression coefficients and 95% confidence intervals for the relation between six pollutants exposure during three critical windows and sperm quality.

This is the first meta-analysis to analyze potential impacts of ambient air pollution exposure during the whole window and three critical windows on semen quality in China. Sperm motility, a conventional semen parameter, is one of the common indicators of fertility assessment. Sperm motility is commonly used as one of the most important sperm functions to determine whether female partners can successfully conceive without any assisted reproductive

FIGURE 4
Distribution of northern and southern China.

technology (ART). Sperm motility parameters are also sensitive indicators of male reproductive toxicity (76). PM_{10}, $PM_{2.5}$ as well as SO_2 exposure were adversely related with total motility during 0–90 days prior to ejaculation. $PM_{2.5}$, CO as well as O_3 exposure were adversely related with total sperm number during 0–90 lag days.

In order to find sources of heterogeneity, we conducted sub-group analyses based on design of the study (cohort and cross-sectional), location (northern China and southern China), and exposure assessment approaches (monitoring station or estimating models). Although subgroup analysis reduced heterogeneity to some extent, heterogeneity remained high level in some subgroups, and it was necessary to continue to explore potential sources of between-studies heterogeneity.

In addition, the possible exposure susceptibility window was also investigated. $PM_{2.5}$ exposure affected total motility (10–14 and 70–90 lag days) and total sperm number (10–14 lag days). PM_{10} affected total sperm number (70–90 lag days). SO_2 influenced total sperm number (0–9 and 10–14 lag days). NO_2 affected total sperm number (70–90 lag days). The findings suggested that pollutants exposure might affect total motility and total sperm number.

Biological mechanisms

The biological mechanisms that environmental pollutant exposure may damage the development of total motility have not been elucidated. PM_{10}, $PM_{2.5}$, and O_3 exposure can lead to elevated concentrations of reactive oxygen species (77, 78), which may disrupt the blood-testis barrier, detriment spermatogenesis and result in declined sperm motility (79–82). PM exposure can also cause systemic inflammatory reactions by elevating tumor necrosis factor (TNF) as well as interleukin-1β (IL-1β) levels (83–86). Higher concentrations of IL-1β and TNF are related with impaired total sperm motility (87–89). Significant reduction in air pollutants emissions was accompanied by improvements in people's markers of inflammatory conditions, thrombosis as well as oxidation stress (90). We hypothesized that environmental pollutant exposure would elevate oxidative stress levels and inflammatory reactions, which could lead to decreased total sperm motility. This hypothesis requires further toxicological studies to elucidate the detailed mechanism of reduced sperm motility caused by environmental pollutant exposure.

Strengths and limitations

This present meta-analysis has three advantages. First, it is the first meta-analysis to analyze whether semen quality is affected by air pollution exposure during the whole and critical windows. Second, the findings are relatively new as a result of most eligible studies being published within recent 4 years. Third, results of different original studies were difficult to compare since the exposure increment units

were different in most cases. Therefore, the comparability of the results was improved by standardizing the data through transformation.

However, the present meta-analysis still has four limitations. First, a high degree of heterogeneity for some pollutants was found, which may be explained by differences in pollutant concentrations, types of air pollutants, chemical components of particulate matter, individual exposure assessment approaches, design of the study, study setting, sample size, study regions, selection bias, and adjustment confounding factors. Due to the high degree of heterogeneity, caution should be given when interpreting some pooled effects. A high degree of heterogeneity may also hinder the detection of publication bias. Second, selective bias may occur due to some of the included studies selecting patients from infertility clinics. Third, subgroup analysis by exposure assessment approaches was not performed as a result of the insufficient sample size. Fourth, the sample size is still inadequate, with only 2 articles from northern China being included. Insufficient data might lead to inescapable errors, and the original researches need to be further supplemented. Fifth, many of the included studies obtained estimates of air pollution exposure from ecological data or modeling and did not examine individual exposure to air pollution.

Conclusion

This evidence suggested that ambient air pollution could reduce semen quality in Chinese men and may even lead to infertility. For Chinese men, there is a need to reduce the duration of exposure. Further studies should be conducted to explore the possible biological mechanisms behind the findings observed in this study.

Author contributions

JL and YD proposed the idea and designed the present study, interpreted the findings, and were responsible for statistical analysis and manuscript writing. RL and JY performed literature retrieval, study selection, and data extraction. QW and LW performed the quality assessment. 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.2023.1219340/full#supplementary-material

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Causal relationship between particulate matter 2.5 and diabetes: two sample Mendelian randomization

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Backgrounds: Many studies have shown particulate matter has emerged as one of the major environmental risk factors for diabetes; however, studies on the causal relationship between particulate matter 2.5 ($PM_{2.5}$) and diabetes based on genetic approaches are scarce. The study estimated the causal relationship between diabetes and $PM_{2.5}$ using two sample mendelian randomization (TSMR).

Methods: We collected genetic data from European ancestry publicly available genome wide association studies (GWAS) summary data through the MR-BASE repository. The IEU GWAS information output $PM_{2.5}$ from the Single nucleotide polymorphisms (SNPs) GWAS pipeline using pheasant-derived variables (Consortium = MRC-IEU, sample size: 423,796). The annual relationship of $PM_{2.5}$ (2010) were modeled for each address using a Land Use Regression model developed as part of the European Study of Cohorts for Air Pollution Effects. Diabetes GWAS information (Consortium = MRC-IEU, sample size: 461,578) were used, and the genetic variants were used as the instrumental variables (IVs). We performed three representative Mendelian Randomization (MR) methods: Inverse Variance Weighted regression (IVW), Egger, and weighted median for causal relationship using genetic variants. Furthermore, we used a novel method called MR Mixture to identify outlier SNPs.

Results: From the IVW method, we revealed the causal relationship between $PM_{2.5}$ and diabetes (Odds ratio [OR]: 1.041, 95% CI: 1.008–1.076, $P = 0.016$), and the finding was substantiated by the absence of any directional horizontal pleiotropy through MR-Egger regression ($\beta = 0.016$, $P = 0.687$). From the IVW fixed-effect method (i.e., one of the MR machine learning mixture methods), we excluded outlier SNP (rs1537371) and showed the best predictive model (AUC = 0.72) with a causal relationship between $PM_{2.5}$ and diabetes (OR: 1.028, 95% CI: 1.006–1.049, $P = 0.012$).

Conclusion: We identified the hypothesis that there is a causal relationship between $PM_{2.5}$ and diabetes in the European population, using MR methods.

KEYWORDS

particulate matter 2.5, diabetes, genetics epidemiology, environmental epidemiology, two sample Mendelian randomization, GWAS

Introduction

Diabetes is a multifactorial disease caused by an interaction of genetic and environmental components (1). Over the past decade there has been a marked increase in its prevalence worldwide and is thus becoming an increasing public health threat (2). Diabetes imposes substantial financial and societal costs upon healthcare systems and society at large (3).

Diabetes's cause is multifactorial and includes genetic and environmental components (1). Some well-established risk factors for diabetes are obesity, sedentary lifestyle habits, an unhealthy diet, family history and increasing age; in addition to these well-recognized risk factors, research is currently investigating any correlation between exposure to ambient air pollution and the development of diabetes (1).

Particulate matter 2.5 ($PM_{2.5}$), an air pollutant that has recently drawn significant media attention for its harmful impacts on respiratory and cardiovascular health, has attracted considerable public attention in recent years (4). $PM_{2.5}$ refers to fine particles with diameters <2.5 micrometers that can penetrate deeply into respiratory systems and enter bloodstream. Sources that emit this pollution include vehicle exhaust emissions, industrial emissions, combustion processes, etc.

Previous studies have investigated the association between $PM_{2.5}$ exposure and diabetes, and its related complications, and intriguing results. Epidemiological studies conducted across various populations have pointed to an association between long-term PM2.5 exposure and an increased risk of diabetes development—often through measures such as air pollution exposure assessments, biomarker analyses and health outcome evaluations (5, 6).

The exact mechanisms connecting $PM_{2.5}$ exposure with diabetes remain to be understood; it has been hypothesized that it may induce systemic inflammation, oxidative stress and endothelial dysfunction which all play key roles in its pathogenesis (7). Furthermore, exposure has been linked to insulin resistance, impaired glucose metabolism and changes in pancreatic beta-cell function; all of which are fundamental aspects of diabetes development (8).

According to previous studies, genetic polymorphism is an important factor to consider when studying the effects of pollutants on different physiological and immunological functions in humans. For instance, a genetics-based study revealed that women with GPX4-rs376102 AC/CC genotype are more susceptible to air pollutants (9). Epidemiological studies conducted in various populations have indicated a positive correlation between long-term $PM_{2.5}$ exposure and the risk of developing diabetes (5, 6). These studies have employed methods such as assessing air pollution exposure, analyzing biomarkers, and conducting detailed evaluations of health outcomes.

Regarding $PM_{2.5}$ and diabetes, MR studies employ genetic variants associated with exposure as instrumental variables. Unaffected by confounders or reverse causation effects, they allow researchers to estimate the causal impact of $PM_{2.5}$ exposure on diabetes risk estimation. By using large-scale genetic data sets along with robust statistical techniques, these MR studies may offer valuable insight into any possible causal relationships between $PM_{2.5}$ exposure and diabetes risk.

Mendelian Randomization (MR), which utilizes genetic variations as instrumental variables and SNP data from GWAS to explore causal relationships, was applied to investigate $PM_{2.5}$'s possible link to diabetes (10). This approach reduces biases and has profound implications for public health interventions and preventive strategies. First, using genetic variants as instrumental variables makes the method more reliable to examine causation than traditional observational research methods; thus, minimizing bias. Second, establishing the link between $PM_{2.5}$ and diabetes through multivariate analysis could have serious ramifications for public health interventions and preventive measures designed to lower air pollution and lessen diabetes risks among the general population. Therefore, we created an alternative hypothesis suggesting a causal relationship between $PM_{2.5}$ and diabetes and performed two-sample MR analysis to accept/reject it using data available through GWAS (11, 12).

Methods

Study population and data sources

The genetic data for this study were retrieved from GWAS summary data. The data is available in the MR-BASE repository. The repository was created by the Medical Research Council Integrative Epidemiology Unit, University of Bristol, for facilitating TSMR created the repository made repository. The GWAS outcomes depicted are insufficiently precise, which destabilize the effective application of this analysis (12). The referred repository (http://www.mrbase.org) comprises 11 billion SNP-trait associations from 1,673 GWAS. The repository is updated regularly (11).

The MRC-IEU UK Biobank genome wide association study (GWAS) pipeline has been optimized to conduct GWAS quickly, effectively, and uniformly on the imputed genetic dataset of the full 500,000 from UK Biobank. Participants were aged between 40 and 69 years when they joined UK Biobank between 2006 and 2010. Each participant attended a baseline assessment at a center in England (89%), Scotland (7%) and Wales (4%) (13).

The IEU GWAS information output $PM_{2.5}$ from the SNPs GWAS pipeline using pheasant derived variables consortium MRC-IEU. The annual relationship of $PM_{2.5}$ (2010) were modeled for each address using a Land Use Regression model developed as part of the European Study of Cohorts for Air Pollution Effects. For the outcome variable diabetes, the GWAS data were obtained from the MRC-IEU. Diabetes GWAS information consortium MRC-IEU were used, and the genetic variants were used as the IVs.

The $PM_{2.5}$ GWAS summary dataset (GWAS ID: ukb-b-10817) included 423,796 participants of European ancestry. $PM_{2.5}$ concentrations at participants' home addresses were estimated using a Land Use Regression (LUR) model (14). The diabetes was diagnosed by doctor (output from GWAS pipeline using pheasant derived variables from UK Biobank) GWAS summary dataset (GWAS ID: ukb-b-10753) contained 461,578 individuals of European descent, including 22,340 cases and 439,238 controls.

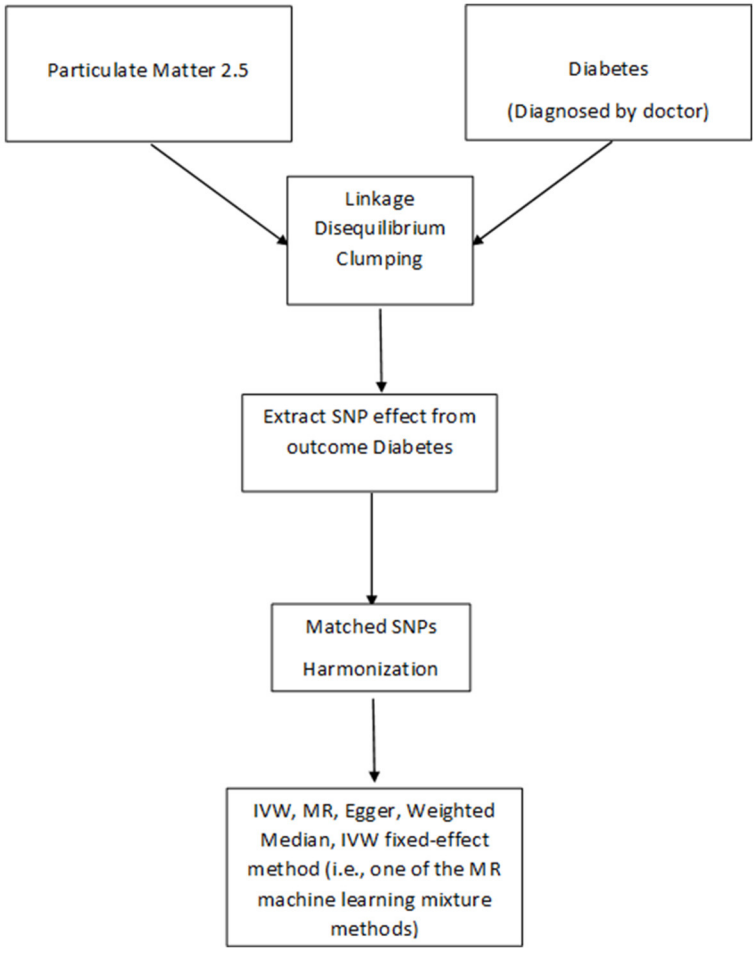

FIGURE 1
Flow chart of Mendelian randomization.

The number of European participants with a $PM_{2.5}$ phenotype was 423,796, while that for diabetes in the same population was 461,578, suggesting predisposition of $PM_{2.5}$ phenotype to diabetes. The GWAS data was retrieved from the MR-BASE repository.

The total 9,851,867 $PM_{2.5}$ SNPs were using a Bonferroni statistical threshold ($p < 5 \times 10 - 8$). Linkage disequilibrium (LD) was used to identify the independent SNPs by using the R^2 threshold <0.005. After adjusting for correlated SNPs, 7 of them were selected as the genetic instruments for evaluating genetic predisposition to being $PM_{2.5.}$ Once the genetic instruments were selected, the final set of harmonized data were completed by extracting information from the outcome GWAS matched to each instrument SNP (Figure 1).

Assumptions of mendelian randomization

In this Study, the TSMR approached was used. Where causal relationship between $PM_{2.5}$ and diabetes are obtained by dividing the instrument outcome associated by the instrument exposure association of each SNP (Figure 2). These association ratios are then combined using the IVW method for the main MR analysis (15).

MR estimate the valid, the instruments must satisfy three key assumptions (Figure 2):

IV1. The instruments must be robustly associated with the exposure.
IV2. The instruments must not be associated with any confounders of the exposure-outcome relationship.
IV3. The instruments can only be associated with outcome via the exposure and not via a different biological pathway independent of the exposure.

Statistical analysis

To evaluate the causal directionality between $PM_{2.5}$ and diabetes, we performed three representative MR methods: IVW, Egger, and Weighted median for causal relationship using genetic variants (16, 17). Furthermore, we applied a mixture-of-experts machine learning framework (MR Mixture) to improve the performance of MR estimation after identifying outlier SNPs. Since the assumption of MR can be violated due to SNPs that have horizontal pleiotropy, there were various attempts to develop

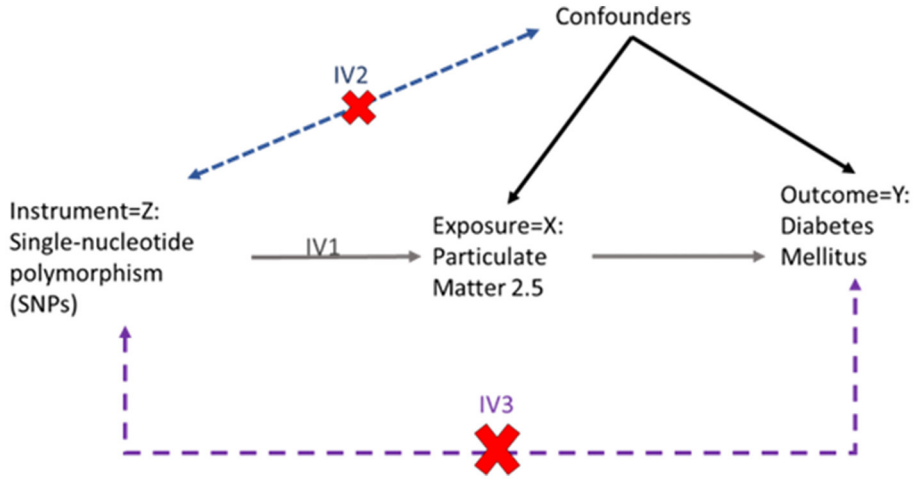

FIGURE 2
Flow diagram of two-sample Mendelian randomization.

TABLE 1 Description of GWAS consortium used for exposure and outcome.

Variable	Phenotype	Population	Sex	Sample size (cases)	Unit	Consortium
Exposure	Particulate Matter ($PM_{2.5}$)[b]	European	All	423,796	SD	MRC-IEU[a]
Outcome	Diabetes diagnosed by doctor	European	All	461,578 (22,340)	Log odds	MRC-IEU[a]

[a]MRC-IEU, MRC integrative epidemiology unit.
[b]UK BIOBNANK ID 24006: Output from GWAS pipeline using Pheasant derived variables from UK Biobank Consortium.
*Standard deviation.

methods lowering level of horizontal pleiotropy (18). Machine learning algorithms can help identify potential pleiotropic variants (genetic variants that affect multiple traits), and assess their impact on multivariate analysis. Furthermore, machine learning approaches may assist in creating genetic risk scores or polygenic risk scores to capture the combined effects of multiple genetic variants. Machine Learning methods commonly utilized in MR include regularized regression and mixture-of-experts machine learning framework (MR Mixture). They can help with variable selection, prediction modeling and exploring complex relationships among genetic instruments, exposures and outcomes (19). The MR Mixture is one of automatic model selection based on Random Forest algorithm to select the most appropriate method across a range of different MR strategies. MR strategies contains the combination of two instrument selections (Top hits, Steiger filtering) to identify outlier and fourteen MR estimation method (IVW fixed effects meta-analysis, IVW random effects meta-analysis, Egger fixed effects, Egger random effects, Rucker point estimate, Rucker mean of the jackknife, Rucker median of the jackknife, simple median, weighted median, penalized weighted median, simple mode, weighted mode, each weighted with or without the assumption of no measurement error in the exposure estimates) (20).

The fixed effects meta-analysis assumes that the only source of differences between relationship across the studies is due to sampling variation. In the MR context this translates to each SNP exhibiting no horizontal pleiotropy. Gene must be valid instruments. If all SNPs exhibit horizontal pleiotropy, then the effect estimate is asymptotically unbiased, but the standard error will be overly precise. Uses weights that assume the SNP-exposure association is known, rather than estimated, with no measurement error (i.e., known as the NOME assumption). Causal effect relationship from the IVW approach exhibit weak instrument bias whenever SNPs used as IVs violate the NOME assumption, which can be measured using the F-statistic with IVW methods (21, 22).

The leave-one-out sensitivity method was performed to compute whether random relationship were affected by an individual genetic locus. For further interpretation, scatterplots, forest plots, and funnel plots were also produced (11).

In this study, all MR analyses were calculated using R packages in R version 4.1.1 from the R Core Team, based in Vienna, Austria.

Results

The inclusion of sample sizes in Table 1 indicates the number of individuals from whose genetic data and pertinent information were acquired for each dataset. These datasets are critical for undertaking Mendelian randomization (MR) analyses, which use genetic variants linked with an exposure (in this case, $PM_{2.5}$) to assess the causal impact on an outcome of interest (in this case, diabetes, and its associated risk factors). For genetic instruments, $PM_{2.5}$, and diabetes GWAS data were obtained for European ancestry.

The fact that the GWAS data were obtained for people of European ancestry implies that the findings and genetic tools

TABLE 2 Causal relationship between particulate matter ($PM_{2.5}$) and diabetes.

Exposure	Outcome	Method	Nsnp[a]	β	SE[b]	OR (95% CI)[c]	*P*
Particulate Matter ($PM_{2.5}$)	Diabetes (diagnosed by doctor)	IVW[d]	7	0.040	0.017	1.041 (1.008–1.076)	0.016
		MR Egger	7	0.016	0.057	1.017 (0.906–1.140)	0.791
		Weighted median	7	0.034	0.017	1.035 (1.001–1.070)	0.040
		Fixed-Effect IVW	6	0.027	0.01	1.028 (1.006–1.049)	0.011

[a]Nsnp, number of (single nucleotide polymorphism, SNP).
[b]SE, standard error.
[c]OR, odd ratio (95% confidence intervals).
[d]IVW, inverse variance weight.

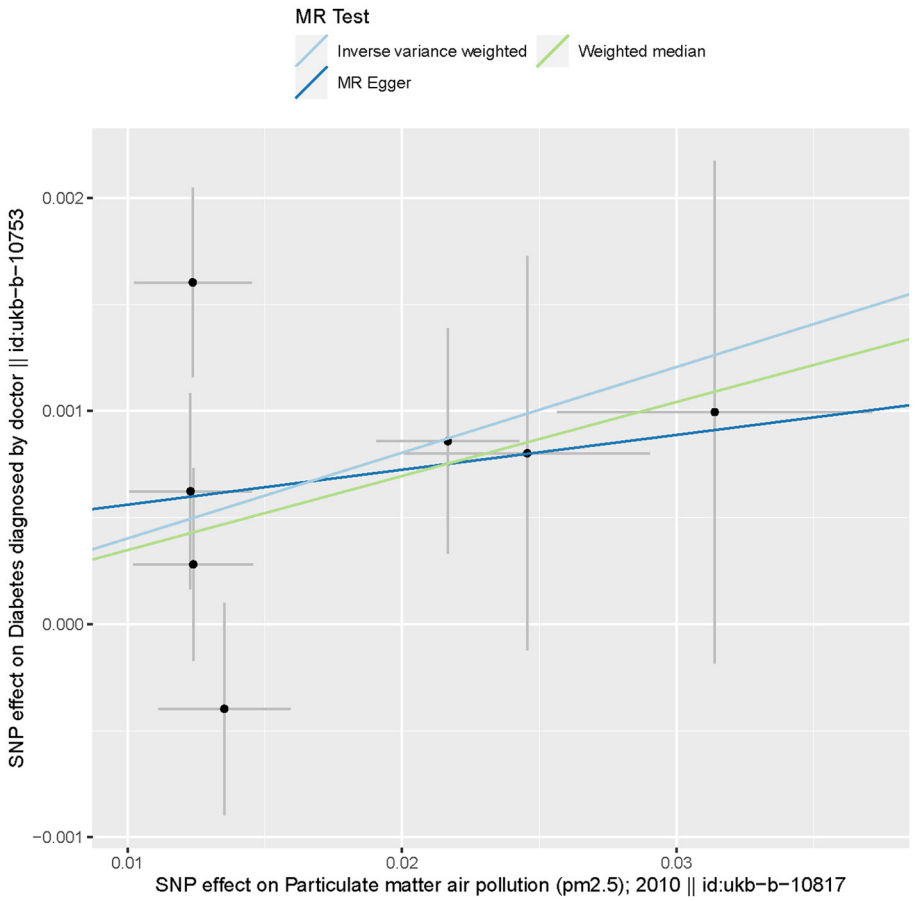

FIGURE 3
Scatter plots of genetic associations with particulate matter 2.5 against the genetic associations with diabetes. The slopes of each line represent the causal association for each method. The blue line represents the IVW estimate, the green line represents the weighted median estimate, and the dark blue line represents the MR-Egger estimate.

found in this investigation are most applicable and relevant to people of European heritage. Because genetic architecture and allele frequencies change between populations, it is critical to consider ancestry while conducting MR analysis or interpreting the results.

The Table 2 shows the IVW method, we revealed the causal relationship between $PM_{2.5}$ and diabetes (Odds ratio [OR]: 1.041, 95% CI: 1.008–1.076, $P = 0.016$), and the finding was substantiated by the absence of any directional horizontal pleiotropy through MR-Egger regression ($\beta = 0.016$, $P = 0.687$). From the IVW fixed-effect method (i.e., one of the MR Mixture methods), we excluded outlier SNP (rs1537371) and showed the best predictive model (AUC = 0.72) with a causal relationship between $PM_{2.5}$ and diabetes (OR: 1.028, 95% CI: 1.006–1.049, $P = 0.012$).

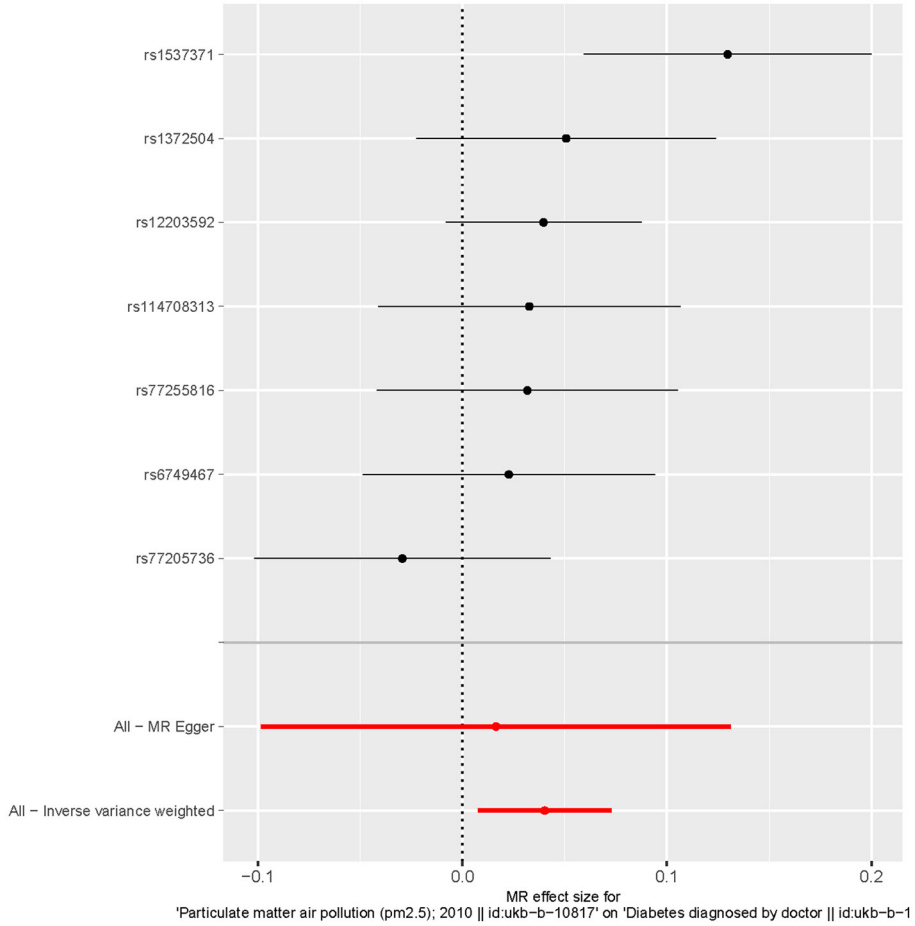

FIGURE 4
Forest plot of the causal effects of particulate matter 2.5 associated SNPs on diabetes.

Based on the two-sample MR randomization, it was revealed that a causal association between $PM_{2.5}$ and diabetes existed. The MR slopes of the plots for the IVW and weighted median regression indicated positive direction plots and were statistically significant suggesting a causal relationship between the measurement variable SNP $PM_{2.5}$ on diabetes (Figure 3). On the contrary, the MR-Egger regression indicated that the slope (causal effect) had no significant relationship with the outcome. This assumption suggests that there might be horizontal pleiotropy or significant outliers that violate the findings of the IVW, and weighted mean regarding the relationship between genetic predispositions to $PM_{2.5}$ and diabetes. The Figure 3 substantiated the assumption as the effect size on SNP-based outcome was lowest for MR-Egger.

MR analysis identified an outlier with the estimated causal effects suggested having been >2 SDs off the average causal effect that was obtained from the 7 $PM_{2.5}$ SNPs. Furthermore, the MR size had an effect on the $PM_{2.5}$'s association with diabetes based on the all IVW and all MR-Egger relationship, indicating varied MR effects for these two measurements (Figure 4). However, all the measurements involving both MR-Egger and IVW relationship for MR-leave-one-out revealed a stronger association between $PM_{2.5}$'s and diabetes. Such assumptions were ruled out when one of the SNPs were left out from the analysis (Figure 5). The respective SNP could be considered a potential outlier for the relationship between $PM_{2.5}$ and diabetes. On the other hand, the funnel plot (Figure 6) showed that MR-Egger produced relatively more asymmetry for the effects of $PM_{2.5}$ on diabetes compared to IVW.

Discussion

This study explored the causal relationship between $PM_{2.5}$ and diabetes as a function of TSMR using suitable platforms. The MR-Egger estimate reflected the absence of horizontal pleiotropy on diabetes as its intercept was positive but non-significant ($\beta = 0.016$, $P = 0.687$). Genetically predisposed $PM_{2.5}$ was significantly related to the increased risk of diabetes as depicted by the IVW estimation (Odds ratio [OR]: 1.041, 95% CI: 1.008–1.076, $P = 0.016$).

MR is gaining high popularity in epidemiological studies because it helps to establish whether a modifiable exposure has a causal relationship with the pathophysiology of a disease (16). Also, MR is increasingly used due to the availability of GWAS that provides an opportunity to use a large number of genetic variants in the referred analysis. If the variants in totality could explain a larger proportion of variance in the exposure variable, it would lead to more precise relationship of the causal effects.

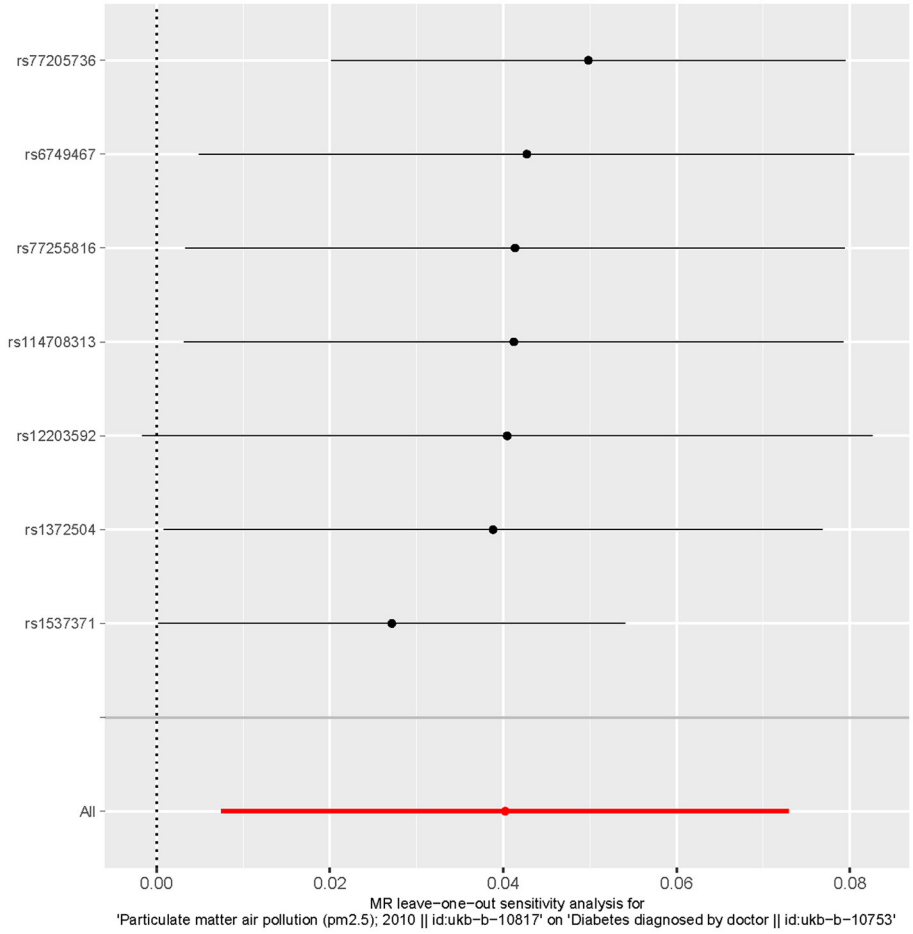

FIGURE 5
Leave one out the sensitivity analysis plot-the causal effect of particulate matter 2.5 on diabetes.

The precise estimation would increase the reliability of the cause-effect relationships with the referred variables. On the contrary, analysis conducted with an enlarged set of genetic variants is more likely to incorporate invalid instrument variables due to the violations of the assumptions of MR. One such set of variants are those causing horizontal pleiotropy. This is in contrast to vertical pleiotropy, where two traits that are biologically related are correlated irrespective of the gene or variant that is responsible for the effect. The study explored whether genetically predisposed $PM_{2.5}$ significantly increases the risk of diabetes.

$PM_{2.5}$ acts as a mediator linking endothelial dysfunction and insulin resistance. Alterations in endothelial function have been implicated in reduced peripheral glucose uptake (18). In addition, tumor necrosis factor (TNF-a), interleukin-6 (IL-6), resist in, and leptin levels were elevated with $PM_{2.5}$ exposure, in keeping with a proinflammatory insulin-resistant state.

In addition, PM exposure results in elevations in prothrombotic adipokines such as plasminogen activator inhibitor 1 and increased circulation adhesion molecules such as intracellular adhesion molecule-1 and E-selectin.

Sun et al. also reported experimental evidence of mouse model (23). $PM_{2.5}$ exposure exaggerates insulin resistance and visceral inflammation and adiposity, so these findings proved a new link between air pollution and type 2 DM. PM exposure was associated with impairment in phosphatidylinositol 3-kinase–Akt–endothelial nitric oxide synthase signaling in the aorta and decreased tyrosine phosphorylation of IRS-1 in the liver, providing evidence for abnormal insulin signaling in the vasculature. In addition, Liu et al., also suggested that $PM_{2.5}$ -mediated alterations in glucose homeostasis and $PM_{2.5}$-mediated inflammation in visceral adipose tissue (24). Toll-like receptors (TLRs) and nucleotide oligomerization domain receptors (NLRs) can be mediated as particular matter sensors. Long et al. studied systemic increase in IL-6 may play an important role in the deterioration of the type 2 DM via IL-6/signal transducer and activator of transcription 3 (STAT3)/suppressor of cytokine signaling (SOCS) pathway in liver after short-term exposure to $PM_{2.5}$ (25).

Evidence from epidemiological studies, combined with animal and toxicologic experiments, supports the notion that inflammatory responses to environmental factors are the key mechanism that helps explain the emerging epidemic in metabolic diseases like diabetes. Both genetic and environmental factors undoubtedly play a role, in the emergence of such diseases but the contributions of the physical and social environment determining

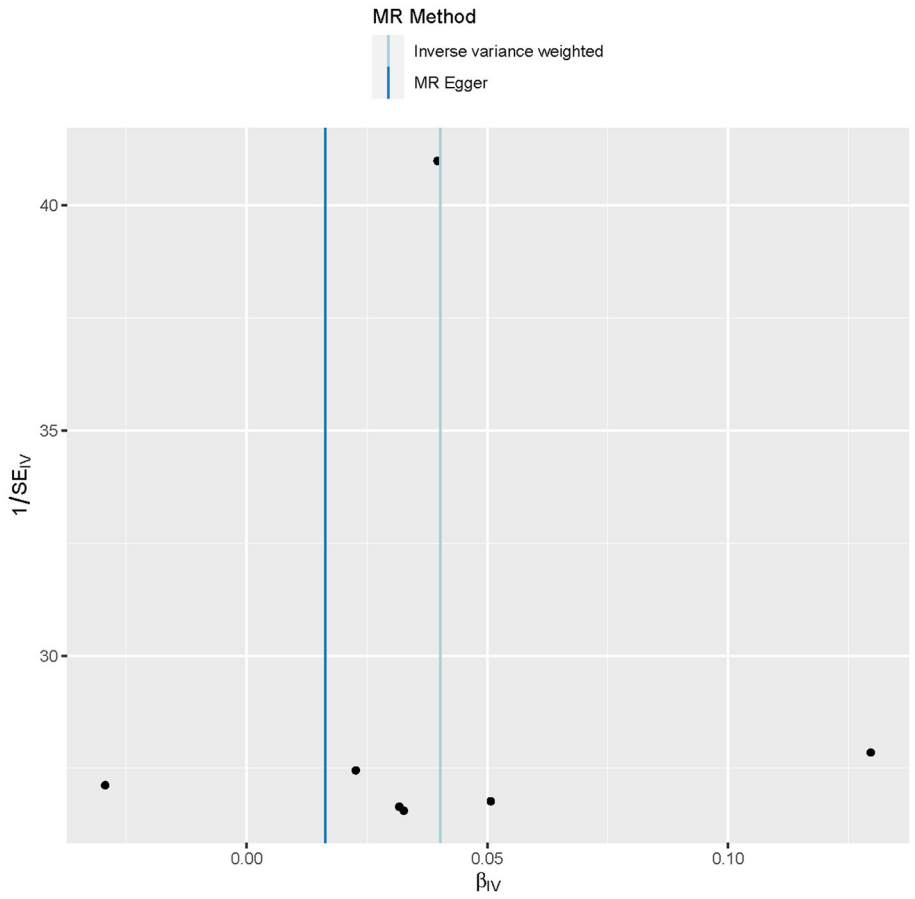

FIGURE 6
Funnel plot showing the relationship between the cause-effect of particulate matter 2.5 and diabetes.

susceptibility may also be critical. Nontraditional factors such as air pollution that are pervasive in the urban environment may together with other dominant factors provide synergism in accelerating the propensity for T2DM.

Future studies are warranted to gain greater insight into the molecular mechanisms involved (e.g., intermediary, and intracellular signaling pathways), the responsible pollutants (e.g., components, sizes/sources), the role of combined exposures to mixtures (e.g., ozone plus PM), and susceptibility factors (e.g., gene-environment interactions, vulnerable populations).

The purpose of a machine-learning application is different by its field or data but mainly could be used for improving performance of a predictive model. However, despite the popular use of machine learning, prior studies show that applying machine learning to GWAS is still rare. In the current study, MR mixture based on machine-learning algorithm showed its potential for making higher performance in estimation and lowering bias in estimates. This is because it was possible not only to improve the prediction of causal estimates but also to select important instrumental variables through automatic data-driven methods. In addition, MR mixture turned out to predict unbiased causal estimates with higher power compared to existing traditional methods (20). Although further evidence needs to be accumulated in future, we could suggest that machine-learning applications for GWAS (e.g., MR mixture) had quite a degree of feasibility and efficiency.

Strengths and limitations

The main strength of this study is large-scale GWAS data was used for the MR analysis. The large sample size allowed for reliable causal effect estimation, assessing the consistency of associations across different MR methods. The MR-Egger approach reduced the bias due to reverse causality and confounding. The IVW coupled with MR-Egger increased the reliability and reproducibility of the study across different comorbid conditions related to diabetes. Second, we robustly confirmed the causal relationship between $PM_{2.5}$ and diabetes through traditional MR estimation and machine-learning MR estimation. Traditional methods alone cannot thoroughly exclude the potential possibility of violating the horizontal pleiotropy assumption. It takes a lot of effort to find the best method among several MR strategies that had the most predictive and lower level of horizontal pleiotropy for the data. The data-driven MR-Mixture method can automatically find the best combination of the outlier filtering method and the MR estimation method based on the machine-learning method. Both traditional and MR-mixture methods showed a prominent

causal relationship between $PM_{2.5}$ and diabetes, and we found that the estimation of causal effects could be improved when outliers were removed from traditional methods based on the MR-Mixture method.

The major limitation of this study is that we only used the data from individuals of European descent. Therefore, it should be cautious about generalizing our findings to other populations. Another limitation of this study was the small sample size that might have increased the risk of Type-I error. Also even if diabetes was diagnosed by a doctor in UKB platform, it is not well known to determine what the diagnostic criteria were type 1 diabetes or type 2 diabetes.

Moreover, no power estimations were conducted for selecting the sample size, which might have further reduced the reproducibility of the findings. Nevertheless, the limited availability of population-specific information on genetic associations, genetic instruments tend to show poor statistical power. On the contrary, different MR frameworks substantiated the causal relationship between the genetic predisposition of being $PM_{2.5}$ and diabetes after removing the outliers. Such measures increased the reliability and validity of the findings of our study.

Conclusion

We identified the hypothesis that there is a causal relationship between $PM_{2.5}$ and diabetes in the European population, using MR methods. Therefore, the findings from this study discovered that person exposed to more $PM_{2.5}$ was strongly related to higher risk of diabetes in European population.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.mrbase.org/.

Author contributions

JK: conceptualization, methodology, investigation, formal analysis, data curation, and writing—original draft. EK: conceptualization, methodology, and writing—original draft. DS: introduction, methodology, and writing—original draft. Y-JK and JL: methodology and writing—original draft. EH: conceptualization, methodology, writing—original draft, 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

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Carbon footprint generated by individual port websites. The missing idea in the concept of green ports

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One of the objectives of European Union policy, as well as the assumptions of cooperation as part of United Nations, is to ensure sustainable development. The gradual decarbonisation of the economy is a significant element in this case. This is particularly important in transport, including maritime transport. That is why the concept of Green Ports is so important. It contains various infrastructure solutions that maximize the benefits of maritime transport while minimizing environmental damage. However, the term Green Ports is defined in the literature it is difficult to have a clear definition, a formula that defines the term and there is still a place for scientific research in this area. The purpose of the research is to analyze the assumptions of the Green Ports concept in economic terms, but also in legal terms. The authors want to focus on Internet infrastructure as a link in reducing the carbon footprint in maritime transport. For this purpose, they studied the carbon footprint generated by the websites of selected seaports (seaports considered by the Transport and Environment report (https://www.transportenvironment.org/discover/port-carbon-emissions-ranking/) the most polluting European ports and ports considered by the Leading Maritime Cities 2022 report to be the most technologically advanced (DNV, Menon Economics, 2022 https://www.dnv.com/maritime/publications/leading-maritime-cities-of-the-world-2022.html). Both at the United Nations and at the level of organizations of a regional nature (such as the European Union), the use of new technologies is closely linked to economic development or social progress. For example, access to the Internet has been recognized by the United Nations General Assembly as a human right. This is because it has been recognized that the Internet provides an opportunity to realize other rights, such as freedom of expression, the right to information, and education. However, there are also risks associated with the use of new technologies, if only in terms of the right to privacy, intellectual property, security or a clean environment. According to the authors, far less attention is paid to the risks than to the benefits. That's why it's worth building awareness to prevent harm rather than repair it. An important aspect of the research is to show that websites consume large amounts of energy. In addition, they have a negative impact on the environment, influencing the production of a significant amount of carbon dioxide. The main finding from the empirical part is that there is a certain relationship between the generation of CO_2 by the ports and the "cleanliness" of their websites.

KEYWORDS

green ports, carbon footprint, new technologies, pollution, environment

1 Introduction

This is not an article arguing for the discontinuation of the Internet and the technologies that use it. The digital acceleration, which can be seen, for example, in the emergence and diffusion of the GPT 3 generative AI model and now the (generally available) GPT-4, has also led to a revival of discussions (imminent) about the risks associated with the use of artificial intelligence. On a normative level, the result of these discussions is a draft regulation establishing harmonized rules on artificial intelligence (Artificial Intelligence Act, 2021). The dangers of new technologies, no longer limited to addiction, are therefore recognized. However, there is still not enough talk about the environmental damage that results from digital devices.

One of the global challenges of modern economic policy is to ensure sustainable development, i.e., economic and civilizational progress, which would be the least harmful to the natural environment. Tasks in this direction have been set at the international level (i.e., by the United Nations and the European Union).

In the first of these areas, the UN Sustainable Development Goals (United Nations, 2022) provide a matrix of actions. From the perspective of the subject of the article, attention should be paid primarily to Goal 13: "Take urgent action to combat climate change and its impacts" and Goal 7: "Ensure access to affordable, reliable, sustainable and modern energy for all".

At the European level, the EU has taken an initiative in the area of sustainable development by creating the concept of the Green Deal (European Parliament, 2022). This concept presents a roadmap that covers ideas, plans, legal acts aimed at strengthening the European economy while caring for the natural environment (European Commission, 2022). The primary objective of the Deal is to achieve climate neutrality by 2050. Social and economic transformation is necessary, based on the assumptions of cost-effectiveness, justice and social balance. The concept of the Green Deal also clearly applies to the maritime economy. The EU has comprehensive rules on the environmental aspects of maritime transport, and the European Commission has published a package of legislative changes, called the Fit for 55 package.

Sustainable development requires many comprehensive actions, taking into account international cooperation, changes in the functioning of the economy, but also rethinking individual attitudes (entrepreneurs and consumers). One of the problematic areas is transport, which on the one hand is indispensable, on the other hand generates significant carbon dioxide emissions into the atmosphere, contributing to global warming.

A study by Transport & Environment (https://www.transportenvironment.org/discover/port-carbon-emissions-ranking/) points to the carbon footprint of the maritime transport industry. Due to the rapid growth of trade associated with the development of e-commerce sales, the shipping industry has become a very fast-growing sector, accompanied by an increase in the prices of cargo volumes (an increase in the price of container transport). The record high financial performance of shipping companies is not only profitable for a number of companies in the supply chain, but also generates revenues on the order of magnitude equal to such well-known companies as Apple and Facebook. The entire supply chain of just one industrial area, which is the port, has a direct impact on climate change. When analysing this supply chain (i.e., ships and tankers entering and leaving ports), it should be kept in mind that this process is responsible for significant emissions of harmful gases. This industry also leaves its mark on the environment and climate when the ship is already on the port quay (i.e., during loading, unloading or refuelling). The European Environment Agency report's authors also noted that it will be necessary to adapt port infrastructure to the expected rise in sea levels due to climate change (https://www.eea.europa.eu/highlights/eu-maritime-transport-first-environmental).

Moreover, scholars have discussed also the impacts of the COVID-19 epidemic on the shipping industry (Xu et al., 2023).

The COVID-19 epidemic have changed the maritime transport significantly, compared with the year 2019 total carbon emissions in 2020 from oil tanker, bulk carrier increase but carbon emissions from cruise ship and vehicle carriers have turned overall situation of carbon emissions and were reduced during this time (Xu et al., 2021a).

The main purpose of the article is to point out that attention on carbon footprint generation is mainly focused on transportation, roads and buildings while emissions from the Internet remain often unnoticed (Guerrero-ibanez, Zeadally, Contreras-Castillo, 2015; Ozcan and Apergis, 2018; Wang and Xu, 2021). It is important to remember that on the road to net zero, every action counts.

The authors focus on a very narrow issue—the generation of a carbon footprint by websites. Furthermore, they have chosen the maritime transport sector, which has ambitions to achieve climate neutrality in the near future. This example is intended to be a starting point for a discussion on the fact that we cannot separate the pollution generated by the using of the internet from the benefits we can achieve through it in another sector. It is therefore important to approach the problem holistically and not to overlook any link leading to the final chain.

The authors show one element of port operations (port infrastructure) that generates a carbon footprint, and also point out that new technologies, even as simple as a website, generate a carbon footprint. Given the growth of the new technology industry and its encroachment into virtually every activity of human activity, one needs to work on the cost consciousness resulting from the use of these technologies.

Currently, the political (UN's and EU's) efforts do not include strategies related to reducing the carbon footprint of new technologies. Even the Artificial Intelligence Act focuses mainly on the positive impact of artificial intelligence in high-impact sectors, including climate change, environment (see point 3 of the recitals, Articles 47(1) and 54(1) of the Artificial Intelligence Act). However, the Explanatory Memorandum of the draft emphasizes that the benefits of artificial intelligence must be balanced with the need to ensure fundamental rights including the right to a high level of environmental protection and the improvement of the quality of the environment, as enshrined in Article 37 of the Charter of Fundamental Rights of the European Union and implemented in Union policies. (see also point 28 of the recitals, Article 3(44) of the Artificial Intelligence Act). The lack of adequate regulation on environmental sustainability has been pointed out by the European Economic and Social Committee: compliance with the requirements set for medium- and high-risk AI does not necessarily mitigate the risks of harm to health, safety and fundamental rights for all high-risk AI. The EESC recommends

that the AIA provide for this situation. At the very least, the requirements of 1) human agency, 2) privacy, 3) diversity, non-discrimination and fairness, 4) explainability and 5) environmental and social wellbeing of the Ethics guidelines for trustworthy AI should be added. (para. 8; the European Economic and Social Committee, 2021). For high-risk artificial intelligence systems, see also point 4.10 of the Opinion. The proposed conditions are included in the Ethics Guidelines for Trustworthy Artificial Intelligence (the High-Level Expert Group on AI, 2019).

Also the European Committee of the Regions has indicated that the members of the European Artificial Intelligence Board should reflect the interests of European society. These interests include, *inter alia*, climate and the energy-efficient use of AI systems (Amendment 12, he European Committee of the Regions, 2022).

The purpose of the article (empirical part) is to present the problem of generating a carbon footprint by seaport websites. This problem, of course, applies to all websites and tools related to the use of the Internet. The authors took up the subject of seaports to indicate a certain paradox—both at the level of individual countries and at the international level, initiatives related to the pursuit of climate neutrality of maritime transport are undertaken, for this purpose, first of all, solutions based on new technologies (using the Internet as a necessary component) are implemented, not noticing that they also emit carbon dioxide and have a harmful impact on the environment, for example, by creating e-waste. Of course, the purpose of the article is not to deny the digitalization of ports and the use of the Internet, but to make people aware that at the moment the Internet is not a climate-neutral tool.

The article deals with both theoretical issues and presents the results of own research. The authors briefly presented the impact of maritime transport on the environment and the solutions adopted at the UN and EU level in the area of reducing the environmental harm of maritime transport. What is more, the authors base their considerations on the concept of Green Ports. The issue of digitalization was also addressed, with particular focus placed on ports. To check to what extent the use of Internet tools generates carbon dioxide into the atmosphere, empirical studies were carried out. The authors selected the websites of the ports that were subject to the study. First, European ports were selected, which, according to the Transport & Environment ranking (https://www.transportenvironment.org/discover/port-carbon-emissions-ranking/), generate the most pollution. The second stage involved checking the sites of ports, which according to the ranking of The Leading Maritime Cities of the World 2022 are considered the most technologically advanced (DNV, Menon Economics, 2022 https://www.dnv.com/maritime/publications/leading-maritime-cities-of-the-world-2022.html).

In general, theoretical and empirical studies concern combating climate change in the maritime sector. The environmental and carbon impacts of new technologies (including Information and Communication Technology—ICT) are much less often analyzed. There are some studies that indicate a positive relationship between ICT usage and CO_2 emissions (Erdmann and Hilty, 2010; Ishida, 2015; B.V; Mathiesen, Lund, Connolly, Wenzel, Ostergaard, Moller, 2015; Pamlin and Pahlman, 2008; Chavanne et al., 2015; Toffel and Horvath, 2004; Wissner, 2011). Others find that the use of ICT puts pressure on energy consumption (Moyer and Hughes, 2012; Salahuddin and Alam, 2015) which is the main source of CO_2 emissions (Hamdi, Sbia, Shahbaz, 2014).

The structure of the article is as follows. In the introduction described will be the nature of our research problem—carbon footprint generated by port websites and the background of the concept of the Green Port. Further discussed will be the environmental impact of maritime transport with particular emphasis on carbon emissions. Then will be presented, based on the literature studies conducted, the approaches of various researchers to capture the essence of the concept of Green Ports. The method section will provide sufficient details regarding authors own research on carbon footprint generated by the websites of individual ports. It is worth mentioning that the empirical part is based on two parts. The first part relates to the explanation that authors choose ports considered in the T&A report as the most polluting ports in Europe and examined the websites of those ports. The second part of the study covered ports that are considered to be the most technologically advanced versus websites that generate the greatest load on the environment. In the authors' study, it became apparent that there is a connection between the CO_2 generation of ports and the "cleanliness" of their websites.

2 Environmental impact of maritime transport

Emissions related to port infrastructure are becoming an increasingly frequent subject of research. It is estimated that 90% of everything we consume is transported by sea (https://www.weforum.org/agenda/2021/10/global-shortagof-shipping-containers/). This translates into 940,000,000 tons of CO_2 per year, which constitutes 2.5% of global carbon dioxide emissions into the atmosphere (https://www.ukri.org/news/shipping-industry-reduces-carbon-emissions-with-space-technology/). It has not been known for a long time that an increase in shipping activity will result in an increase in carbon dioxide emissions (Xu et al., 2023).

The European Environment Agency indicates that approximately 1/4 of the EU's total CO_2 emissions in 2019 came from the transport sector (https://www.eea.europa.eu/en/topics/in-depth/transport-and-mobility), of which 71% from road transport, 13,5% from maritime transport, 14.4% from civil aviation, 0.5% from other transport and 0.5% from rail (European Environment Agency, European Maritime Safety Agency, 2021, pp. 40). According to the EMTER 2021 Report (EMTER 2021), maritime transport (maritime and inland waterway transport) was responsible for 13.5% of greenhouse gas emissions in the EU (European Environment Agency, European Maritime Safety Agency, Raport EMTER 2021; Stefaniak, 2022). The report indicates that maritime and inland waterway transport are responsible for greenhouse gas emissions. Therefore, the EU Fit for 55 package also covers the transport sector, including maritime transport.

Analyses of the relationship of the federation of green organizations in the EU—Transport & Environment indicate the 10 ports that recorded the highest carbon dioxide emissions in 2020. CO_2 emissions cover three scopes, i.e., scope 1 direct emissions (from the core activities of ports—loading of goods, unloading, refuelling), scope 2 indirect emissions (generated during the production of purchased electricity and heat) and scope 3 indirect emissions, i.e., throughout the supply chain caused by ships entering and leaving European ports (Greenhouse Gas

Protocol, 2022). The division of emissions into three scopes was introduced by the Greenhouse Gas Protocol initiative (Greenhouse Gas Protocol, 2022; DNV; Menon Economics and Publication, 2022).

The carbon footprint is one way to measure human impact on the environment. The publication of T&E's ranking of the ten most polluting European ports calls for reducing carbon dioxide emissions to avoid catastrophic climate change and demonstrates the high climate impact of these entities. According to the T&E report (https://www.transportenvironment.org/wp-content/uploads/2022/02/2202_Port_Rankings_briefing-1.pdf), the port of Rotterdam is the most polluting seaport in Europe (the only greenhouse gas reported was CO_2). The first infamous place on the list of so-called top-10 largest ports in Europe when it comes to CO_2 emissions was taken by the largest port in Europe, i.e., the port of Rotterdam with a result of 13.7 million tons. The second place in the ranking for transhipments larger by less than 30 percent was taken by the port of Antwerp. The level of emissions of the port of Antwerp amounted to 7.4 million tons. It is worth mentioning here that the Dutch port in relation to its largest competitor—Antwerp emits almost twice as much carbon dioxide per year. To show the enormous impact of the port of Rotterdam on the climate, it is compared with the fifth largest industrial polluter in Europe—the German Weisweiler coal-fired power plant.

Another European port that should significantly reduce its carbon footprint is the port of Hamburg, which ranks third among the largest CO_2 emitters with a result of 4.7 million tons. Three Spanish ports are also very high on the Top-10 list of the largest CO_2 emitters. Fourth place is taken by Algeciras, the highest rank among Spanish ports, with a volume of discharges of 3.3 million tons. While fifth and seventh places were taken by Barcelona and Valencia respectively, they follow Algeciras with a discharge volume of 2.8 and 2.7 million tonnes respectively. In the ranking with the same volume of discharges as the port of Valencia of 2.7 million tons per year, the Greek port of Piraeus was also included.

The eighth to ninth places are occupied by the German port of Bremen/Bremerhaven (2.3 million tons) and the French port located in Marseille (2.3 million tons) respectively. Among the 10 ports that recorded the highest carbon dioxide emissions in 2020, the port of Amsterdam achieved the lowest volume of discharges at 2.1 million tonnes per year. The presented results on the most poisonous European ports served as a reference for conducting the authors' own research.

3 The concept of green ports

Ports located all over the world want to become as green as possible, meaning environmentally friendly. Recently, scientific studies have emerged describing the operation and management policies of ports and shipping companies in emergency situations and daily management, providing a basis and reference for the development of green shipping development strategies (Xu et al., 2023). The concept of Green Port is difficult to define due to the multiple attempts to classify activities aimed at the so-called greening of ports, resulting in the fact that there is no unambiguous definition of this phenomenon in the literature. Certainly, however, it is a process involving port activities, which include, management, introduction of regulations and undertaking investments that raise environmental standards. According to Czermański, Pawłowska and Oniszczuk-Jastrząbek "The Green Port concept includes the idea of protecting the environment in all its infrastructure works, in the sustainable development policies that it follows, and in all the activities and operations conducted in the area" (Czermański, 2019, pp. 6). Żukowska noticed that the concept of Green Ports focuses on undertaking pro-ecological initiatives in three main areas—environment, economy and society. Green Ports are the growth poles intensifying projects aimed at reducing their negative impact, while implementing a set of actions to improve conditions and quality of life, in particular at the port-city interface (Żukowska, 2021). Promoting energy conservation, reducing emissions, and improving the port's end-to-end competitiveness through the use of shore-to-ship (SSE) electricity technology is increasingly resounding in the scientific literature (Xu et al., 2021b).

In the literature, the concept of Green Ports is also presented as a direction for the development of seaports, taking into account the achievement of the following priorities: improvement of air quality, reduction of energy consumption, reduction of noise emissions, improvement of water quality, improvement of waste, waste and sewage management and improvement of relations with the environment (Czermański, 2019). The concept of Green Ports very often appears in the context of sustainable development, which took the form of a global trend of the turn of the 20th century (Bergqvist, Monios, 2019; UNESCAP, 2021). It is believed that this issue has developed in recent years in connection with the study of the impact of maritime transport on environ-mental degradation. In this context, Green Ports are most often mentioned as sources of noise, dust, waste and water pollution (Ng, Song 2010; Lam, Notteboom, 2014). The maritime transport sector and in particular clean infrastructure solutions at the port level are of particular importance in view of the European Union's ambitious objectives for the decarbonisation of maritime transport. Ports have an impact on the climate change and it is huge (https://www.eea.europa.eu/highlights/eu-maritime-transport-first-environmental). The authors of the article wanted to show that the UN but especially the EU is introducing solutions to ensure climate neutrality in the future, these measures are based on the use of new technologies (such as the Internet). Green Ports, which by con-ducting their basic activity, applying development and investment strategies, providing adequate infrastructure to improve energy efficiency, implementing new eco-friendly solutions and implementing intelligent digital solutions, can achieve climate neutrality and zero pollutant emissions. The Green Port concept relies heavily on advanced technological solutions associated with the use of technologically modern infrastructure in port and terminal operations, which is related to the use of the Internet.

The concept of Green Ports is closely related to the use of new technologies in port functioning. The European Commission indicates digital technologies as the main pillar of the green transition. The main objective of the European Green Deal is for the European Union to achieve climate neutrality by 2050. Innovative digital technologies such as artificial intelligence, machine learning, 5G, cloud, edge computing or the Internet of Things are increasingly mentioned as a transition to green tracks and the key to green transformation. At the same time, it should be

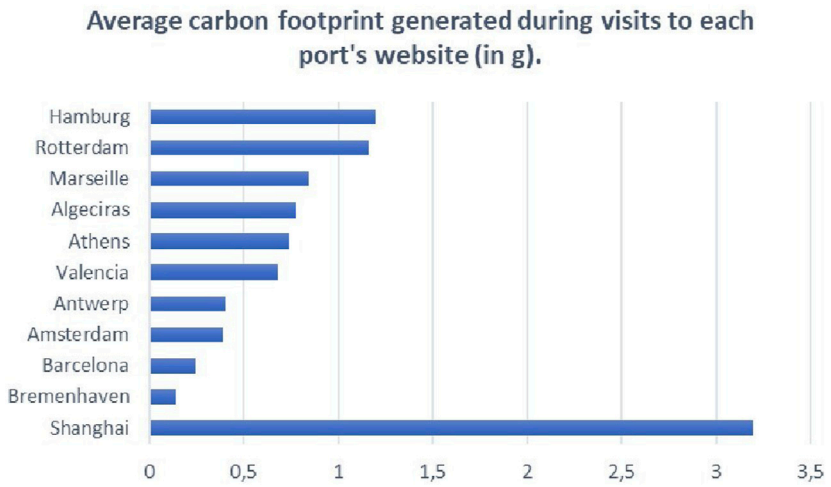

FIGURE 1
Average carbon footprint generated during visits to each port's website (in g).

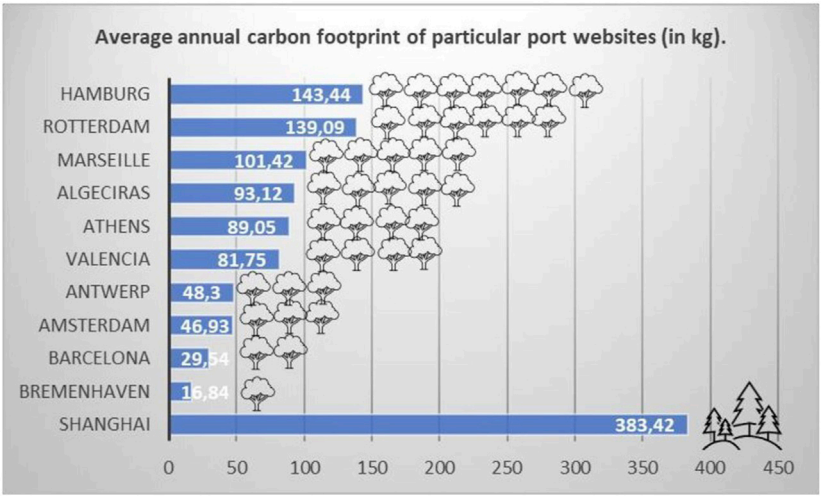

FIGURE 2
Average annual carbon footprint of particular port websites (in kg).

kept in mind that advanced technologies, also called in the literature 'The fourth Industrial Revolution (4IR) technologies' were considered to be a key factor in achieving the Sustainable Development Goals (SDGs). A smart port is a port that uses automation and innovative technologies, including AI, Big Data, IoT and Blockchain to improve its performance (UNESCAP, 2021, pp. 15). The use of these tools requires the use of the Internet.

The digitalization of the economy is an aspect that raises the hope of reducing/stopping environmental degradation. The role of modern technologies and the use of artificial intelligence is to improve processes in every area of the economy, but they also introduce solutions that facilitate everyday life (as exemplified by smart home solutions and optimizing the use of energy in households) These instruments are based on Internet access, the universality and importance of which have translated into the recognition of Internet access as a human right by the United Nations. The figures show a steady increase in Internet access, which currently covers more than 63.1% of the population. Of course, there are still significant disparities between regions, as in the Scandinavian countries it reaches 98%, and in Central Africa it covers only about 25% of the population (We Are Social Ltd, 2022).

The benefits of using new technologies are indisputable. An increased level of relocation of economic and private activities is also inevitable. However, it should be kept in mind that solutions based on the Internet also generate a burden on the environment. Every click has a huge impact on the climate (or to put it better, has a great importance for the climate change), as it is associated with the emission of greenhouse gases into the atmosphere. On the one hand,

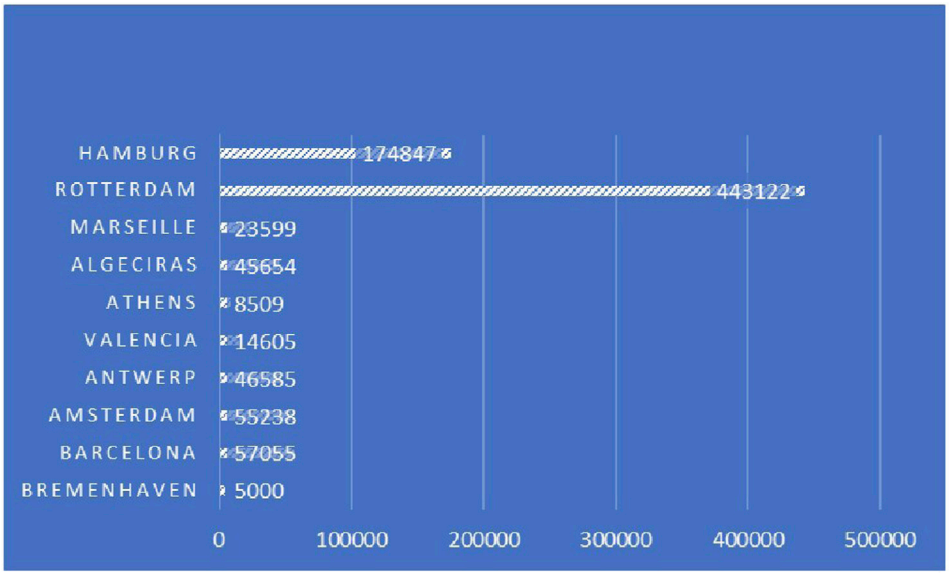

FIGURE 3
Monthly number of visits to websites in the period from June to August 2022.

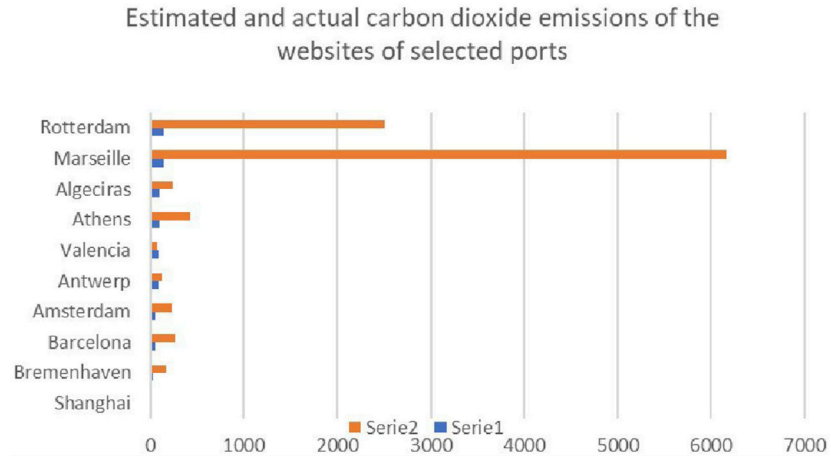

FIGURE 4
Estimated (in orange) and actual (in blue) carbon dioxide emissions of the websites of selected ports.

a fairly significant carbon footprint left by the use of electronic devices (computers, phones, tablets) or the functioning of websites should be noticed. On the other hand, using the Internet causes leaving waste also in the digital sphere (e-waste) Shorter product lifespans, rapidly advancing technological development and ever-lower prices for IT products mean that billions of metric tons of electronic products are being discarded. To present the severity of the situation and the scale of the problem, the data on the number of current users of the websites of the selected ports (10 ports that recorded the highest carbon dioxide emissions in 2020—analyses performed by Transport and Environment and ports considered by the Leading Maritime Cities 2022 report to be the most technologically advanced) and the associated estimates of greenhouse gas emissions will be summarized below.

4 Own research on carbon footprint generated by the websites of individual ports

4.1 The most polluting ports in Europe

Using the Web Site Calculator, it was checked how many grams of carbon dioxide are emitted into the environment when visiting a given site (Wholegrain Digital, Scamper Ltd., 2022 https://www.websitecarbon.com/faq/). The authors used two existing solutions to test carbon emissions of web pages. The Website Carbon Calculator designed by world leaders in digital sustainability aiming to develop and refine a methodology for this purpose. WebsiteCarbon.com is a project of Wholegrain Digital (Scamper Ltd), the developer of this

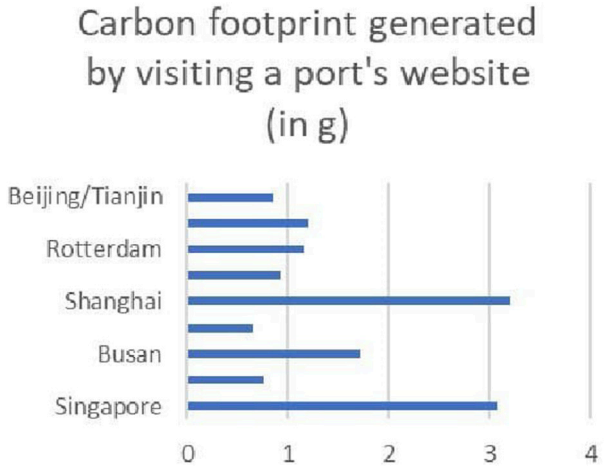

FIGURE 5
Carbon footprint generated by visiting a port's website (in grams).

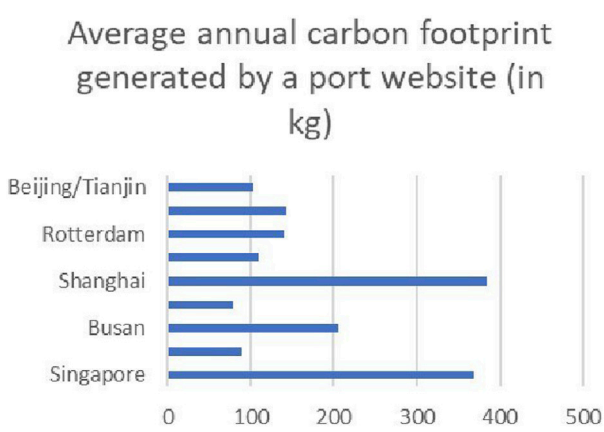

FIGURE 6
Average annual carbon footprint generated by a port's website (in kilograms).

tool claims that to calculate the energy and emission of a web page they use the following data points: data transfer over the wire; energy intensity of web data; energy source used by the data centre; carbon intensity of electricity and website traffic. The tool also makes it possible to calculate pollution generated by a single visit as well annual emissions with an average monthly number of visits of 10,000 and indicate how many trees are needed to neutralise such a carbon footprint. Of course, the assumption of 10,000 visits per month is not reliable, so it was necessary to obtain data on the actual number of visits to a given website.

The average monthly number of visits to a given website was calculated using the SimilarWeb tool (SimilarWeb, 2022). This way, it was possible to approximate the actual environmental load on a given website. It should be noted that all SimilarWeb data are estimates and approximations. The tool does not have exact data on site traffic (only site owners know that), but it collects publicly available information on web traffic and builds reports from it. Similarweb Ltd., together with its group companies. The tool has been researching for over 10 years the digital world. It collects daily 10 TB digital signals and analyses 2 TB data. However, the data obtained from SimilarWeb should be treated only as a signal, a clue to take further pro-environmental measures.

Obtaining data as to the pollution generated by a single input and the level of the number of hits on a given page, the authors presented the amount of CO_2 emissions into the atmosphere generated by individual seaport websites. The research was conducted from June to September 2022.

In a study carried out by the authors, the carbon footprint of 11 websites of ports, considered in the T&A report as the most polluting ports in Europe and, for comparison, the port of Shanghai (see Figure 1). The Website Carbon Calculator (WCC) is a measurement tool. After entering the address of the website, the emission data of a single visit to the website is displayed. It also specifies an estimate of the pollution generated annually by a given website, assuming that 10,000 users visit the website per month. The WCC also shows the energy source used by the website and indicates the scale of the generated pollution, indicating at least the number of trees needed to neutralise emissions. The port in Bremen/Bremerhaven has the cleanest website, whose one-time visits will generate only 0.14 g of CO_2. This represents 16.84 kg of carbon dioxide emissions per year, which consume 1 tree (see Figure 2). Not much worse is the port of Barcelona, whose website generates 0.25 g per visit and the port in Amsterdam (0.39 g). The top five also included Antwerp (0.4 g) and Valencia (0.68 g). In terms of the average annual footprint generated by a website in kg, the port of Barcelona generated 29.54 kg, which takes two trees to absorb. Another growing trend was the port in Amsterdam—46.93 kg (three trees are needed). A similar result was obtained by Antwerp 48.3 kg (and also three trees). Similarly, presenting the results in kg in the top five, there was also the port in Valencia 81.75 kg. Slightly worse in the comparison was the port of Athens, whose single visit generates 0.74 g of CO_2. This amounts to 89.05 kg of carbon dioxide emissions per year, which can be neutralised by 4 trees. Next in the ranking is the port of Algeciras, which generates 0.78 g of CO_2 with one visit. This represents 93.12 kg of carbon dioxide emissions per year, which should absorb 5 trees. Marseille is next (0.85 g). This amounts to 101.42 kg of carbon dioxide emissions per year, which will neutralise 5 trees, similarly to the previous place in the ranking. Rotterdam (1.16 g), Hamburg (1.2 g) and Shanghai (3.2 g) are among the most emitting ports. This constitutes an annual carbon dioxide emission in the amount of: Rotterdam (139.09 kg), Hamburg (143.44 kg) and Shanghai (383.42 kg) with an average annual number of visits of 10,000. More figuratively, in order to reduce the carbon dioxide produced by port websites, two trees are needed (in the case of Rotterdam and Hamburg, in the extreme case—Shanghai, it would be 18 trees). The fact that it's not that much of a burden compared to others doesn't mean that you shouldn't pay attention to it.

Examination of the amount of carbon dioxide generated by the websites of the ports that, according to T&E, emit the most carbon dioxide has shown that there is a certain relationship between the generation of CO_2 by the ports and the "cleanliness" of their websites. The higher the port is in the infamous T&A ranking, the more solutions used on the website do not take into account the possibility of minimizing the carbon footprint generated by their websites.

TABLE 1 The actual carbon footprint generated by a port's website. P, Port; C1, Amount of CO_2 generated by a single visit to a website (in g); C2, Amount of CO_2 generated during the year when visiting the website on average 10,000 times a month (in kg); T, Number of new trees needed to eliminate the CO_2 generated annually by the website; W, Number of new trees needed to eliminate the CO_2 generated annually by the website; V, Number of visits in August 2022; C3, Actual amount of CO_2 generated during the year with website traffic at the August 2022 level.

P	W	C1	C2	T	V	C3
Singapore	https://www.mpa.gov.sg/home	3.08	369.41	17	256,385	**9,456.9**
Oslo	https://www.oslohavn.no/	0.75	90.12	5	89,150	**802.07**
Busan	https://busanpa.com/eng/Main.do	1.71	205.29	10	88,500	**1806.55**
London	http://www.pla.co.uk/	0.65	78.27	4	217,792	**1,698.46**
Shanghai	https://en.portshanghai.com.cn/	3.2	383.42	18	8,028	**306.74**
Tokyo	https://www.kouwan.metro.tokyo.lg.jp/	0.92	109.84	5	440,618	**4,832.96**
Rotterdam	https://www.portofrotterdam.com/en	1.16	139.07	7	443,122	**6,160.8**
Hamburg	https://www.hafen-hamburg.de/de/startseite/	1.2	143.44	7	174,847	**2,495.86**
Beijing/Tianjin	https://www.ptacn.com/	0.86	102.91	5	6,539	**61.746**

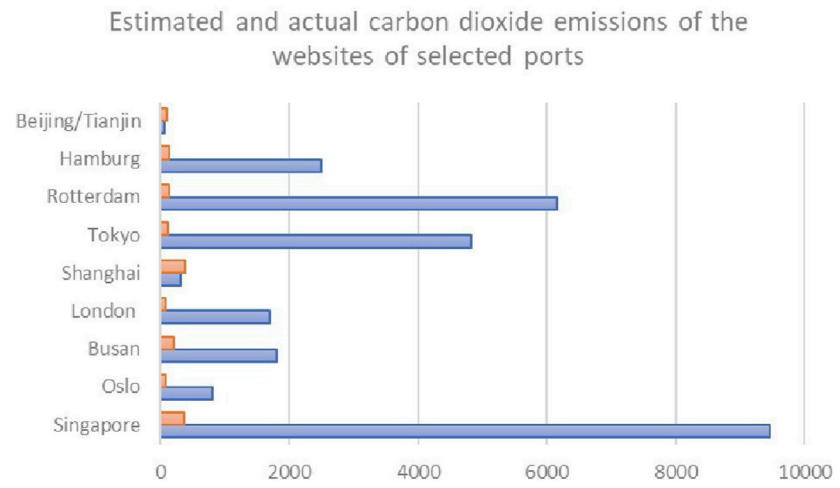

FIGURE 7
Estimated (in orange) and actual (in blue) carbon dioxide emissions of the websites of selected ports.

It is worth noting, however, that in many cases the actual share in the production of the carbon footprint will be much greater than assumed by the Website Carbon Calculator. It all depends on the actual traffic on the site. Another tool used for research—SimilarWeb—makes it possible to examine the monthly number of page views. The amount of pollution generated annually given in Figure 2 assumes that a given website will be visited 10,000 times a month. In fact, the traffic on a given website turns out to be much greater (see Figures 3, 4). In the case of Rotterdam it will be almost 44 times the assumed number, so it will not be 139.09 kg per year but instead, 6,160.80 kg. Only in two cases (Bremerhaven and Athens), the monthly traffic on the website was lower than assumed in the carbon footprint calculator of websites. This leads to a simple conclusion that the actual carbon footprint is very likely to be greater than the WCC predicted. In addition, the inclusion of data from Figures 1–4 shows that more emitting websites (ports in Rotterdam and Hamburg) are also relatively more frequently visited than other websites included in the study. No similar pattern was observed for the other sites. The third and fourth places in terms of the number of visits were taken by the websites of ports in Barcelona and Amsterdam, and which took second and third places respectively in terms of environmental friendliness. It is worth noting, however, that the website of the port in Bremerhaven is the cleanest and least visited one.

4.2 The most technologically advanced ports in the world

The second part of the study covered ports that are considered to be the most technologically advanced based on the Leading Maritime Cities 2022 report. It is worth noting that one of the factors affecting the results were solutions that have an impact on the

port's climate neutrality. The port of Singapore was considered as the most technologically advanced port, followed by ports in Oslo and Busan. Then there were ports in London, Shanghai, Tokyo, Rotterdam, Hamburg and Beijing. By definition, the digitisation of ports should have a smaller negative impact on the environment. From this point of view, it was interesting to examine the carbon footprint of the most technologically advanced ports left by websites. Figure 5 shows the estimated CO_2 emissions generated by a single visit to the website, specified in grams. The infamous first place went to the website of the port of Shanghai. In the ranking lead the port websites in Singapore and Korean Busan.

Figure 6 shows the annual burden on the atmosphere of individual websites, assuming that 10,000 Internet users visit them every month. The data do not reflect reality without referring to the actual traffic on a given page. Table 1 presents data that allow for a more realistic estimation, calculated according to the formula: C3 = C2 x (V/10.000), where it means the actual amount of CO_2 generated during the year with traffic on the website at the level in the period from June to August 2022, C2 - the amount of CO_2 generated per year when visiting the website on average 10,000 times a month (in kg) and V - the number of visits in August 2022.

The table above shows a significant discrepancy between the amount of CO_2 emitted into the atmosphere by visiting a given website determined by the Website Calculator Carbon and the actual load on specific websites. However, there is not much discrepancy when it comes to the order in the ranking of the amount of pollutant emitted. The websites that generate the greatest load on the environment are as follows (in order): Singapore, Busan and Rotterdam, while due to the number of views, the "most contaminated" pages are the websites of ports in Singapore, Rotterdam and Tokyo (see Figure 7).

It is worth noting that the ports that are considered to be the most technologically developed, including due to work on tools aiming to reduce greenhouse gas emissions, do not pay proper attention to solutions that reduce the amount of carbon dioxide generated by their websites. In addition, it is interesting that the two ports that have been identified as the most environmentally harmful ports in Europe (Hamburg and Rotterdam) are simultaneously among the most technologically advanced and environmentally aware. In other words it means that the authors wanted to emphasize that the overall impact of the use of new technologies on the state of the climate is not studied, the benefits are taken into account first of all, while it is not taken into account whether the mechanism itself (saving shipping emissions) generates a burden on the climate. In the report we have very advanced solutions, while already such a basic element as a website is not created in an environmentally "economical" way. These data are derived from reports, not from our calculations. This is an interesting situation worth noting, while the explanation of the reason is beyond the matter of the article.

Of course, the load generated by individual port websites is a drop in the ocean when it comes to the amount of carbon dioxide emitted by ports. This does not mean, however, that this source should be ignored. For example, the use of a greener energy source or a more transparent structure of the website would allow to reduce emissions in a fairly easy and low-cost way.

5 Conclusion

The digitalization of ports and the use of new technologies bring many benefits, making maritime transport more efficient, while ensuring that it has the least negative impact on the environment. However, it should be kept in mind that new technologies based on the use of the Internet are also energy-intensive and generate a carbon footprint. Being aware of this fact can contribute to noticing the sources of the threat and minimize the negative effects of using the Internet.

The carbon footprint generation of websites analysed in the article is an exemplification of a broader problem. The authors are aware of the fact that in maritime transport the use of seaport websites is not a priority. The amount of information contained on individual pages varies and for some ports individual terminals have separate pages. In the forwarding process, one of the main tools are emails and tools created by individual ship owners (e.g., Tango). The size of the carbon footprint generated by port websites is therefore only a fraction of the carbon footprint of digital instruments used in maritime transport. The choice of websites to conduct research only allowed to indicate the existing problem.

Although the scale of pollution generated by websites is much smaller than that generated by individual ports, it is worth being aware that digital tools are also responsible for carbon dioxide emissions. Based on the research, it can be concluded that the websites of seaports generate significant amounts of carbon dioxide into the atmosphere. This applies both to ports that are considered the "most contaminated" in Europe, as well as those that are considered technologically advanced and striving for climate neutrality. This problem is not sufficiently taken into account at the level of climate policy. Clean transport is a goal outlined by both the UN and the European Union. The same applies to the digitalisation of the economy, including maritime transport. However, there are no references to the sustainable use of digital devices that are not climate neutral, which is a significant dissonance between the above organisations' goals. As a result of this study, authors formulated recommendations and paths that should be followed. First, programs and policies at the European Union level should pay some attention to the impact that new technologies have on the environment. Secondly, clean energy would also be an adequate response to global challenges. Broadly speaking, changing habits so that they become more environmentally friendly. In the case of the port websites analyzed by the authors of the article, a good path for ports to follow is green website design (minimal loading times, intuitive design, ease of finding key information on the site higher SEO ranking). Reducing the carbon footprint of the website in the case in question can be done if only by keeping the size and weight of the website as low as possible. The aforementioned page weight is influenced by the images placed and the font used.

The purpose of the study was not to question the legitimacy of the development of the Internet and new technologies but raise awareness and encourage more eco-friendly approaches among politicians, entrepreneurs, including the web design industry, but also individual users. It's about using more energy-saving tools, prudent use of the Internet. Renewable energy sources are also a key issue, without them new technologies are not able to ensure climate neutrality. Unfortunately, the research does not cover the whole use of the Internet by the maritime sector, but only focuses on the websites of the selecte seaports. In the future, it would be worth examining the real impact on the climate of maritime transport

taking into account emissions of the CO_2 generated by new technologies used in this sector.

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

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

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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Causality of particulate matter on cardiovascular diseases and cardiovascular biomarkers

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Background: Previous observational studies have shown that the prevalence of cardiovascular diseases (CVDs) is related to particulate matter (PM). However, given the methodological limitations of conventional observational research, it is difficult to identify causality conclusively. To explore the causality of PM on CVDs and cardiovascular biomarkers, we conducted a Mendelian randomization (MR) analysis.

Method: In this study, we obtained summary-level data for CVDs and cardiovascular biomarkers including atrial fibrillation (AF), heart failure (HF), myocardial infarction (MI), ischemic stroke (IS), stroke subtypes, body mass index (BMI), lipid traits, fasting glucose, fasting insulin, and blood pressure from several large genome-wide association studies (GWASs). Then we used two-sample MR to assess the causality of PM on CVDs and cardiovascular biomarkers, 16 single nucleotide polymorphisms (SNPs) for PM2.5 and 6 SNPs for PM10 were obtained from UK Biobank participants. Inverse variance weighting (IVW) analyses under the fixed effects model were used as the main analytical method to calculate MR Estimates, followed by multiple sensitivity analyses to confirm the robustness of the results.

Results: Our study revealed increases in PM2.5 concentration were significantly related to a higher risk of MI (odds ratio (OR), 2.578; 95% confidence interval (CI), 1.611–4.127; $p = 7.920 \times 10^{-5}$). Suggestive evidence was found between PM10 concentration and HF (OR, 2.015; 95% CI, 1.082–3.753; $p = 0.027$) and IS (OR, 2.279; 95% CI,1.099–4.723; p = 0.027). There was no evidence for an effect of PM concentration on other CVDs. Furthermore, PM2.5 concentration increases were significantly associated with increases in triglyceride (TG) (OR, 1.426; 95% CI, 1.133–1.795; $p = 2.469 \times 10^{-3}$) and decreases in high-density lipoprotein cholesterol (HDL-C) (OR, 0.779; 95% CI, 0.615–0.986; $p = 0.038$). The PM10 concentration increases were also closely related to the decreases in HDL-C (OR, 0.563; 95% CI, 0.366–0.865; $p = 8.756 \times 10^{-3}$). We observed no causal effect of PM on other cardiovascular biomarkers.

Conclusion: At the genetic level, our study suggested the causality of PM2.5 on MI, TG, as well HDL-C, and revealed the causality of PM10 on HF, IS, and HDL-C. Our findings indicated the need for continued improvements in air pollution abatement for CVDs prevention.

KEYWORDS

particulate matter, cardiovascular diseases, cardiovascular biomarkers, Mendelian randomization, causal association

1. Introduction

Globally, one in three deaths is caused by cardiovascular diseases (CVDs) which place a heavy burden on health systems (1). It is essential to find ways to prevent and treat CVDs to reduce their global burden. It's been a hot topic lately the connection between air pollution and CVDs. The increasing urbanization of the world has led to the exposure of more than 90% of the world's population to levels of air pollution that exceed the guidelines set by the World Health Organization. As a result of air pollution, both developed and developing countries are facing serious public health concerns. Exposure to outside air pollution is generally identified as a challenge for public health agencies and physicians, especially to fine particulate matter (PM). PM are made up of an intricate mixture of liquid and solid particles, as well as inorganic and organic compounds. Particles are generally classified by size into coarse (aerodynamic diameter < 10 μm; PM10), fine (diameter < 2.5 μm; PM2.5) fractions (2). Due to its high level of danger for human health, PM can be used as a reliable proxy for ambient air pollution related morbidity and mortality (3). During the past decade, researchers have examined the association between PM and human health using epidemiological methods (4–6). Furthermore, despite the fact that PM exposure used to be thought to pose a threat to health, especially the lungs (7), the comprehensive clue now shows the greatest inverse impact occurs in the cardiovascular system (8, 9). A cross-sectional study undertaken in Ahvaz megacity showed that exposure to air pollution is significantly associated with cardiovascular mortality (CM), hospital admissions for cardiovascular disease (HACD), and hospital admission for respiratory disease (HARD) (10). Besides, a study by Dastoorpoor et al. also showed that a higher concentration of PM10 is associated with an increased risk of hospitalization for CVDs (11). Similarly, Moradi and his colleagues noted that exposure to PM, even at low concentrations, is related to an increased risk of cardiovascular diseases hospitalizations (12). Furthermore, several studies also demonstrated that PM increases the risk of CVDs such as atrial fibrillation (AF), heart failure (HF), myocardial infarction (MI), and ischemic stroke (IS) (13–16). However, several studies reported inconclusive conclusions (17–21). In addition, most of the evidence is based on observational studies. Due to residual confounding and reverse causation, these studies have difficulty identifying causality conclusively.

When evaluating the health risks of air pollutant exposure, individual health risks may be better comprehended by considering genetic diversity. It is becoming clearer that the impacts of air pollution vary by individual, with some populations being more vulnerable to its adverse effects. Genetic predisposition appears to play a crucial role in response to air pollution (22). Previous studies have revealed that exposure to PM2.5 causes negative health consequences driven by alteration of gene expression (23, 24). A study conducted by Yao et al. showed that participants with 2 alleles of SIRT1_391 can counteract the adverse effect of PM2.5 and reduce the 26.1% risk of premature mortality (25). Poursafa et al. revealed that synergistic effect of the TM-33G / A polymorphism and air pollutants on factors associated with the onset of atherosclerosis (26). To analyze the effect of genetic polymorphisms and PM on CVDs and cardiovascular biomarkers, we conduct Mendelian randomization (MR) analysis to examine the relationship between them by using data from the publicly available genome-wide association study (GWAS) and UK Biobank.

2. Method

2.1. Study design

MR analysis is applied to investigate the relationship between exposure and outcome, which can provide robust causality by utilizing one or multiple genetic variants, such as single nucleotide polymorphisms (SNPs) (27, 28). The MR study was built on the Mendelian inheritance rule, which states that the parents' genetic alleles are randomly dispersed to the descendants during the process of meiosis, which is supposed to be equivalent to RCT. As a result, the MR design can be used to account for some intractable questions of causality due to high costs or ethical issues, avoiding the biases of observational studies. Therefore, this study intends to examine the causal relationships of PM with CVDs and cardiovascular biomarkers by MR analysis. CVDs included AF, HF, MI, IS, and stroke subtypes. Cardiovascular biomarkers contained body mass index (BMI), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), fasting glucose, fasting insulin, diastolic blood pressure (DBP), and systolic blood pressure (SBP). MR analysis must satisfy three assumptions. First, IVs must be closely related to exposure. Second, the SNPs have no relationship to potential confounders. Third, IVs can only cause outcomes through exposure (29) (Figure 1).

2.2. Data sources

2.2.1. GWAS summary data for PM and CVDs

GWAS summary statistics for PM were obtained from the UK Biobank, including about 423,796 participants from Europe, both male and female, which assessed the relationship between PM and SNPs. Briefly, this GWAS examined two PM phenotypes, including PM10 (n = 423,796) and PM2.5 (n = 423,796). In the case of AF (n = 103,083,6), we acquired summary-level data from the GWAS meta-analysis reported by Nielsen et al. (30), which included 60,620 AF cases and 970,216 controls and revealed 142 independent risk variants at 111 loci and prioritized 151 functional candidate genes likely to be involved in atrial fibrillation. MI (n = 395,795) was obtained from the GWAS conducted by Hartiala et al., which contained 395,795 participants from Europe, both male and female (31). HF (n = 977,323) was gained from the Heart Failure Molecular Epidemiology for Therapeutic Targets consortium (HERMES) conducted by Shah et al. (32). The GWAS comprised 47,309 HF cases and 930,014 controls, showing 12 independent variants at 11 genomic loci were associated with HF. IS (n = 440,328), large artery stroke (n = 150,765), small vessel stroke (n = 1988,048) and cardioembolic stroke (n = 211,763) was had access to the results conducted by Malik et al. (33), who tested 8 million SNPs in up to 67,162 stroke cases and 454,450 controls and revealed twenty-one additional loci were associated with stroke in this study. Descriptions of the datasets used in the analysis can be found in Table 1.

2.2.2. GWAS summary data for cardiovascular biomarkers

The GWAS summary statistics of BMI were accessible to the study conducted by Wood et al., including 119,688 individuals from European (34). The GWAS summary statistics for lipid traits were available from the Within family GWAS consortium, containing TG,

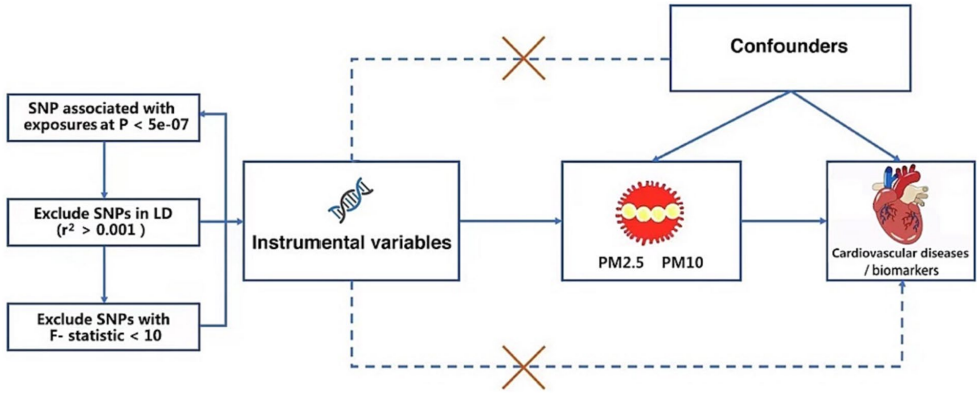

FIGURE 1
The specific steps for selecting SNPs and three crucial hypotheses of the Mendelian randomization study. PM, particulate matter. SNP, single nucleotide polymorphism.

HDL-C, LDL-C, which included 78,700, 77,409, and 70,814 participants from Europe, both male and female. The GWAS summary statistics for fasting insulin and fasting glucose were obtained from the study conducted by Chen et al. (35). The GWAS summary statistics for blood pressure were accessible to the consortium of the MRC-IEU, including DBP and SBP. Descriptions of the datasets used in the analysis can be found in Table 1.

2.3. Selection and validation of SNPs

After we set the threshold of the p value as 5×10^{-8}, we did not obtain any independent SNPs from the GWAS of PM10. In order to contain more SNPs that are concerned with PM10, we used a more lenient criterion ($p<5\times10^{-7}$) which had been applied to previous MR research (36). Then we identified 16 SNPs connected with PM2.5 and 6 independent SNPs connected with PM10 at the genome-wide significance level ($p<5\times10^{-7}$), showing the low likelihood of weak instrumental variable bias in MR analysis. No SNP was directly associated with CVDs or cardiovascular biomarkers. Using the TwoSampleMR R package, we conducted clumping functions in order to pick genetic variants without any linkage disequilibrium (LD) ($r^2<0.001$ across a 10,000 kb window) (37). At last, 16 independent SNPs related to PM2.5 and 6 independent SNPs related to PM10 were determined; details can be found in the Supplementary Table. In addition, when the F-statistic is greater than 10, the SNPs were regarded as adequate to moderate the effect of potential bias, using the following formula: $F=R^2\times(N-2)/(1-R^2)$ (38). No SNP was excluded from the MR analyses (The specific steps for selecting SNPs are shown in Figure 1).

2.4. MR analysis

This study used the two-sample MR method. As a primary analysis, we used inverse variance weighted (IVW) analyses under the fixed effects model as our main method because no heterogeneity was found in most analyses. Additionally, to ensure the results are robust, multiple complementary analyses were conducted like IVW under the random effects model, weighted median, and MR-egger. Sensitivity analyses like the MR-PRESSO test, Egger-intercept test, and the leave-one-out analysis are used to test whether the result of MR estimate is reliable. The Cochran Q test is mainly used to test and evaluate the heterogeneity of the selected IVs, which refers to the difference between the GWAS samples of exposure and outcome (39). We performed the MR-Egger intercept test in order to detect potential directional pleiotropy. It was determined that a significant pleiotropic bias existed when the intercept p-value <0.05 (40). We used the MR-PRESSO method to detect outliers before IVW methods were proceeded. MR-PRESSO eliminated abnormal SNPS (outliers) to detect potential horizontal pleiotropic and test whether there is a difference between the results before and after correction (41). The leave-one-out method was applied to analyze the sensitivity of the results by sequentially removing one SNP at a time to examine whether a single SNP with a large horizontal pleiotropy effect might affect the MR estimates. A total of MR analyses was performed using the R package "TwosampleMR."

3. Result

3.1. Causal effect of PM and CVDs

According to the IVW analysis, PM2.5 concentration increases were significantly related to a higher risk of MI (OR, 2.578; 95% CI, 1.611–4.127; $p=7.920\times10^{-5}$). Using the weighted median method, identical risk estimates were obtained as well (OR, 2.559; 95% CI, 1.303–5.029; $p=6.368\times10^{-3}$) (Figure 2). Suggestive evidence was found between PM10 and HF (OR, 2.015; 95% CI, 1.082–3.753; $p=0.027$) and IS (OR, 2.279; 95% CI, 1.099–4.723; p = 0.027) (Figure 3). In contrast, no causal relationship was found between PM2.5 and other CVDs (Figure 2). Furthermore, we did not observe the causality of PM10 on the risk of MI, AF, or stroke subtypes (Figure 3).

3.2. Causal effect of PM and cardiovascular biomarkers

The IVW analysis revealed that the genetically predicted PM2.5 concentration increases were significantly associated with increases in TG (OR, 1.426; 95% CI, 1.133–1.795; $p=2.469\times10^{-3}$).

TABLE 1 Detailed information of studies and datasets used for analyses.

Phenotype	Data source	Sample size	Population	Web source
PM2.5	UK Biobank	423,796	European	https://gwas.mrcieu.ac.uk/datasets/ukb-b-10817/
PM10	UK Biobank	423,796	European	https://gwas.mrcieu.ac.uk/datasets/ukb-b-18469/
AF	Nielsen et al.	103,083,6	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006414/
HF	HERMES	977,323	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST009541/
MI	Hartiala et al.	395,795	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST011364/
IS	MEGASTROKE	440,328	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST005843/
LAS	MEGASTROKE	150,765	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006907/
SVS	MEGASTROKE	198,048	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006909/
CS	MEGASTROKE	211,763	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006910/
BMI	Wood et al.	119,688	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006802/
TG	Within family GWAS consortium	78,700	European	https://gwas.mrcieu.ac.uk/datasets/ieu-b-4850/
HDL-C	Within family GWAS consortium	77,409	European	https://gwas.mrcieu.ac.uk/datasets/ieu-b-4844/
LDL-C	Within family GWAS consortium	70,814	European	https://gwas.mrcieu.ac.uk/datasets/ ieu-b-4846/
Fasting insulin	Chen et al.	151,013	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90002238/
Fasting glucose	Chen et al.	200,622	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90002232/
DBP	MRC-IEU	39,749	European	https://gwas.mrcieu.ac.uk/datasets/ukb-b-18240/
SBP	MRC-IEU	39,749	European	https://gwas.mrcieu.ac.uk/datasets/ukb-b-6503/

HERMES, heart failure molecular epidemiology for therapeutic targets; PM, particulate matter; AF, Atrial fibrillation; HF, Heart failure; MI, Myocardial infarction; IS, Ischemic stroke; LAS,Large artery stroke; SVS, Small vessel stroke; CS, Cardioembolic stroke;BMI, body mass index. TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure.

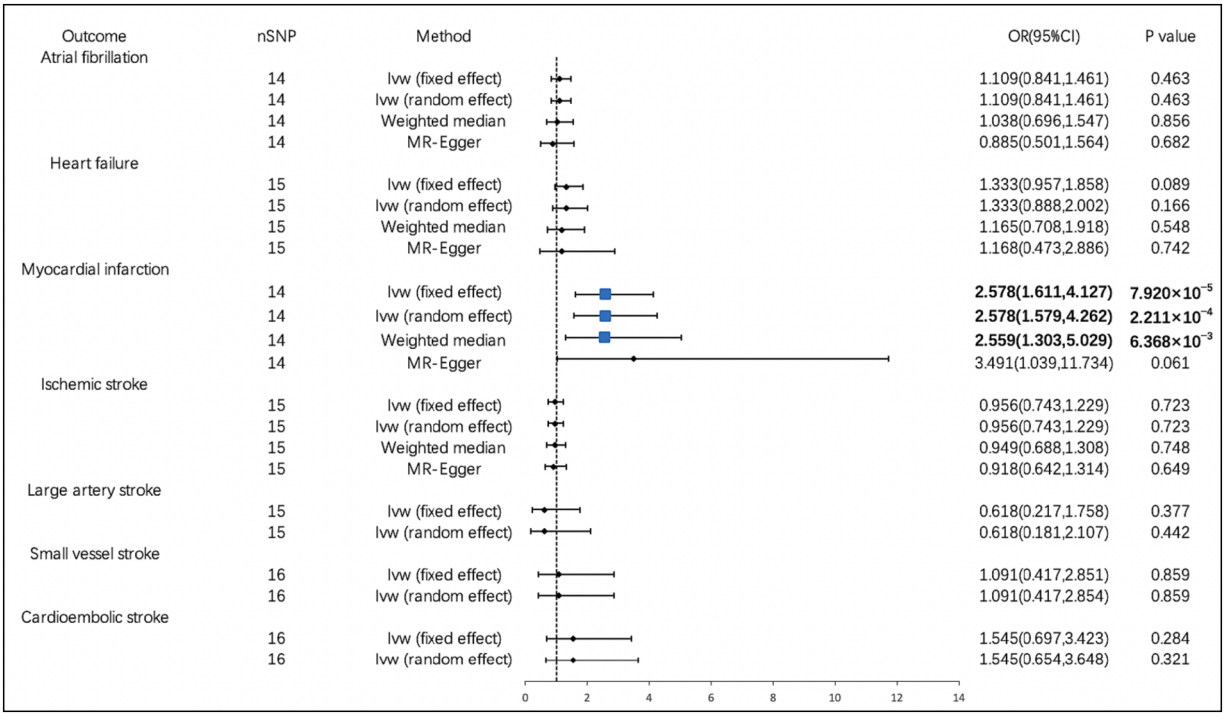

FIGURE 2
Associations of PM2.5 with cardiovascular diseases. CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

We also found that the increases in PM2.5 concentration were associated with the decreases in HDL-C (OR, 0.779; 95% CI, 0.615–0.986; $p = 0.038$). The PM10 concentration increases were also closely related to the decreases in HDL-C (OR, 0.563; 95% CI, 0.366–0.865; $p = 8.756 \times 10^{-3}$). We observed no causal effect of PM on BMI, LDL-C, fasting glucose, fasting insulin, DBP, or

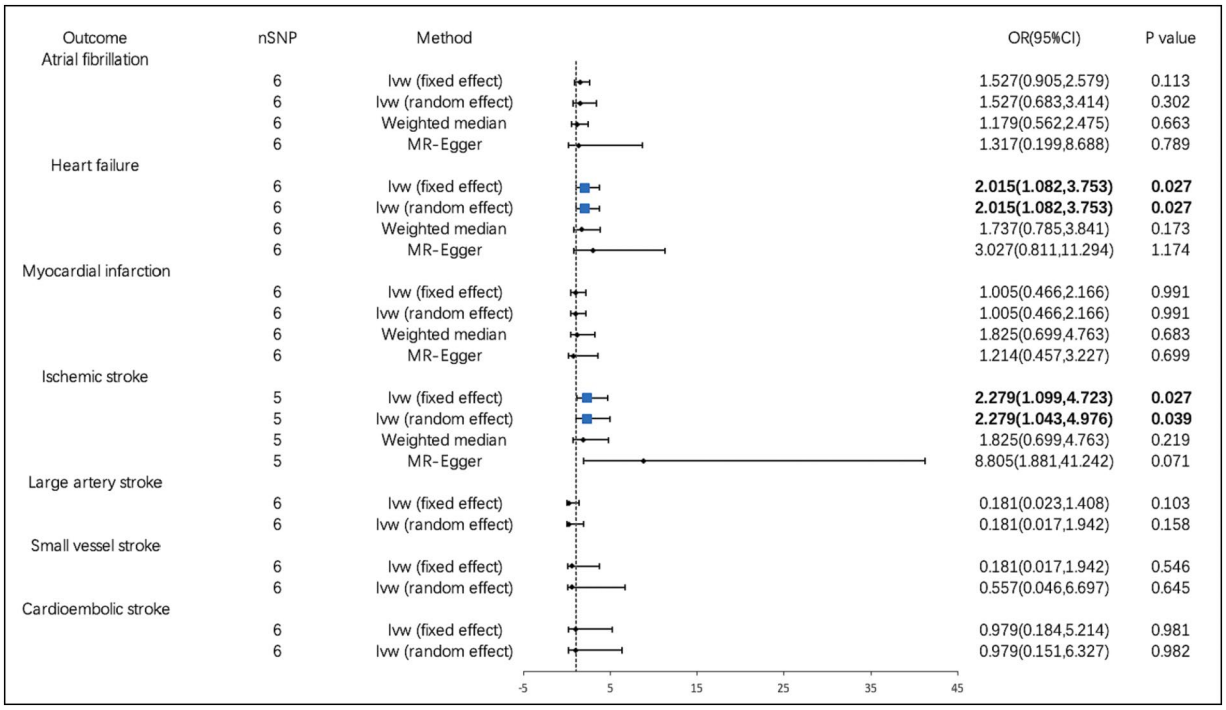

FIGURE 3
Associations of PM10 with cardiovascular diseases. CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

SBP. The results of the remaining methods can be found in Supplementary materials (Figure 4).

3.3. Sensitivity analysis

In sensitivity analysis, before we conducted the MR estimate, we used the method of MR-PRESSO to correct for the horizontal pleiotropy via outlier removal. After excluding these pleiotropic variants, no horizontal pleiotropy was found by conducted the MR-PRESSO method. For all outcomes, according to the MR-Egger regression, there did not appear to be horizontal pleiotropy based on the intercept term (Pintercept >0.05). We used the leave-one-out study to test the robustness of the results. All error lines are to the left of 0, indicating that the results are reliable and demonstrating that no SNPs with a large horizontal pleiotropic effect. We found modest heterogeneity in several analyses. However, heterogeneity did not affect the reliability of our conclusion. Plots of the leave-one-out analyses were also exhibited in Supplementary Figures. Details of the sensitivity analyses can be found in Tables 2–5.

4. Discussion

In the present MR study, we examined the causality of PM on CVDs and cardiovascular biomarkers. Our findings showed PM2.5 was significantly related to a higher risk of MI and revealed a suggestive causal association between PM10 and the risk of HF and IS, which might be explained by deleterious effects on blood lipid levels.

With the increasing abundance of GWAS data, many scholars conducted MR analysis to infer causality between PM2.5 and diseases (42, 43). Zhang et al. identified 7 SNPs related to PM2.5 and conducted two sample MR methods to conclude that PM2.5 concentrations can increase the risk of hypothyroidism (43). Yang et al. used 85 SNPs as genetic variants for PM2.5 and demonstrated a causal relationship between PM2.5 and gestational diabetes mellitus (42). Our research is the first MR Study focusing on the causal effect of PM on CVDs and cardiovascular biomarkers. Previous analyses have shown that exposure to PM is associated with an increased risk of MI, IS, and HF (44). To identify whether PM2.5 contributes to a rise in the incidence of MI, Li et al. carried out a meta-analysis that comprised twenty-seven cohort studies involving 6,764,987 participants and 94,540 patients with MI. The analysis concluded that long-term exposure to PM2.5 plays a role in MI (45). A meta-analysis by Li et al., which included 27 cohort studies involving more than 6.5 million people, showed a positive association between exposure to PM2.5 and the risk of MI (45). Farhadi and his colleagues noted the severity of the relationship between PM2.5 and MI in a meta-analysis of 26 studies, confirming the notion that PM2.5 levels are a key factor in the development of MI hospitalization (15). Studies have confirmed that air pollutants can trigger oxidative stress and inflammation in the body through direct entry into the blood or indirectly through particles, metals, and other components in the substance, leading to vasoconstriction, endothelial dysfunction, platelet hyperresponsiveness, and even autonomic nervous system disorders, thus increasing the risk of CVDs (46–48).

A meta-analysis of 35 studies showed that exposure to PM pollution was associated with an increased risk of hospitalization or death from HF. For every 10 $\mu g/m^3$ increase in exposure to PM10, the risk of hospitalization or death from HF increased by 1.6% (49). A study of

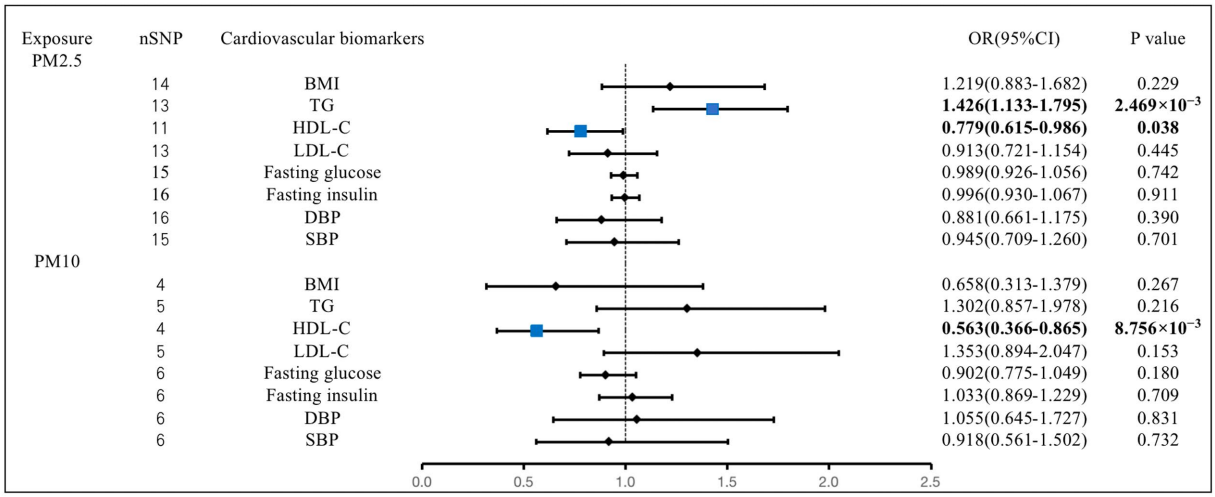

FIGURE 4
Associations of PM with cardiovascular biomarkers. CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism. BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 2 Sensitive analyses for the Mendelian randomization analysis between PM 2.5 and cardiovascular diseases.

Outcomes	Pleiotropy test (outliers-corrected)		Heterogeneity test (outliers-corrected)			Outliers
	MR-PRESSO global test *p* value	MR-Egger intercept test *p* value	Cochran's Q	Degrees of freedom	Cochran's Q *p* value	
AF	0.899	0.393	7.471	13	0.876	rs114708313 rs1537371
HF	0.135	0.752	19.542	13	0.107	rs1537371
MI	0.385	0.598	14.843	13	0.317	rs12203592 rs1537371
IS	0.748	0.766	11.382	14	0.656	rs1537371
LAS	0.127	0.095	19.266	14	0.155	rs1537371
SVS	0.432	0.619	15.036	15	0.449	NA
CS	0.303	0.149	17.497	15	0.291	NA

AF, Atrial fibrillation; HF, Heart failure; MI, Myocardial infarction; IS, Ischemic stroke; LAS,Large artery stroke; SVS, Small vessel stroke; CS, Cardioembolic stroke.

more than 100,000 hospitalizations for HF from 26 major cities in China analyzed the association between various air pollutants and hospitalizations for HF. The concentration of PM10 increased by one quartile (76.9 μg/m^3), the risk of hospitalization for HF increased by 1.3% (50). As Brook and his colleagues reported, PM has been linked with higher systemic blood pressure and vasoconstriction (51). Exposure to PM increases right ventricular and pulmonary diastolic filling pressures (52). Air pollution will dramatically raise the requirements based on the failing heart, possibly precipitating acute decompensation.

Our results concerning the potential causal relationship between PM10 and the risk of IS cohere with a systematic review that included 94 studies from 28 countries that reported that the short-run exposure concentration of PM10 increased by 10 μg/m^3, the risk of hospitalization and death from stroke increased by 0.3%. On the other hand, Hossein et al. expressed that the level of PM was immediately connected with the number of stroke inpatients in the emergency room. Long-run changes in PM10 also increased the risk of IS (53). Research has speculated that increased blood pressure triggered by acute increases in pollutant concentrations can contribute to the development of IS (54, 55).

In terms of cardiovascular biomarkers, our study showed that PM2.5 concentration increases were significantly associated with increases in TG and decreases in HDL-C. The PM10 concentration increases were also closely related to the decreases in HDL-C. Information concerning the relationship between PM and changes in lipids and lipoproteins was disputable, especially regarding HDL-C (56–59). Multiple studies have demonstrated an inverse relationship between high concentrations of PM exposure and the level of HDL-C (60–62). Zhang et al. revealed that PM10 was negatively associated with HDL-C (63). A study conducted by Wang et al. showed that each increase in PM2.5 was associated with higher levels of TG and lower levels of HDL-C (64). A health study involving 33 communities concluded that per 10-μg/m3 increment in PM2.5 was significantly associated with 1.1% (95% CI: 0.4, 1.8%) increases in TG and 1.1% (95% CI: 0.8, 1.4%) decreases in HDL-C (65). Consistently, a longitudinal study performed in a multiethnic US cohort free of cardiovascular disease showed that higher exposure to PM2.5 was associated with lower HDL particle numbers or lower HDL-C levels (57). The precise mechanisms between PM

TABLE 3 Sensitive analyses for the Mendelian randomization analysis between PM 10 and cardiovascular diseases.

Outcomes	Pleiotropy test (outliers-corrected)		Heterogeneity test (outliers-corrected)			Outliers
	MR-PRESSO global test *p* value	MR-Egger intercept test *p* value	Cochran's Q	Degrees of Freedom	Cochran's Q *p* value	
AF	0.063	0.869	11.796	5	0.038	NA
HF	0.594	0.529	3.949	5	0.557	NA
MI	0.758	0.657	2.711	5	0.744	NA
IS	0.374	0.147	4.594	4	0.332	NA
LAS	0.275	0.693	6.689	5	0.245	NA
SVS	0.167	0.760	8.591	5	0.127	NA
CS	0.311	0.819	6.224	5	0.285	NA

AF, Atrial fibrillation; HF, Heart failure; MI, Myocardial infarction; IS, Ischemic stroke; LAS,Large artery stroke; SVS, Small vessel stroke; CS, Cardioembolic stroke.

TABLE 4 Sensitive analyses for the Mendelian randomization analysis between PM 2.5 and cardiovascular biomarkers.

Outcomes	Pleiotropy test (outliers-corrected)		Heterogeneity test (outliers-corrected)			Outliers
	MR-PRESSO global test *p* value	MR-Egger intercept test *p* value	Cochran's Q	Degrees of freedom	Cochran's Q *p* value	
BMI	0.102	0.507	19.611	13	0.086	NA
TG	0.326	0.894	13.935	12	0.305	NA
HDL-C	0.947	0.386	4.079	10	0.944	rs72808024 rs1318845
LDL-C	0.018	0.111	24.691	12	0.016	NA
Fasting insulin	0.069	0.926	26.547	15	0.033	NA
Fasting glucose	0.660	0.630	12.072	14	0.601	NA
DBP	0.425	0.586	14.407	14	0.420	NA
SBP	0.928	0.472	7.123	14	0.930	NA

BMI, body mass index. TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure.

TABLE 5 Sensitive analyses for the Mendelian randomization analysis between PM 10 and cardiovascular biomarkers.

Outcomes	Pleiotropy test (outliers-corrected)		Heterogeneity test (outliers-corrected)			Outliers
	MR-PRESSO global test *p* value	MR-Egger intercept test *p* value	Cochran's Q	Degrees of Freedom	Cochran's Q *p* value	
BMI	0.457	0.771	3.790	3	0.285	NA
TG	0.945	0.523	0.751	4	0.945	NA
HDL-C	0.435	0.332	3.153	3	0.369	rs117671171
LDL-C	0.357	0.822	4.901	4	0.298	NA
Fasting insulin	0.269	0.856	6.552	5	0.256	NA
Fasting glucose	0.952	0.486	1.078	5	0.956	NA
DBP	0.858	0.597	1.986	5	0.851	NA
SBP	0.448	0.649	5.100	5	0.404	NA

BMI, body mass index. TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; DBP, diastolic blood pressure; SBP, systolic blood pressure.

exposures and lipid metabolism have not been fully determined. Several studies have shown that exposure to air pollution can lead to adverse lipid metabolism and lipid oxidation through systemic inflammation and oxidative stress (66–68). Other studies suggested that ambient air pollution might cause DNA methylation, leading to changes in particular genes associated with lipid metabolism (69, 70). Larger and more controlled studies are needed to fully address this issue.

4.1. Limitations and strengths

The advantages of our research are as follows. Our research is the first MR study focusing on the effect of PM on CVDs and cardiovascular biomarkers. MR estimates can avoid the interference of confounding factors and reveal the causal relationship between PM and CVDs more confidently. MR estimates can avoid the interference of confounding factors and reverse causality compared with other observational studies.

However, this study also has some limitations. Firstly, the GWAS of exposure failed to distinguish the time of PM pollution, so our results cannot explain the time of exposure effect, which limited us from conducting a further analysis. Several studies have also proposed a difference between "long-term" and "short-term" outcomes. Short-term exposure to air pollution is thought to cause acute CVDs events by destabilizing susceptible plaques, although long-term exposure may increase the risk of atherosclerosis by accelerating dyslipidemia, hypertension, and other metabolic disturbances (71). The future GWAS study of PM needs to distinguish the duration of exposure. Secondly, when we selected IVs, we used a more lenient threshold ($p < 5 \times 10^{-7}$). Although this may boost statistical power, the more instrumental variables included in the study, the greater the possibility of producing more pleiotropy. In order to eliminate horizontal pleiotropy, we conducted MR sensitive analyses such as the MR-Egger intercept, MR-PRESSO, and leave-one-out method. However, it is very difficult to completely exclude directional pleiotropy because SNPs affect exposure and outcome through unknown pathways, which has decreased the reliability of the findings. At last, the GWAS selected in this study are from European populations, and whether the findings of this study are applicable to other populations remains to be determined. In particular, there are regional differences in PM pollution, especially in some developing countries, but Europe, the main body of this study, is mostly developed countries. Therefore, our results could not be easily generalized to populations in high-pollution areas. Finally, there was modest sample overlap between the GWAS of PM and the GWAS of AF, HF, MI, SBP, and DBP, which might result in bias. Nevertheless, the F-statistic was large enough to moderate the effect of potential bias by sample overlap (72). Moreover, if the genetic link with PM was solely evaluated in non-cases, this sample overlap would not result in bias.

4.2. Perspectives and future research

Several epidemiological and experimental studies have regarded all components of PM as associated risk factors for the occurrence and deterioration of cardiovascular disease, which is independent of other conventional risk factors, including smoking, obesity, and diabetes. Our findings demonstrated the different effects of PM10 and PM2.5 on CVDs and cardiovascular biomarkers. Despite many studies suggesting that smaller size fractions are more harmful, especially PM2.5 (73, 74), the risks to human health posed by coarse particles like PM10 cannot be ignored. It was reported that PM10 contained more lipopolysaccharide (LPS) than PM2.5, which could trigger inflammation by directly activating Toll-like receptors and induce metabolic syndromes (75–77). Furthermore, a study conducted by Chang et al. suggested that heart rate variability (HRV) changes are reliant on PM10 as opposed to smaller particles (78). It is urgent for us to conduct more research to identify the nature of PM in all its size fractions and investigate the molecular mechanisms underlying the effects of PM with different sizes on the CVDs. Randomized controlled trials on this topic should be conducted in the future, although this is highly challenging. Besides, a handful of studies have shown that higher levels of PM impair the function of HDL (60, 79, 80), which might affect the development of CVDs beyond possible changes in plasma HDL-C levels. Larger and more controlled studies are needed to investigate the mechanisms by which HDL functionality and levels are affected by PM exposure and explore the potential efficiency of preventative interventions like statins and antioxidant therapy. To protect the earth together, we hope that all countries will strengthen the effective control of pollution sources, adopt strict law enforcement and management measures, and pay attention to the efficient combination of policy and scientific and technological innovation.

5. Conclusion

At the genetic level, our study provides evidence supporting the causality of PM on CVDs and cardiovascular biomarkers. Regarding CVDs, PM2.5 concentration increases were significantly associated with a higher risk of MI. PM10 concentration increases were significantly associated with a higher risk of HF and IS. In terms of cardiovascular biomarkers, PM2.5 concentration increases were significantly correlated with increases in TG and decreases in HDL-C. The PM10 concentration increases were also closely correlated with the decreases in HDL-C. The underlying pathophysiological mechanisms need to be further studied. Therefore, more research should be carried out to explore the mechanism and prevention of PM exposure in CVDs to better contribute to people's healthy lives.

Data availability statement

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

Author contributions

QW came up with the concept and designed the study and prepared the manuscript. ZW, MC, WM, and ZX processed the data. MX polished the draft. 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1201479/full#supplementary-material

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Assessing the impacts and feasibility of emissions reduction scenarios in the Po Valley

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This study is focused on a pivotal objective: enhancing air quality and attaining pollutant concentrations in accordance with WHO guidelines. The study extensively evaluates the feasibility of reducing emissions, specifically targeting an 80% decrease in SO_X, NO_X, PM, NH_3, and NMVOC emissions within a limited timeframe. Despite notable emission curtailments of 50% and 80%, the research reveals that recommended pollutant levels are unlikely to be met across most areas of the Po Valley region. Even when implementing the finest available technologies across various sectors, particularly within the Lombardia region, this goal remains unattainable without simultaneous reductions in activity levels. This involves diminishing factors like vehicle miles traveled, energy consumption for heating, and industrial, agricultural, and livestock production. Overall, achieving improved conforming to the new AQG limits is a multifaceted endeavor involving numerous stakeholders and diverse strategies. Successful adherence to Air Quality limits mandates the implementation of Source-Specific emissions standards at the EU level, alignment of the National Emission Reduction Directive with limits specified in the Air Quality Directive, and the formulation of comprehensive Air Quality Plans at national, regional, and local tiers.

KEYWORDS

air pollution, Po Valley, air quality guidelines, CTM, emission reductions, feasibility

1 Introduction

Air pollution is a significant public health issue affecting millions of people worldwide. Over the past 3 decades in Europe, visible improvements in air quality have been achieved, thanks to strong common efforts driven by the European Union (EU), national, regional and local authorities in the Member States (Bourdrela et al., 2018; Lim et al., 2019). However, exposure to high concentration of fine particulate matter ($PM_{2.5}$) has been linked to various adverse health outcomes, including respiratory diseases (i.e., asthma, chronic pulmonary disease) and cardiovascular disease. It is estimated that air pollution causes millions of premature deaths each year (EEA, 2021; Khomenko et al., 2021; WHO, 2021). Moreover, air pollution has also been associated with neurological diseases such as dementia and has a disproportionate impact on vulnerable populations such as children and the elderly.

Recognizing the growing body of evidence on the health impacts of different air pollutants, the World Health Organization (WHO, 2021) has introduced Air Quality

Guidelines (AQG) with stricter values for several pollutants, including PM_{10}, $PM_{2.5}$, and NO_2, aiming to protect public health. As a result, many countries need to revise their regulations to meet these guidelines. In Europe, the European Commission (EC) concluded that the Directives (EU, 2004; EU, 2008) have been partially effective in improving air quality and achieving air quality standards. As part of the European Green Deal (European Commission, 2021), the EC is committed to improve air quality and aligning EU air quality standards with the recommendations of WHO. Consequently, the EC has proposed a new revision of the air quality Directive, which includes a progressive alignment of the standards with a vision for 2050 to reduce air pollution to levels that are no longer considered harmful to health and natural ecosystems. Furthermore, interim targets have been formulated for several pollutants, including $PM_{2.5}$, PM_{10}, O_3, NO_2, SO_2, and CO. Despite the ambitious objective of achieving a non-toxic environment by 2050 (referred to as AQG levels), meeting these guidelines remains a significant challenge, particularly in reducing emissions of $PM_{2.5}$ (Cohen et al., 2017). The reduction of PM2.5 concentrations continues to be a challenging goal, that requires also to act on the emissions of ammonia (NH_3) and other precursors (NO_x, COV) (Thunis et al., 2021; Wang et al., 2021; ApSimon et al., 2023).

In the European Union, many Member States have exceeded environmental objectives for one or more of the main pollutants, and the Po Valley stands out as one of the most critical hotspots for pollution in Europe. The Po Valley can be considered as a distributed megacity in Europe, with a population of over 20 million and a significant concentration of Italian livestock, industry and agricultural production take place (Finardi et al., 2014; Clappier et al., 2021; Thunis et al., 2021; Khomenko et al., 2023). The high density of pollutant sources in Po Valley is one of the main reasons why the thresholds limits for pollutants such as NO_2, PM_{10}, O_3 are not being met. Additionally, the orographic feature of the Po Plain, surrounded by the Alps to the north and the Apennines to the South, contribute to the air quality challenges due to the stagnation of air and the limited exchange of pollutants. Although the emissions of air pollutants have been significantly reduced in all sectors, thanks to regional plans developed for the Po Valley, the concentrations of pollutants still remain significantly above the WHO AQG (D'Elia et al., 2018; De Angelis et al., 2021).

Several studies have demonstrated the positive effects of emission reduction measures on air quality and the health impacts in Europe (Crippa et al., 2015; Turnock et al., 2016; Carnell et al., 2019; Velders et al., 2020). Recently, there has been a significant effort to estimate the spatial and sector-specific contributions of emissions to ambient air pollution in European cities (Khomenko et al., 2023). This assessment aims to evaluate the effects of source-specific reductions in pollutants on mortality rates, with the goal of supporting targeted actions to address air pollution and enhance population health. By understanding the sources responsible for pollution and their impact on public health, authorities can implement more effective and tailored strategies to mitigate air pollution and improve the wellbeing of residents in urban areas. However, it is crucial to consider the most realistic scenarios to determine what represents the maximum technically feasible options and the consequences of implementing more stringent requirements.

Chemical transport models (CTMs) are powerful tools that can be used to understand the transport and transformation of air pollutants, including photochemical smog and secondary aerosols, in the atmosphere. By simulating the dispersion of pollutants, CTMs can help quantify the impacts of emissions reductions strategies. In recent years, CTMs have become increasingly important for air quality management and policymaking (Chemel et al., 2014; Baklanov and Zhang, 2020), particularly in regions with high levels of air pollution like the Po Valley (Squizzato et al., 2013; Vander Hoorn et al., 2022).

In this paper, we started from the results of NINFA-ER CTM, a model systems runned in the LIFE IP-PREPAIR (Po Regions Engaged to Policies of AIR) project and used to investigate the effects of hypothetical emission reduction scenarios on pollutant concentrations in the Po Valley within the project (https://www.lifeprepair.eu/index.php/sdm_downloads/evaluation_scenarios-2022_who/).

During the project, it has been evaluated the effects on concentrations of a strong emission reductions of all anthropogenic sectors reducing SO_X, NO_X, PM, NH_3, NMVOC by 50% and 80% based on 2017 emissions. It has been evaluated the impacts of these scenarios on $PM_{2.5}$, NO_2, and PM_{10} annual limit concentrations, and assessed their potential to meet the WHO AQG. Additionally, we have considered the feasibility of implementing a "technical" emissions scenario, considering factors such as cost and technical feasibility. At the national level, ENEA, as part of the National Control Programme of Air Pollution, recently developed emission and air quality scenarios to assess compliance with the limits set by the Directive 2016/2284 (NEC) (Piersanti et al., 2021), too.

Based on an inventory simulation reduction, we identified the most feasible emission reduction scenario. Previous studies have indicated that reducing $PM_{2.5}$ emissions can lead to improvements in air quality and a reduction in health impacts in the Po Valley (Klimont, 2011; Klimont et al., 2017). However, implementing effective emissions reduction strategies can pose challenges, and the most feasible approach depends on various factors, including local conditions, air quality plan and available technical resources. By providing insight into the impacts and feasibility of different emissions reduction strategies, our study aims to inform decision-making processes and support efforts to enhance air quality in the Po Valley. It demonstrates that achieving compliance with the WHO AQG is technically difficult in the Po Valley, which is affected by air pollution, without considering significant reduction in various sectors.

2 Materials and methods

2.1 NINFA-ER: a CTM model set-up

Simulations, presented in briefly herein, were performed within LIFE IP-PREPAIR (https://www.lifeprepair.eu/index.php/sdm_downloads/evaluation_scenarios-2022_who/). In this work, we reported the main set-up of the CTM model and main results already obtained. Further details and a more comprehensive description of the methodology employed, are described in the references mentioned, including (Marongiu et al., 2022a) for

emission inventory data and (Veratti et al., 2023) for a detailed description of the CHIMERE set-up and domain application.

The NINFA-ER CTM (Northern Italy Network to Forecast Aerosol Pollution) is an operational air quality (AQ) model used by the Environmental Agency of the Emilia-Romagna Region (Arpae). It incorporates a Chemical Transport Model (CTM), a meteorological model and a pre-processing emissions tool. The CHIMERE model serves as the chemical transport model, facilitating simulations of air pollutant and aerosol transport, dispersion, chemical transformations, and deposition (both dry and wet). The study considers natural emissions (biogenic, sea-salt, and dust), as well as emissions from various anthropogenic sources in the region and neighboring areas. The emissions data for the model come from specific proxy variables associated with each emission activity (e.g., SNAP3 network for traffic emissions, population and urban fabric data for domestic heating, etc.). This model serves as a valuable tool for understanding air quality and pollution dynamics in the study area. The meteorological hourly input for the study is obtained from COSMO, the National numerical weather prediction model utilized by the Italian National Civil Protection Department. COSMO is a hydrostatic, limited-area atmospheric prediction model that employs primitive thermo-hydrodynamical equations to describe compressible flow in a moist atmosphere. It incorporates a range of physical processes through dry and moist parameterization schemes. The initial and boundary conditions (IC/BC) for the Chemical Transport Model (CTM) simulations are sourced from the PrevAir European Scale Air Quality Service project (http://www.prevair.org). The CTM simulations have a horizontal resolution of 0.09 × 0.07°, which corresponds to approximately 5 km, covering the entire northern Italy region.

Furthermore, a data fusion post-processing step is applied to adjust the output of the CHIMERE model using available measured concentrations. This process involves a Kriging with External Drift algorithm, considering the model itself and the elevation above sea level as spatial explanatory variables (Bertino et al., 2003). The validation of the CTM output has been presented in (Supplementary Figure S1 presents the scatter plot of simulated vs. observed values and Supplementary Table S1 shows-statistical scores bias and root mean square error).

Measured PM_{10}, NO_2, and $PM_{2.5}$ concentrations used in the study were derived from the dataset (data flows E1a stand for ambient air measurement validated) reported annually to the European Environmental Agency (EEA, 2021). Only background stations were included in the model adjustment, and annual average concentrations were considered for all examined pollutants (PM_{10}, NO_2, $PM_{2.5}$).

2.2 Emission dataset

One of the objectives of the LIFE-IP PREPAIR was to implement short- and long-term measures to reduce pollution emissions and improve air quality in the Po Valley region. To achieve this, a task was assigned to harmonize and collect anthropogenic emission data from eight Italian regions of the Po Valley and Slovenia (Marongiu et al., 2022b). This task resulted in the creation of a comprehensive air pollutant emission dataset for the entire domain, covering the years: 2013, 2017, and 2019.

The Italian Regions and autonomous provinces have varied functions in the monitoring and management of air quality, according to European and national legislation and must create and update an emission inventory on their own territory every two or 3 years. The EEA-EMEP Guidebook is the key technical reference in updating emission inventories (www.eea.europa.eu) at both national and local levels, and it plays an important role in estimating comparability (EMEP/EEA, 2016, 2019).

Local emission inventories in Italy are usually compiled at a municipal level and use the SNAP classification. This high spatial resolution can help to better depict the emission pressure on the domain, but it can also make it more difficult to provide consistent time series due to variations in local information availability. In Po Valley, the great part of the Regions developed jointly these local inventories, calling the database "INEMAR system" resulting in a significant level of harmonization in the realization of atmospheric emission estimates (www.inemar.eu). INEMAR is a database that may provide findings for pollutants of interest for air quality, greenhouse gases, PAHs, carbonaceous portion of particle, and heavy metals from a combination of more than 250 activities and 35 fuels.

The process of compiling a local emission inventory in the INEMAR system begins with the collection of a massive amount of information such as activity indicators (e.g., fuel consumption, traffic flows, industrial production), emission factors, and statistical data for the spatial and time-based distribution of emissions.

As reported by the EEA-EMEP Guidebook, with the term tier is described the level of methodological sophistication: tier 1 is the simplest (most basic) technique, tier 2 is the intermediate, and tier 3 is the most demanding in terms of complexity and data needs. The top tier algorithms are integrated into database modules as part of the INEMAR system.

The emission inventories obtained with INEMAR system can be summarized by the following:

$$E_i = \sum_m \sum_s \sum_f I_{s,f,m} EF_{s,f} \quad (1)$$

Where E_i represents the annual emission for pollutant i (e.g.,: PM_{10}, NH_3, NO_x, ecc), m represents the municipality of the domain, s represents the source type according to SNAP classification and f is the fuel type (e.g.,: wood, gasoline, natural gas, . . .); $I_{s,f,m}$ represents the activity indicator for source s, fuel type f and municipality m and $EF_{s,f,i}$ is the emission factor for pollutant i, source s and fuel f.

Total emissions are obtained by multiplying the activity indicators by the corresponding emission factors and aggregating the values of all municipalities, all sources and all fuel types during a full year. In higher tiers approaches the emission factors and activity indicators are calculated from more complex algorithms.

The NINFA-ER CTM simulation as mentioned in (Veratti et al., 2023), utilized the 2017 emission dataset of LIFE-IP PREPAIR based on the collection of all the data of the INEMAR system and of the data available for the areas not covered by this database relatively to Slovenia and other areas not covered by the system. However, it is

TABLE 1 Definition of the hypothetical emission scenarios.

Reduction (%)	NO_X, VOC, NH3, PM, SO_X
0	R0 (base case)
10	R10
50	R50
80	R80

not worth noting that a more recent emission inventory referring to 2019 has been managed for Lombardy Region. This updated inventory has been used for the evaluations of the Maximum Reduction Rate (MRR) described in the following sections.

2.3 Hypothetical emission scenarios

In this study, we reported the results obtained by simulations already done with NINFA-ER CTM (https://www.lifeprepair.eu/index.php/sdm_downloads/evaluation_scenarios-2022_who/).

The four simulations specifically for NO_2, $PM_{2.5}$, and PM_{10} were performed, including a reference scenario based on the work by Marongiu et al. (2022a). Emissions of SO_X, NO_X, PM, NH_3, and NMVOC were progressively reduced from 10% to 80% across the entire investigation domain. For a more detailed description of these scenarios, you can refer to Table 1.

In addition to the NINFA-ER CTM simulations, two additional scenarios were developed to assess the maximum achievable emission reductions. These scenarios involved implementing the best available technologies and combining them with activity level variation. Section 2.4 and Section 2.5 of the study provide further explanations regarding these scenarios.

2.4 The maximum reduction rate MRR (technological) scenario in Lombardy Region

This section aims to present the maximum achievable emission reduction through the implementation of the best possible technologies. The emission calculations are based on an annual and regional basis using the Lombardy regional emission inventory updated to 2019, obtained through the INEMAR system (Lgs, 2010; Lombardia, 2017; Lombardia, 2017).

The analysis includes key sectors such as road traffic, wood burning in domestic heating, livestock management and agriculture fertilization. Assuming like the base scenario (E0) the regional emission inventory of Lombardy updated to 2019, the MRR is calculated under the following assumptions.

1. Replacement of all vehicles, except heavy commercial vehicles, with electric vehicles
2. Replacement of heavy goods vehicles with Euro VI vehicles
3. Replacement of all wood-burning appliances with 5 s appliances (dell'Interno, 2017)
4. Conversion of all farms to use the most efficient technologies for NH_3 emission reduction in all phases of manure management.
5. Implementation of fertilizers that reduce ammonia volatilization into the atmosphere.
6. Maintenance of all other indicators such as the number of vehicles, distances traveled, electricity production, farms sizes, and areas to be fertilized, at their current levels.

2.4.1 Road transport and complete electrification of mobility demand

The application of the best available technologies involves replacing all heavy-duty vehicles with Euro VI vehicles and converting cars, light duty vehicles, city buses, coaches, mopeds, and motorcycles to electric powered vehicles. For the latter categories, the conversion of internal combustion engines to electric motors will result in emissions only from brake, tire and road wear assuming a constant mileage of the vehicles. Table 2 summarizes the number of vehicles, annual mileage, and average wear emission factor of PM_{10} obtained from Lombardy emission inventory of 2019. These emission factors also depend on the vehicle weight and usage mode (for example, the average emission factor of mopeds is slightly higher than that of motorcycles due to their predominant use in urban areas).

The almost complete electrification of the circulating fleet will result in an increased demand for electricity. However, the effects on the electricity production system have not been evaluated. It is assumed that the higher consumption will be met through imports or non-emissions causing systems within Lombardy.

2.4.2 Biomass burning in the domestic heating

Italian National legislation has introduced an emissive classification for domestic biomass burners, with five stars (5-s) indicating the lowest emission appliances. In the scenario of maximum reduction, we assume the complete conversion of all existing single user appliances into 5-s pellet appliances and all the existing boilers into 5-s boilers. The total consumption of woody biomass remains unchanged at approximately 19 PJ (Peta joule). It is estimated that the complete conversion of biomass-fired devices would involve replacing over 600,000 appliances. The emission factors 5-s devices have been estimated on the specified limits provided by (dell'Interno, 2017), taking into account the condensable fraction of emissions. The assumed emission factors are 47 g/GJ for PM in single-user pellet stoves and 9 g/GJ for PM in pellet boilers (Marongiu et al., 2022a).

2.4.3 Agriculture and livestock

We consider the complete conversion of effluent management techniques currently implemented in farms to the best performing technologies in terms of ammonia emissions. The maximum emission reduction is calculated while maintaining the same number of livestock units in farms that use these technologies, allowing for the greatest possible reductions in ammonia emissions during housing, field application and complete coverage of all storages. The conversion of farms has been hypothesized for the most representative animal categories in the region, including dairy cows, other cattle, pigs, sows, laying hens and broilers. The emission factor at the farm level that yields the lowest ammonia emissions was calculated using the farm-scale BAT-Tool Plus software implemented within the LIFE IP PREPAIR. The Table 3 presents the technologies for managing livestock manure (LIFE, 2021),

TABLE 2 Number of vehicles circulating in Lombardy in 2019, mileage and PM_{10} emission factors form tires, braeks and roads.

Vehicle type	Number	Mileage [millions of km]	Emission factor [mg/km]
Cars	6,212,475	55,220	24
Light duty vehicles (<3.5 t)	631,448	8,071	33
Heavy duty vehicles	113,073	5,472	102
Mopeds	449,529	359	13
Motorcycles	1,095,683	2,028	12
Bus and coach	10,853	318	93

TABLE 3 Agriculture and livestock technique to comply the MRR.

	Dairy cattle/non diary cattle	Swine/Sow	Laying hens	Broilers
Housing	Air conditioning (10%)	30.c. Air treatment (80%)	31.c. -Air treatment (80%)	32.d overlapping floors with ventilation (90%)
	- roof insulation			
	- automated control of air conditioning systems			
	- artificial ventilation (wind channels, wind cascades) Urine removal (20%)			
	- lanes with underfloor urine drainage			
	Feed lanes (20%)			
	- lanes with solid floor and removal >4 v/d			
	- slotted lane or channel with under cracked scraper passage >4 v/d			
	Bedding, cleaning frequency (20%)			
	- slanted bedding, lanes cleaning >2 v/d			
	- flat litter without feeding lane or on slanted bedding: addition of litter material everyday			
	Complete bedding renewal (20%)			
	- flat bedding without feeding lane: complete renewal of litter material >60 days			
	Slatted floors (20%)			
	- housing on slatted floor or slatted slats with passage of under-slit scraper >4 v/d			
Storage	Slurry: 16.b.1–covered tanks (90%)	Slurry: 16.b.1–covered tanks (90%)	Solid: 14.b.1–covering the stock in manure (40%)	
	Slurry: 16.b.1–floating covers (90%)			
	Solid: 14.b.1–covering the stock in manure (40%)		Solid: 15.e – covered storage at the foot of the field (40%)	
	Solid: 15.e – covered storage at the foot of the field (40%)			
Spreading	Slurry (90%)–distribution of purified sewage	Slurry–21.d—deep injection, closed slot (90%)	Solid—Incorporation within 4 h (60%)	
	Slurry (90%)–low pressure fertirrigation	Slurry—Distribution of purified sewage (90%)		
	Solid—Incorporation within 4 h (60%)	Slurry—low pressure fertirrigatio (90%)	Solid—Immediately by non-inversion cultivation incorporation (60%)	
	Solid—Immediately by non-inversion cultivation incorporation (60%)			

categorized by phase and animal type, that correspond to the greatest reductions in ammonia emissions.

The emission factors obtained result in the following reductions compared to the emission factors reported by ISPRA in the Informative Inventory Report 2021 (ISPRA, 2021). The expected reduction for livestock in terms of emission factors, representative of the national average, are as follows.

- 47% for dairy cows and 76% for other cattle.
- 68% for pigs and 82% for sows.
- 17% for laying hens and 31% for chickens.

2.4.4 Agriculture fertilization

The maximum reduction in ammonia emissions can also be obtained by considering the management and/or substitution of synthetic fertilizers in crops. An 80% reduction in NH_3 emissions is assumed, considering the replacement of ammonia-releasing mineral fertilizers such as urea with non-ammonia releasing mineral fertilizers (e.g., ammonium nitrate) or by adopting practices such as burying or injecting urea (LIFE, 2021).

2.5 Activity level variations in addition to the maximum reduction rate MRR (technological) scenario

In addition to the MRR scenario, calculations were set up to evaluate an additional reduction by considering possible variations in activity indicators (e.g., reducing the number of cars or their mileage). These scenarios, referred to as the MRR + Indicators, are estimated using the following approach:

$$E_{MRR\_IND} = E_{MRR} \cdot (1 - r_n) \cdot (1 - r_{ind}) \quad (2)$$

These scenarios involve the percentage reduction of two indicators.

a) r_n, represents the percentage reduction in the number of vehicles on the road, wood-burning appliances or number of animals.
b) r_{ind} represents the percentage reduction in average mileage for road transport, energy consumption of wood-burning appliances or the effect of animal weight.

To ensure comprehensive coverage of activities in the emission inventory, the estimation also includes the possibility of assessing the effects of reducing entire macro-sectors or sectors using a single aggregate variable.

3 Results

This section presents the main output obtained from CTM simulations in different scenarios to assess air quality compliance with the proposed limits by WHO and EU for each pollutant, including the R50 and R80 scenarios. Moreover, the Maximum Reduction Rate Technological Scenario is presented to demonstrate that achieving a reduction of, for instance, 80% is not possible solely through technical measures; it also requires a significant reduction in activities.

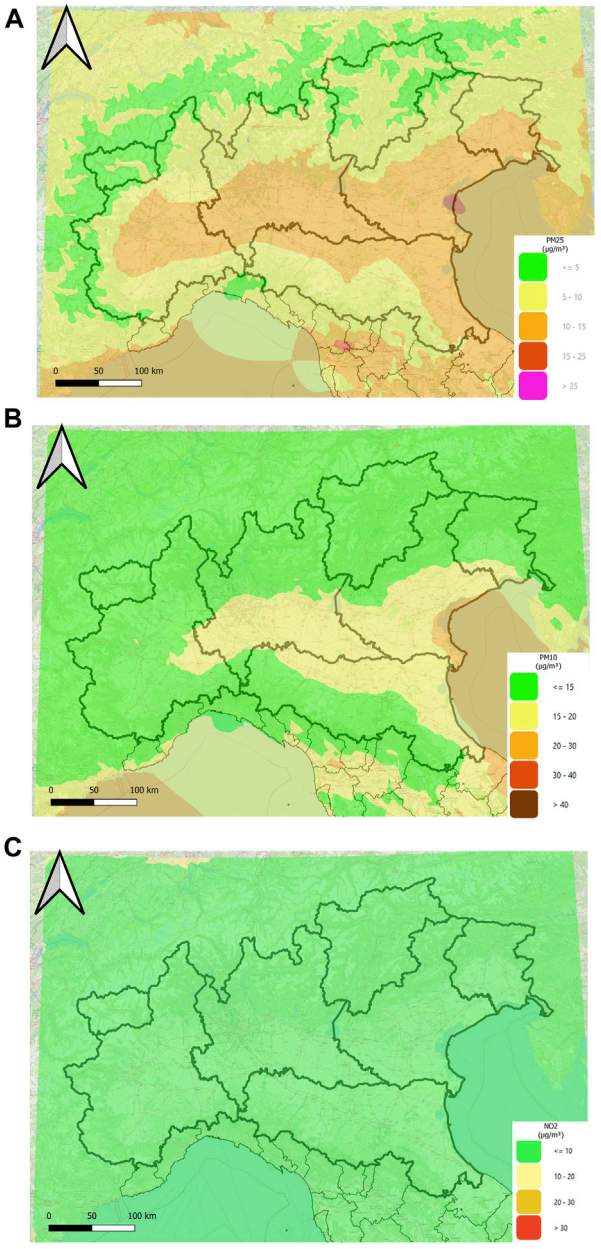

FIGURE 1
(A) Annual average PM2.5 concentration field (R80 scenario−80% reduction) **(B)** Annual average PM10 concentration field (R80 scenario−80% reduction) **(C)** Annual average NO2 concentration field (R80 scenario−80% reduction).

3.1 Scenarios results: air quality assessment

To enhance the realism of the pollutant model outputs and ensure a more quantitative representation of their spatial distribution, an adjustment factor obtained from the base scenario R0, is applied to the annual average concentration produced by R10, R50, R80 scenarios (see Figure 1). The model results have been analyzed by considering the most critical indicators in relation to the annual limit values established by the 2008/50/EC Directive (EU, 2008) and the new values proposed by WHO (Table 4).

TABLE 4 WHO recommended AQG levels, interim target and EU 2008/50/EC Directive for R50 and R80 scenarios. The green/red colored cells indicate respectively achievement/non achievement of selected target, while yellow means achievement at most monitoring stations.

Pollutant	Average time	Interim target 1		Interim target 2		Interim target 3		Interim target 4		AQG (air quality guidelines)		AAQ directives (actual limit)	
$PM_{2.5}$ µg/m³	y	35	R50	25	R50	15	R50	10	R50	5	R50	25	R50
			R80		R80		R80		R80		R80		R80
PM_{10} µg/m³	y	70	R50	50	R50	30	R50	20	R50	10	R50	40	R50
			R80		R80		R80		R80		R80		R80
NO_2 µg/m³	y	40	R50	30	R50	20	R50	—		10	R50	40	R50
			R80		R80		R80				R80		R80

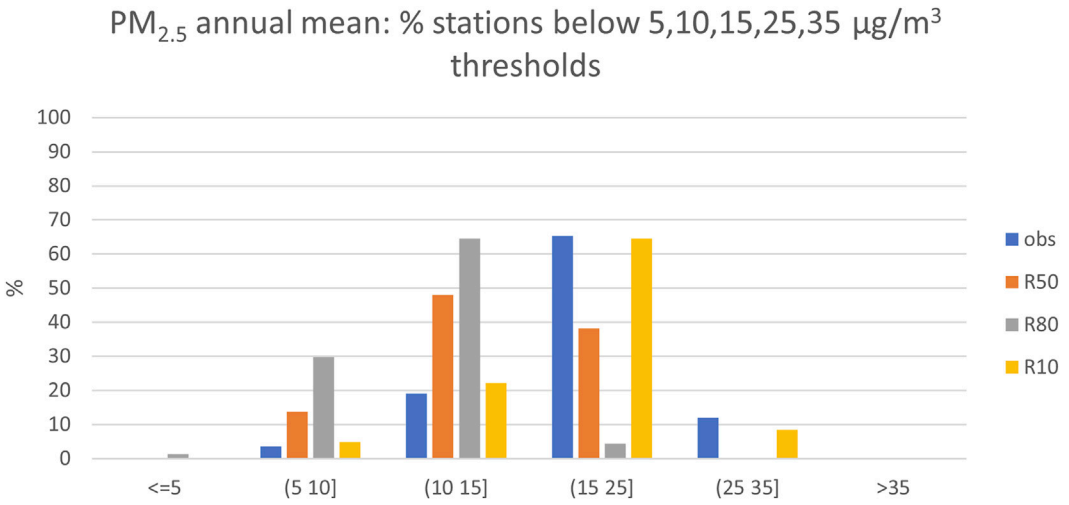

FIGURE 2
$PM_{2.5}$ annual averages for 2017, 2018, 2019: percentage of all stations below the interim target and AQG level observed (obs) and predicted data in R10, R50, R80 emission scenarios.

The figures below illustrate the spatial distribution of $PM_{2.5}$, PM_{10}, NO_2 annual average concentrations for the more effective R80 emission scenario, based on the year 2018. It is important to note that the year 2018 serves at the reference for the meteorological driver COSMO and as based on the previous analysis, it exhibits an intermediate behavior between the year 2017 and 2019. Some validation indicators about the R0 are presented in Supplementary Material.

In the R80 emission scenario, where all primary pollutants and precursors (such as NOx, VOC, NH3, PPM, SOx) are reduced by 80% across most of the Po Valley, the annual mean concentration of $PM_{2.5}$ (Figure 2) ranges between 5 and 15 µg/m³. Similarly, the PM_{10} concentration (Figure 2) falls between 15 and 20 µg/m³, while NO_2 levels (Figure 2) remain below 10 µg/m³.

Please refer to Figure 1 for a visual representation of the spatial distribution of these pollutant concentrations in the R80 emission scenario for the year 2018.

When considering all the stations in the Po Valley, it becomes evident that only 30% of them would meet the proposed $PM_{2.5}$ annual limit if there is an 80% reduction in emissions of SO_X, NO_X, PM, NH_3, and NMVOC. This suggests that achieving the desired air quality standards would be challenging, as the majority of stations would still exceed the $PM_{2.5}$ limit even with a substantial reduction in emissions.

It's important to note that the specific distribution and concentration of pollutants can vary across different locations within the Po Valley, and these results are based on the given scenario and assumptions. Further analysis and evaluation may be necessary to explore alternative strategies or additional measures to attain the desired air quality targets in the region.

3.2 Emission scenario results: MRR and MRR + in Lombardy Region

This section presents the results of the Maximum Emission Reduction (MRR) scenario, which represents the maximum achievable emission reduction through the application of all available technological measures. It also considers the MRR +

TABLE 5 Emissions for the base year (E0) and MRR emissions scenario in Lombardy. TSP is the total suspended particulate. The percentage is the variation of E0-MRR with respect MRR.

	SO_2 (ton/year)	NOx (ton/year)	COV (ton/year)	CH_4 (ton/year)	CO (ton/year)	CO_2 (kton/year)	N_2O (ton/year)	NH_3 (ton/year)	$PM_{2.5}$ (ton/year)	PM_{10} (ton/year)	TSP (ton/year)
E0	10.476	99.234	247.628	342.476	162.022	58.625	7.419	90.727	12.122	14.496	18.101
MRR	10.363	52.908	229.341	338.894	72.343	43.480	7.071	35.002	6.092	8.336	11.670
Var	**−1.1%**	**−46.7%**	**−7.4%**	**−1.0%**	**−55.3%**	**−25.8%**	**−4.7%**	**−61.4%**	**−49.7%**	**−42.5%**	**−35.5%**

scenario, which incorporates the effects of limiting activity levels in addition to the technological measures.

It is important to note that the MRR scenario does not take into account the techno-socio-economic feasibility of completely replacing biomass appliances, vehicle fleets, breeding and manure management technologies in the livestock sector. Therefore, these assessments represent a lower limit estimation of emissions in Lombardy without considering the feasibility and time profile of implementing such measures. Factors such as costs, socioeconomic factors and sustainability in meeting the increasing demand for energy vectors (e.g., electricity and biomass pellets) may make complete implementation challenging.

Table 5 provides a quantification of emissions for the base year (E0), which represents Lombardy region's emission inventory for 2019, as well as the emissions for the MRR scenario based on the assumptions outlined in Section 2.4.

Please note that further analysis and evaluation are necessary to assess the feasibility, costs, and implications of implementing the proposed emission reduction measures in practice.

The comparison between MRR and MRR + Indicator scenario demonstrates the additional reduction in emissions that can be achieved by acting on one or more of activity indicators. In the case of road traffic, it is possible to influence both the number of vehicles and the annual mileage, while in the case of biomass heaters, the number of appliances and average annual consumption can be adjusted. As explained in Section 2.4 and represented by formulation (1), the emission reduction combines the potential reductions in the indicators and uses the overall result to adjust the emissions. For example, if there is a 25% reduction (r_n) in the number of cars and a 25% reduction (r_{ind}) in their mileage, the correction factor for the remaining emission would be (1–0.25) × (1–0.25) = 0.56.

For each of the sources considered (road traffic, biomass heating and livestock sector), as well as for aggregated sources, it is possible to estimate the maximum additional contribution to the MRR scenario by assuming a 100% reduction in the indicator. The values presented in the table below represent the maximum achievable values for each sector, and the indicators are estimated as an additional change compared to the E0 scenario.

For instance, in the case of the total removal of cars in the MRR scenario, an additional reduction in TSP (total suspended particulate) emissions equal to 11% of the total emissions in the E0 scenario is achieved. It's important to note that these values represent theoretical maximums and may not be feasible or practical to achieve in reality. They provide insights into the potential impact of further reductions in the activity indicators on emissions.

In Table 6 the indicators are calculated using the following formula:

$$R_{MRR\_IND\_SECT}(\%) = \frac{E_{MRR\_IND\_SECT} - E_{MRR}}{E_0} \cdot 100 \qquad (3)$$

The formula compares the emissions of the MRR_IND_SECT scenario to the base year emissions E_0.

a) $E_{MRR\_IND\_SECT}$, represents the emissions obtained by applying a zero-level indicator to a specific sector. The sectors are listed in Table 6.
b) E_{MRR} represents the total emissions calculated in the MRR as reported in Table 5.
c) E_0 represents the base year emissions as reported in Table 5.

To illustrate with an example, looking at Table 5, it shows that there is a reduction of −38.9% for PM_{10}. By removing all cars (100% indicators, in Table 5) a further reduction of −9% can be achieved. The total reduction would be the sum of these two contributions, resulting in −48%.

Furthermore, if all the sectors listed in Table 5 are completely removed, in addition to the MRR reduction, the emissions would reach zero, effectively creating a zero-emissions situation.

4 Discussions

Improving air quality and achieving the suggested pollutants concentrations provided by WHO guidelines is a crucial objective for European, national, and local institutions to safeguard public health. However, achieving near-zero emission limits within a limited timeframe poses significant challenges. This study aims to facilitate a comprehensive and nuanced discussion on the feasibility of emission reduction strategies and whether it is possible, within the given time frame, to attain interim and WHO AQG levels through an 80% reduction of SO_X, NO_X, PM, NH_3, and NMVOC emissions.

The findings of this study demonstrate that despite substantial and ambitiously scaled emission reductions (−50% and −80%), the recommended level will not be met in most areas of the Po Valley at least for some pollutants. Table 4 provides a summary of compliance with the WHO and EU limits for each pollutant,

10.3389/fenvs.2023.1240816

TABLE 6 Additional emission reduction after the application of MRR to each sector obtained by switching to zero all residual activity indicator.

	SO_2	NO_x	COV	CH4	CO	CO_2	N_2O	NH_3	$PM_{2.5}$	PM_{10}	PTS
Cars	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	−5.93%	−9.17%	−11.28%
Light commercial vehicles (< 3.5 t)	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	−1.19%	−1.83%	−2.18%
Heavy commercial vehicles	−0.06%	−2.06%	−0.08%	−0.01%	−0.52%	−5.23%	−3.17%	−0.05%	−2.70%	−3.98%	−5.03%
Mopeds	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	−0.02%	−0.03%	−0.04%
Motorcycles	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	−0.10%	−0.16%	−0.19%
Bus and coach	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	−0.12%	−0.20%	−0.25%
Wood-fired generators	−1.98%	−1.34%	−0.06%	−0.03%	−2.59%	0.00%	−3.56%	−0.25%	−5.63%	−4.71%	−3.90%
Other poultry	0.00%	0.00%	0.00%	−0.08%	0.00%	0.00%	−0.42%	−0.55%	−0.14%	−0.24%	−0.27%
Other cattle	0.00%	0.00%	−0.02%	−16.49%	0.00%	0.00%	−11.34%	−5.65%	−0.23%	−0.63%	−1.26%
Fur animals	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	−0.06%	0.00%	0.00%	0.00%
Donkeys and mules	0.00%	0.00%	0.00%	−0.01%	0.00%	0.00%	−0.02%	−0.03%	0.00%	0.00%	0.00%
Buffalo	0.00%	0.00%	0.00%	−0.17%	0.00%	0.00%	0.00%	−0.18%	0.00%	0.00%	−0.01%
Goats	0.00%	0.00%	0.00%	−0.14%	0.00%	0.00%	−0.04%	−0.15%	0.00%	0.00%	0.00%
Horses	0.00%	0.00%	0.00%	−0.14%	0.00%	0.00%	−0.14%	−0.23%	0.00%	0.00%	0.00%
Rabbits	0.00%	0.00%	0.00%	−0.01%	0.00%	0.00%	−0.09%	−0.18%	0.00%	0.00%	0.00%
Hens	0.00%	0.00%	0.00%	−0.12%	0.00%	0.00%	−1.80%	−2.79%	−0.60%	−1.01%	−1.16%
Fattening pigs	0.00%	0.00%	−0.03%	−12.30%	0.00%	0.00%	−13.47%	−7.37%	−0.68%	−1.91%	−3.83%
Sheep	0.00%	0.00%	0.00%	−0.25%	0.00%	0.00%	−0.05%	−0.17%	0.00%	0.00%	0.00%
Pollasters	0.00%	0.00%	0.00%	−0.07%	0.00%	0.00%	−1.55%	−1.39%	−0.52%	−0.87%	−1.00%
Sows	0.00%	0.00%	0.00%	−1.96%	0.00%	0.00%	−0.91%	−0.59%	−0.05%	−0.13%	−0.26%
Dairy cows	0.00%	0.00%	−0.01%	−24.42%	0.00%	0.00%	−12.44%	−14.44%	−0.13%	−0.36%	−0.71%
Comb. Non-industrial	−2.86%	−6.81%	−0.80%	−0.23%	−6.15%	−17.91%	−2.82%	−0.01%	−6.17%	−5.28%	−4.57%
Industry	−81.08%	−26.19%	−39.76%	−13.57%	−29.49%	−50.66%	−9.43%	−0.62%	−17.44%	−18.28%	−19.31%
Waste	−10.31%	−2.93%	−0.29%	−18.38%	−0.75%	−3.31%	−6.16%	−0.60%	−0.36%	−0.31%	−0.27%
Air traffic	−1.45%	−2.43%	−0.08%	0.00%	−0.89%	−0.86%	0.00%	0.00%	−0.12%	−0.10%	−0.08%
Total	−97.74%	−41.75%	−41.14%	−88.37%	−40.40%	−77.96%	−67.42%	−35.33%	−42.14%	−49.21%	−55.58%

comparing the R50 and R80 scenarios. Key observations are as follows.

1) $PM_{2.5}$: the R50 scenario (50% reduction) results in compliance with interim target 2, while interim target 3 can only be achieved through the R80 scenario (80% reduction). A closer examination of the 2018 data reveals that only in the R80 scenario does one background station exhibit a concentration value below 5 μg/m³, while the remaining monitoring stations show concentrations between 5 and 15 μg/m³. Figure 2 illustrates that only 30% of stations have the potential to achieve the proposed $PM_{2.5}$ annual limit.
2) PM_{10}: concentrations in both R50 and R80 scenarios fall between interim target 3 and interim target 4. Further analysis of the 2018 data indicates that in the R80 scenario (80% reduction) nearly all background monitoring stations register concentrations below 20 μg/m³, with 50% of these stations recording values below 15 μg/m³. Only a small number of background stations show annual averages below 10 μg/m³ while concentrations below 15 μg/m³ are observed in just 15% of monitoring traffic stations.
3) NO_2: concentrations in traffic stations appear to be significantly higher than those in background. Overall, the more ambitious AQG level can only be met in all background stations through an 80% reduction. Analyzing in more detail the R80 scenario for the year 2018, all background monitoring stations have concentrations below 10 μg/m³, while only a few traffic stations surpass this threshold in terms of annual averages.

The MRR (technological) scenario indicates that achieving an 80% reduction solely through technical measures may not be feasible

(Table 4) by 2030 at least in Lombardy Region. This aligns with the findings of the IASA work (GAINS models) at the European Level, where the Maximum Technical Feasible Reduction (MTF) for all the pollutants by 2030 is less than 80%.

To achieve an 80% reduction in emissions within the Lombardy Region, in addition to MRR application, it would be necessary to implement drastic reduction in activities. For example, achieving an 80% reduction could involve, among other possible choices: a) removing 75% of vehicles and b) removing 75% of methane domestic heating systems and 100% of biomass domestic heating systems (already with the best technologies) c) reducing pigs and cattle populations by 60% and d) eliminating 75% of industrial activities. It is evident that achieving an 80% reduction, even after implementing the best technologies (i.e., available nowadays), would requires substantial effort to reduce activity level.

It is important to note that the emission reduction activities presented in this study are purely theoretical hypothesis aimed at quantifying the real effort required to comply with the AQG Limits and WHO Guidance Target that would be considered in the new Directive. We should emphasize that these scenarios are based on the currently available technical elements, and we cannot definitively assess their feasibility or prioritize them.

5 Conclusion

This study aims to address the crucial objective of improving air quality and achieving pollutant concentrations recommended by WHO guidelines. The feasibility of emission reduction strategies, particularly an 80% reduction of SO_X, NO_X, PM, NH3, and NMVOC emissions, is thoroughly examined within a limited timeframe. Despite substantial emission reductions (−50% and −80%), the study's findings reveal that the recommended pollutant levels will not be met in most areas of the Po Valley. For $PM_{2.5}$, only the R80 scenario achieves interim target 3, while PM_{10} concentrations in both R50 and R80 scenarios fall between interim target 3 and 4. The more ambitious AQG level for NO_2 can only be met through an 80% reduction in all background stations.

Moreover, to reduce the emissions of all the principal pollutants of 80% is a strong task, not achievable also applying all the best available technologies at all the sectors at least in Lombardia region, but it is necessary also a reduction of the activities levels (such as kilometers done by vehicles, energy used for domestic heating, industrial, agricultural, and breeding production).

Achieving compliance with the new AQG limits is complex process involving multiple stakeholders and different tools. Meeting Air Quality limits requires the adoption of Source-Specific emissions standards at EU level, National Emission reduction Directive that align with the limits defined in Air Quality Directive, and the development of Air Quality Plans at the national, regional, and local level. Only through a strong integration of policies across different sectors and governance levels can compliance with these limits be achieved. Furthermore, the discussion surrounding activity reductions should also include an evaluation of the potential impact of these actions and policies (directives, regulations, and plans) also on different outcomes (GDP, unemployment and so on). Further research efforts, such as employing advanced modeling techniques with the 2019 inventory emissions and applying feasible technical scenarios to multiple models, could provide a deeper understanding of the feasibility and cost implications associated with achieving the desired emission reductions. Additionally, such studies could help identify the key stakeholders and actors involved in the process, which is crucial for effectively implementing the WHO Guidelines.

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

AM and GF organized the emissions database. LC wrote the first draft of the manuscript. LC and AM wrote sections of the manuscript. 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

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New directions for the realisation of SDGs given the economic and welfare costs incurred by air pollution

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Air pollution is a multidisciplinary research field, which affects sustainable development (SD) and Sustainable Development Goals (SDGs). Its multi-level cause and effect shows the direct influence of air pollution on human health, standards and costs of living, health treatment, and the economies of states. Poor air quality, as an SDG factor, may affect both lower wellbeing and economic growth. As developed economies have faced problems due to poor air quality, they have worked out solutions based on their technological engagement. However, emerging economies are still facing poor air quality as a main problem affecting their economic growth. The particulate matter factor, according to the air quality study, was used as the basis for comparative and statistical research. The findings of the study indicate that air pollution causes a serious impact relating to workforce productivity, absence from work, mortality, and even lower crop yields. There is an obvious research gap in the investigated field of comparative studies considering air pollution as an SD factor, understood as an economic concept. Therefore, the current study is proposed to fulfil this gap, contribute to the knowledge base of the factors affecting human development, and expand the statistical data based on the findings from a comparison between Poland and Germany on their performance in air quality tests. This is a novel approach pointing to air pollution as the proposed focus of research for the realisation of SDGs.

KEYWORDS

sustainable development goals, air pollution, sustainable development, socio-economy, welfare, economic costs

1 Introduction

The relationship between economic development and environmental pollution has been the subject of intense research (Fodha and Zaghdoud, 2010; Landrigan, 2016; Tan et al., 2021; Torkayesh et al., 2022). In addition, policymakers have long attempted to promote and sustain economic growth (Sultana et al., 2022) as the basis for the stable and prosperous development of societies. Furthermore, for the development to be sustainable, it must consider social, ecological, and economic issues; the basis of living and non-living resources; and the long- and short-term benefits and drawbacks of alternative actions (Sustainable Development: Evaluation of the Concept and its Economic, Ethical, Political and Cultural Dimension, n.d.). This is typically thought to operate at the crossroads of environmental, economic, and social concerns.

Economic growth, based on the concept of sustainable development, enables emerging economies to gradually close the gap with more developed economies. Activities that develop an

economy in transition may include increasing the standards of living, developing a competitive industrial and commercial base, and improving the infrastructure. Economic growth may also consider access to resources, such as solar energy, clean soil, and air. Moreover, developed economies are not free from the challenges of Sustainable Development Goals (SDGs)—they still reduce the influence of their economics on the natural environment.

Agenda 2030 of the SDGs of the United Nations (Sustainable Development Goals, 2022a) points to goals such as Goal 3, which aims at improving healthcare and wellbeing; Goal 6, which aims at improving access to clean water and sanitation; Goal 8, which is concerned with decent work and economic growth; Goal 10, which aims at reducing equalities; Goal 12, which is regarding responsible consumption and production; and Goal 13, which emphasises climate action for achieving sustained economic growth. Creativity, know-how, technology, and financial resources from all societies are needed to achieve SDGs in every context (Sustainable Development Goals. The SDGs in action. Sustainable Development Goals, 2023). Economic development is not promoted by human or technological capital; instead, it is fuelled by natural resources (Rahim et al., 2021). Furthermore, by 2030, SDG 3.9 aims at substantially reducing the morbidity, mortality, and illnesses caused by hazardous substances and pollution and contamination of air, water, and soil (UNDP, 2022b).

In the European Union, air pollution is considered to be the greatest hazard to the health of the EU residents (Widera et al., 2022). According to Dr Maria Neira, WHO Director, Department of Environment, Climate Change and Health, air pollution is one of the world's biggest public health issues (WHO, 2022). Poisonous air may affect the proper functionality of the immune system and increase the risk of chronic illnesses. Furthermore, it causes vast comprehensive socio-economic disruption, direct and indirectly, positive and negative effects on the environment, like reduction in the water and air quality, ecological restoration, and noise reduction (Chakraborty and Maity, 2020). Table 1 presents the air pollution levels in the two countries examined.

This study aims to formulate a new direction for the realisation of SDGs through an investigation of the role of air pollution as a socio-economic factor in the environmental dimension of sustainable development economic theory. It contemplates air pollution as a factor that influences welfare and has economic costs. However, this exploratory attempt is limited to two countries (Germany and Poland) and is only concerned with data for the year 2020. The results add to the economic knowledge of the development of sustainable development as a concept, especially its environmental dimensions and best practices. Furthermore, this study aims to provide knowledge of current trends in both emerging and developed economies; however, it may be limited by the specificity of the economies on which it focused during the research. The conclusions show that there is a need to conduct research in other economies to fully recognise this problem.

TABLE 1 Air and GHG emissions.

Year	Germany	Poland
2000	9.970	7.570
2001	10.200	7.550
2002	10.030	7.390
2003	10.060	7.680
2004	9.880	7.770
2005	9.680	7.760
2006	9.840	8.080
2007	9.470	8.040
2008	9.580	7.910
2009	8.950	7.570
2010	9.450	7.980
2011	9.110	7.870
2012	9.270	7.710
2013	9.470	7.600
2014	8.930	7.260
2015	8.930	7.350
2016	8.920	7.630
2017	8.700	7.960
2018	8.380	7.920
2019	7.750	7.490
2020	7.040	6.980

Source: Authors' elaboration based on OECD data indicators for CO_2 emissions (OECD, Environmental Performance Reviews: Finland, 2021). Carbon dioxide (CO_2) in tonnes *per capita* for the year 2000–2020 (inclusive).

2 Literature review

Sustainable development means different things to different people, such as ecologists, environmental planners, economists, and activists. The discussion on sustainable development is partly interesting because the concept has been borrowed from both natural and social sciences (Redclift, 1991). The literature indicates that different economies have different policies and standards, particularly related to the environment. Developed economies typically adopt stricter environmental control policies and advanced technologies to reduce environmental pollution (Abdouli and Hammami, 2017). The extant body of literature concerning air pollution can be divided into the following areas: sustainable development as a socio-economic concept and air pollution along an environmental dimension.

Sustainable development is a resource-use pattern that attempts to meet human needs while maintaining the environment; therefore, these needs can be addressed not just now but also in the future. The literature highlights a crucial matter concerning the future of humans (Zhao et al., 2020). As an economic concept, sustainable development is characterised by three dimensions: economic, social, and environmental. Integrating these into public policies presents specific challenges at every stage of the policy cycle (ESCAP and Scientific, 2015). Figure 1 presents sustainable development using the intersecting circle and concentric circle approaches.

Thus, air pollution can be classified as an environmental factor. According to the literature, air quality is a major environmental concern because of rapid changes in pollutant emissions driven by

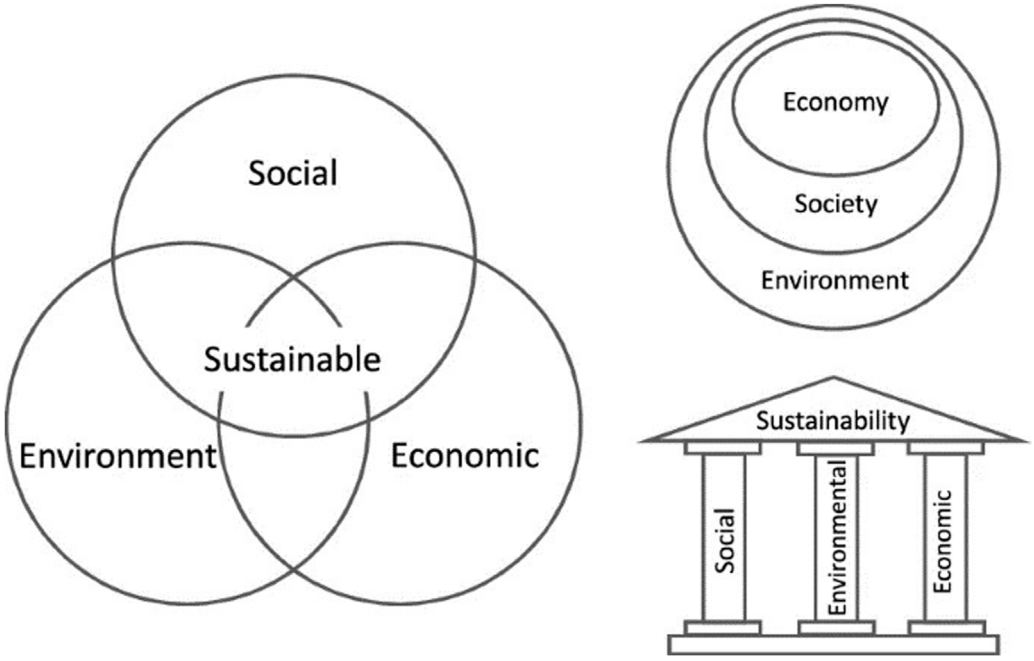

FIGURE 1
Representation of sustainability as three intersecting circles and its alternative depictions using literal pillar and a concentric circle approach. Source: Three pillars of sustainability: in search of conceptual origins (Purvis et al., 2019).

complex and intensive human activities (Tan et al., 2021). In addition to climate change, air pollution and quality are key challenges for cities globally and have significant impact on human health and economic development (Liu et al., 2019). The phenomenon has also been linked to environmental and population health (Watt et al., 2015; Shindell et al., 2017). The description of air pollution has gradually developed to be based on the physical and chemical characteristics of specific pollutants, and the focal point has gradually shifted from single to multiple contaminants (Dominici et al., 2010; Carvalho et al., 2019). Many developed countries with superior air quality have implemented pollution control measures, while developing countries with large populations are entering or about to enter the stage of severe air pollution (Han et al., 2018). Table 2 presents the Global Burden of Diseases (GBD) 2017 risk factor hierarchy based on air pollution.

Reducing air pollution, including greenhouse gas (GHG) emissions originating from the extensive use of fossil fuels, is critical for European countries to improve their environment and achieve carbon neutrality by the middle of this century. To optimally reduce air pollutants and mitigate climate change, national and European Union level regulations and international agreements, such as the SDGs, Kyoto Protocol, and Paris Climate Agreement, must be included in these strategies (Torkayesh et al., 2022). Understanding the extent to which air pollution influences the process of achieving the SDGs may help estimate the benefit of reducing air pollution, so as to improve the attempts at sustainable development and for evaluating the necessity and urgency required to reduce air pollutants and, thus, improve air quality (Zhao et al., 2020). As a large number of people are adversely affected by pollution, the following question arose: "Should environmental concerns not encompass social concerns?" Consequently, not only have the studies in environmental and social fields begun to dovetail, but the study of environmental economics itself has emerged (Rogers et al., 2012).

3 Hypotheses

First, a desk research was conducted. The data used as the base of the research were secondary and included the environmental indicators generated from the 2020 Organisation for Economic Cooperation and Development (OECD). As the comparative method was chosen to verify the hypotheses and the practical aim of the study was to compare emerging and developed economies, Poland and Germany were chosen for analysis. The statistical method, such as the multiple correlation test, was used.

From the aggregate Air Quality Index (AQI), based on the combined effects of five criteria pollutants (CO, SO_2, NO_2, O_3, and PM_{10}) and considering European standards, the particulate matter pollutant, as the most common and measured pollutant in most countries, was chosen for analysis. The usefulness of this factor has been confirmed in previous studies (Zeger et al., 2000; Beloconi et al., 2016; Stafoggia et al., 2017).

The literature indicates that Sweden, Latvia, France, Lithuania, Hungary, and Italy were ranked as the top six countries with the lowest emissions. However, Finland, Poland, the Czech Republic, Luxembourg, and Estonia had the lowest overall rankings and highest *per capita* emissions (Torkayesh et al., 2022). The rankings influenced the choice of countries (economies) to be compared: Poland is an emerging economy with one of the highest emissions, and Germany is a developed economy focussing on green economy development. In addition, strong economic bonds exist between these two economies.

TABLE 2 GBD 2017 risk factor hierarchy and its accompanying exposure definitions, theoretical minimum risk exposure levels, and data representativeness index for each risk factor, pre-2007, 2007–17, and the total (across all years)—air pollution.

1	Risk factor	Exposure definition	Theoretical minimum risk exposure level	Data representativeness index	Risk factor		
2					Before 2007	2007–17	Total
3	Air pollution				100.0%	100.0%	100.0%
4	Particulate matter pollution				82.9%	88.6%	96.4%
5		Ambient particulate matter pollution	Annual average daily exposure to outdoor air concentrations of particulate matter with an aerodynamic diameter of ≤2.5 μm ($PM_{2.5}$), measured in μg/m^3	Joint theoretical minimum risk exposure level, for both household and ambient particulate matter pollution, is a uniform distribution between 2.4 and 5.9 μg/m^3, with the burden being attributed proportionally between household and particulate matter pollution on the basis of the source of $PM_{2.5}$ exposure in the excess of the theoretical minimum risk exposure level	17.1%	57.0%	58.0%
6		Household air pollution from solid fuels	Individual exposure to $PM_{2.5}$ due to the use of solid cooking fuel	Ambient particulate matter pollution	82.9%	63.4%	85.5%
7	Ambient ozone pollution		Seasonal (6-month period with the highest ozone level) 8-h daily maximum ozone concentrations, measured in ppb	Uniform distribution between 29.1 and 35.7 ppb	100.0%	100.0%	100.0%

The data representativeness index was calculated as the percentage of locations for which we had data for a given time period. $PM_{2.5}$, particulate matter with an aerodynamic diameter smaller than 2.5 μm, measured in μm/m^3. ppb, parts per billion. Source: GBD, 2017 Risk Factor Collaborators, 2018.

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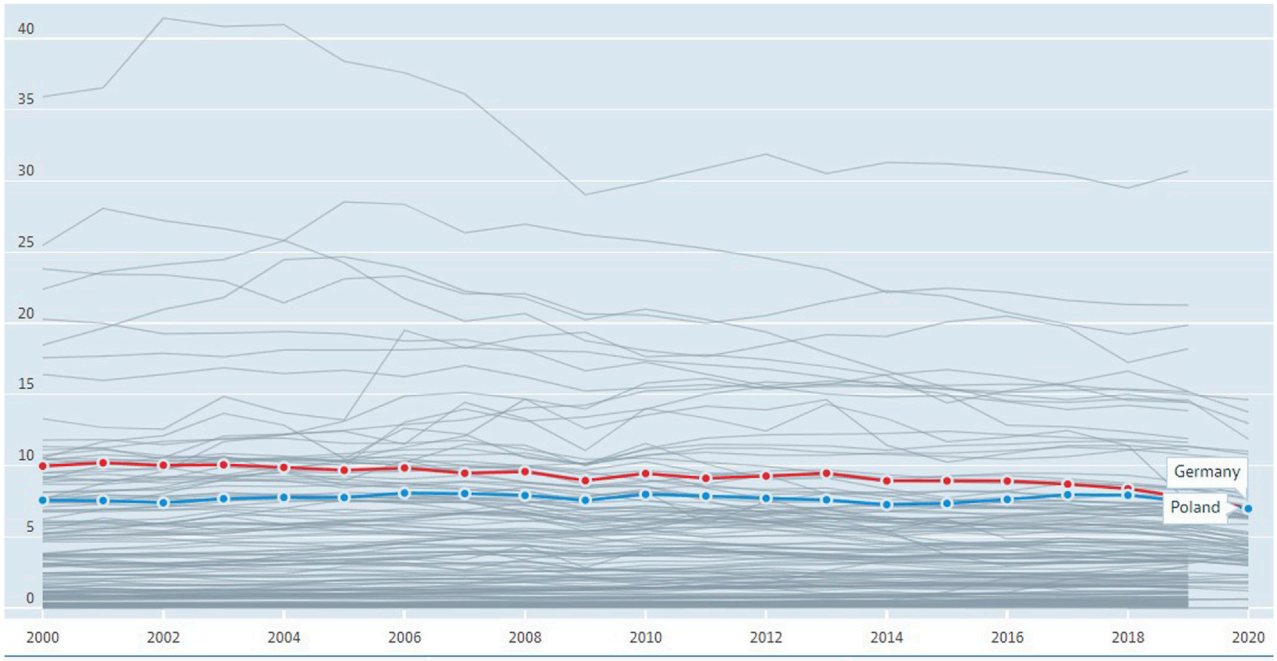

FIGURE 2
Indicators of CO_2 emissions in Germany and Poland during 2000–2020. Source: OECD data indicators for CO_2 emissions.

The proposed methodology consists of the following steps: desk research and data analysis using comparative and statistical methods, in which the use of public statistics data is justified.

To investigate air pollution as a socio-economic factor and to examine its role in the environmental dimension of the sustainable development economic theory concept, based on the aforementioned discussion, the following hypothesis (H) was formulated:

H: Air pollution plays a crucial role in realising SDGs and allows developing sustainable development as an economic concept.

In addition, the following supporting hypotheses were established:

H1: Air pollution is a crucial environmental factor, which helps formulate new directions for SDGs' realisation.

H2: The environmental dimension of sustainable development is becoming increasingly important and is strongly related to healthcare costs.

H3: Air pollution has serious economic implications, particularly at the national level.

4 Results and findings

Here, we consider the impact of generated waste and its collection on the economic, social, and environmental dimensions and the waste collected and treated by or for municipalities. It covers wastes from trade and commerce, hospitals, office buildings, and households, including bulky waste, garden waste, street sweepings, market cleansing waste, and contents of litter containers. These exclude wastes from municipal sewage networks and treatment, as well as waste from construction and demolition activities. This indicator is measured in thousands of tonnes and kilogrammes *per capita* (OECD, Environmental Performance Reviews: Finland, 2021) examined.

At the same time, the purpose of the air, GHG emissions, and CO_2 data was to determine the gross direct emissions from human activities in both Poland and Germany. Figure 2 shows the indicators of CO_2 emissions for both countries during the same period.

Figure 2 shows the position of examined countries at the background of other OECD countries (grey lines).

The data expressed in CO_2 equivalents refer to gross direct emissions from human activities. CO_2 refers to the gross direct emissions from fuel combustion only, and these data are provided by the International Energy Agency (IEA); air and GHG emissions are measured in thousand tonnes, tonnes *per capita*, or kilogrammes *per capita*, except for CO_2, which is measured in million tonnes and tonnes *per capita* (Air and emissions, 2022). For a comparative study, we also compared the data on population exposure to fine particulates in these two countries. This comparison is presented as a percentage in Table 3.

These data are used to find out the percentage of the population that is being exposed to fine particulate ($PM_{2.5}$) concentrations exceeding WHO guidelines (10 μg per cubic metre) and its effect on the population in Poland and Germany. It represents the percentage of the population exposed to fine particulate ($PM_{2.5}$) in the air, which increases the risk of respiratory and cardiovascular diseases in particular. These data indicate the exposure of the population to fine particulate concentrations more than 10 $\mu g/m^3$ and are expressed as annual averages.

TABLE 3 Air pollution exposure of the population of Poland and Germany, at the OECD background, exposed to fine particulates ($PM_{2.5}$), with concentrations exceeding the WHO guidelines (10 µg per cubic metre) in the percentage of the population in years 2000, 2005, and 2010–2019.

Year	Germany	Poland	OECD
2000	99.8	100	87.5
2005	99.3	100	84.2
2010	99.6	100	74.5
2011	99.6	100	76
2012	98.3	100	71.5
2013	98.6	100	69.9
2014	91.9	100	66.6
2015	95.5	100	66.2
2016	88.3	100	61.6
2017	87	100	62.2
2018	88.7	100	62.5
2019	86.8	100	61.7

Source: OECD environmental statistics, air quality, and Health: exposure to $PM_{2.5}$ fine particles—countries and regions (OECD, Environmental Performance Reviews: Finland, 2021) (Environment at a Glance—Climate Change, Compare Your Country, n.d.).

TABLE 4 Mortality attributed to exposure to fine particulates ($PM_{2.5}$), with the annual deaths per million inhabitants during 2000–2019.

Year	Germany	Poland	OECD
2000	505	836	380
2001	482	813	369
2002	468	793	361
2003	454	787	352
2004	431	790	336
2005	422	791	329
2006	419	799	321
2007	424	812	316
2008	434	817	313
2009	445	821	310
2010	447	800	305
2011	432	786	300
2012	412	772	295
2013	391	739	289
2014	360	698	282
2015	349	705	280
2016	331	701	271
2017	320	712	267
2018	320	725	271
2019	324	733	275

Source: OECD environmental statistics, air quality, and health: exposure to $PM_{2.5}$ fine particles—countries and regions (Environment at a Glance—Climate Change, Compare Your Country, n.d.).

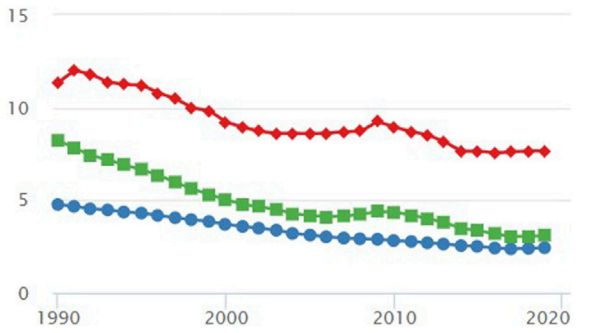

FIGURE 3
Welfare costs of mortality due to exposure to fine particulates in Poland and Germany for the period 1990–2020, as a percentage of GDP equivalent. Presented data are matched with the colours in the following order: Poland, Germany, and OECD overage. Source: OECD environmental statistics, air quality, and health: exposure to $PM_{2.5}$ fine particles—countries and regions (Environment at a Glance—Climate Change, Compare Your Country, n.d.).

The data reveal interesting observations. For example, the emerging economy (Poland) made no progress during the 20-year period, while OECD countries and the developed economy (Germany) made progress on this count during the same period. This is because the developed economy, Germany, made investments in research and development and new technologies, as well as green energy. The economic and social costs incurred by air pollution are mainly related to a shorter life expectancy (real and expected) and health disorders (also understood as healthcare social costs) in the emerging economy (Poland). The social cost of air pollution is also related to mortality, as shown in Table 4.

Figure 3 shows the welfare costs of mortality due to exposure to fine particulates.

The air pollution effect is reflected in the mortality rate per 1,000,000 inhabitants. In 2019, the cost estimate of inhaled fine particulate matter that causes serious health issues, like respiratory and cardiovascular diseases, exerts a significant effect on children and elderly people, increasing their risk of heart diseases and stroke in particular, eventually leading to death. The cost estimate only represents premature mortalities and is calculated using the estimates of the value of a statistical life (VSL) and the number of premature deaths attributable to ambient particulate matter.

Here, the correlations between mortality and air pollution in Poland and Germany were examined. Table 5 shows welfare costs, mortality, and municipal waste.

The data were used to run multiple correlation tests of the following variables: welfare cost of mortality from exposure to fine particulates ($PM_{2.5}$), mortality attributed to the exposure to fine particulates ($PM_{2.5}$), and municipal wastes generated in Germany. Table 6 shows the correlation results.

The results of the correlation test showed that there was a significant positive correlation between the mortality attributed to exposure to fine particulates ($PM_{2.5}$) and the welfare cost of mortality from exposure to fine particulates ($PM_{2.5}$). Compared to that, municipal waste had a less significant positive correlation with both the welfare cost of mortality from exposure to fine particulates ($PM_{2.5}$) and the mortality attributed to exposure to fine particulates ($PM_{2.5}$). The same tests were conducted for Poland, an emerging economy, and the results are shown in Table 7.

TABLE 5 Mortality, welfare costs, and municipal wastes of Germany (the developed economy) for the period 2000–2019.

Variable			
Year	Welfare costs: mortality	Mortality attributed to $PM_{2.5}$	Municipal waste
2000	5	505	648.8
2001	4.8	482	639.3
2002	4.6	468	647.2
2003	4.5	454	608
2004	4.3	431	593.2
2005	4.2	422	570.5
2006	4.1	419	569.8
2007	4.1	424	569.2
2008	4.2	434	596.6
2009	4.4	445	599.1
2010	4.2	447	609.2
2011	4.2	432	621.3
2012	4	412	614.5
2013	3.8	391	610.7
2014	3.5	360	627.4
2015	3.4	349	631.2
2016	3.2	331	634.2
2017	3.1	320	626.6
2018	3.1	320	604.6
2019	3.1	324	606

Source: Authors' own elaboration based on OECD data.

The data were used to run multiple correlation tests of the following variables: welfare cost of mortality from exposure to fine particulates ($PM_{2.5}$), mortality attributed to the exposure to fine particulates ($PM_{2.5}$), and municipal wastes generated in Poland. Table 8 shows the correlation results.

The correlation tests showed a strong positive association between mortality attributed to fine particulate exposure ($PM_{2.5}$) and the welfare cost of mortality from fine particulate exposure ($PM_{2.5}$), whereas municipal wastes showed a less significant positive correlation. In addition, there was a slight negative correlation between the amount of municipal wastes generated and the cost of mortality due to fine particulate exposure.

TABLE 6 Germany: correlation test.

	Year	Welfare costs: mortality	Mortality attributed to $PM_{2.5}$	Municipal waste
Year	1			
Welfare costs: mortality	−0.935504954	1		
Mortality attributed to $PM_{2.5}$	−0.925554468	0.998156632	1	
Municipal waste	0.028839823	0.037511786	0.03574846	1

Source: Authors' own elaboration.

TABLE 7 Correlation test data of mortality, welfare costs, and municipal wastes in Poland (emerging economy) for the period 2000–2019.

Variable			
Year	Welfare costs: mortality	Mortality attributed to $PM_{2.5}$	Municipal waste
2000	836	9.2	317.1
2001	813	8.9	288.3
2002	793	8.7	273
2003	787	8.6	258.2
2004	790	8.6	254.1
2005	791	8.6	317.2
2006	799	8.6	319
2007	812	8.7	319.8
2008	817	8.7	317.9
2009	821	9.2	314.3
2010	800	8.9	313.9
2011	786	8.7	316.8
2012	772	8.5	316.1
2013	739	8.1	296
2014	698	7.6	271.2
2015	705	7.6	285.6
2016	701	7.6	306.8
2017	712	7.6	315.4
2018	725	7.7	329.2
2019	733	7.7	336.6

Source: Authors' own elaboration based on OECD data.

5 Discussion

In 2017, air pollution caused 4.9 million deaths worldwide according to the global burden of death (GBoD) (Stanaway et al., 2018). Owing to the diversity of its diameter and composition type, particulate matter may have multiple effects on the whole body of a person, especially on the cardiovascular and respiratory systems, such as systemic inflammation and oxidative stress, increase in blood pressure, and changes in serum metabolites (Wang et al., 2015; Goudarzi et al., 2018; Mirabelli et al., 2020).

The environmental, behavioural, and metabolic risks that drive injury and disease are the mechanisms through which public health efforts can most efficiently and effectively prevent health loss. Therefore, effective population health improvements require the understanding of not only the injuries and diseases that drive health burdens but also the risks that drive injury and diseases (Landrigan, 2016). Against the backdrop of increasingly diverse multi-contaminant air conditions, human welfare will be seriously threatened if air pollution cannot be scientifically and effectively quantified and properly controlled (Tan et al., 2021). The health effects of particulate matter in Italy have been widely investigated in multicentre projects, evaluating short-term associations between daily particulate matter concentrations and mortality/hospitalisations across several Italian cities (Biggeri et al., 2005). The research on France and Iran (Sicard et al., 2019) showed that long-term exposure to ambient $PM_{2.5}$ and PM_{10} has substantially contributed to mortality and hospital admissions in the selected cities: non-accidental causes, cardiovascular diseases, respiratory diseases, and chronic obstructive pulmonary diseases caused approximately 8,200, 2,400, 540, and 220 deaths, respectively, in 2015; in addition, cardiovascular diseases and respiratory diseases caused 18,800 and 3,400 hospital admissions, respectively. A research, in a national cohort of approximately 2.5 million Canadians, covered pollution exposure and its associations with citizen mortality, which showed that exposure to $PM_{2.5}$, alone, was not sufficient to fully characterise the toxicity of the atmospheric mix or to fully explain the risk of mortality associated with exposure to ambient pollution (Crouse et al., 2015). Increasing evidence suggests that long-term exposure to ambient air pollution is associated with death from cardiopulmonary diseases. A 2002 pilot study reported clear indications that traffic-related air pollution was related to cardiopulmonary mortality in a randomly selected sub-cohort of 5,000 older adults participating in an ongoing Netherlands Cohort Study (Brunekreef et al., 2009). Another study, which was part of the ESCAPE project, measured the concentrations of $PM_{(2.5)}$, $PM_{(2.5)}$ absorbance, $PM_{(10)}$, and PM (coarse) in 20 European study areas at 20 sites per area. Predictor variables (e.g., traffic intensity, population, and land-use) were evaluated to model the spatial variation in the annual average concentrations for each study area. Examination of influential factors and skewed variable distributions was essential for developing stable LUR models, which can be used to estimate air pollution concentrations at the home addresses of participants in the health studies involved in the ESCAPE project (Eeftens et al., 2023). The range and number of studies covered by these topics confirmed and underlined their importance.

TABLE 8 Poland: correlation test.

	Year	Welfare costs: mortality	Mortality attributed to $PM_{2.5}$	Municipal waste
Year	1			
Welfare costs: mortality	−0.8217	1		
Mortality attributed to $PM_{2.5}$	−0.82114	0.973813	1	
Municipal waste	0.391742	0.069979	−0.00643	1

Source: Authors' own elaboration.

For developing risk attribution for particulate matter pollution, the integrated exposure–response curves combine epidemiological data from ambient, household, secondhand, and active smoking sources to construct a risk curve for the full exposure range (Landrigan, 2016). Evidence suggests that exposure to $PM_{2.5}$ might be mechanistically linked to type 2 diabetes through altered lung function, vascular inflammation, and insulin sensitivity (Rajagopalan and Brook, 2012).

Air pollution can affect businesses through reduced workforce productivity, absence from work, premature deaths, and lower crop yields. Air pollution negatively impacts the U.S. economy, costing the U.S. roughly 5% of its yearly gross domestic product (GDP) in damages ($790 billion in 2014) (Mirabelli et al., 2020). The highest costs were on account of early deaths, attributable to the exposure to fine particulate matter ($PM_{2.5}$). While some $PM_{2.5}$ in the atmosphere is due to the result of natural processes, such as forest fires or windblown dust, most damage from $PM_{2.5}$ is related to human activities, most of which can be attributed to different sectors of the economy, such as manufacturing and agriculture. Combining damage with more traditional measures of economic production, such as GDP or gross value added, provides a more accurate picture of a sector's full economic impact (Tschofen et al., 2019). In 2015, the WHO and OECD estimated that the economic cost of premature deaths and disabilities due to air pollution in Europe was close to 1.6 trillion USD. Air pollution takes its toll on the economy in several ways: it costs human lives, reduces people's ability to work, affects vital products, such as food, damages cultural and historical monuments, reduces the ability of ecosystems to perform functions that societies need, and costs money in remediation or restoration (UNECE, 2023). With sustained economic growth, environmental pollution in China has become increasingly serious and displays certain regional differences. Economic growth, energy structure, and industrial pollution in China are spatially correlated, with different agglomeration areas in the spatial distribution. In terms of the temporal dimension, energy consumption and technological pollution effects in China have led to increased environmental pollution, while changes in the structural effect have indirectly improved the environmental situation (Zhang et al., 2020; Zhang et al., 2023). Research indicates that there is a gap between citizens and technologies, which requires the development of more interactive systems and improved citizen education based on the SDGs and air pollution levels (Jasińska-Biliczak, 2022). However, air quality is subjected to many observed and unobserved factors, with evident seasonal changes that may confound the potential impact of enacted policies. Simple before–after comparisons would fail to differentiate the policy impact from such confounding changes and may thus lead to biased and inconsistent results (Qin et al., 2023).

This study summarises a commonly used air pollution measure, which is particulate matter, and the economic consequences of air pollution in countries representing both emerging and developed economies. The sustainability of the integrated approach in the environment and society remains debatable (Fang et al., 2023). It contributes to the discussion on sustainable development as an economic concept for the practical realisation of SDGs. It also contributes to the discussion on the necessity of immediate action toward lowering the welfare cost of mortality due to exposure to polluted air. At the same time, it addresses the research gap regarding the impact of air pollution on economic costs in EU economies. However, the study has a limitation: it considers only two countries (Germany and Poland) and data for the year 2020.

6 Conclusion

This study assesses the environmental risk caused by air pollution across two representative countries. Poland and Germany had similar air quality and GHG emissions *per capita* in 2020. Germany had a score of 7.040, while Poland had a score of 6.980 (approximately 7.000 tonnes *per capita*). This was due to the lockdown measures to prevent COVID-19 from spreading, resulting in a positive effect of COVID-19 in the form of clean air, but only for a short time. Similarly, between 1990 and 2000, the percentage of population of Germany and Poland exposed to fine particles ($PM_{2.5}$) was roughly the same, with Germany having 100%, 99.7%, and 99.8% of its population exposed and Poland having 100%, 100%, and 100% of its population exposed in 1990, 1995, and 2000, respectively. The findings show that pollution poses a high risk of causing negative health effects in both countries' populations; however, there are differences between the emerging and developed economies, with developed economies having an advantage.

In contrast, both countries increased their municipal waste (in kilogrammes *per capita*) from 2019 to 2020. Germany produced twice as much waste as Poland at the same time. It follows that in Germany, the COVID-19 pandemic had a greater impact on waste management than that in Poland. In contrast, from 2000 to 2019, Germany's air and GHG emissions of carbon dioxide (CO_2) in tonnes *per capita* increased, whereas those of Poland decreased. Furthermore, from 2000 to 2019, Germany's average population

exposure to fine particulates ($PM_{2.5}$) in micrograms per cubic metre decreased, while that of Poland increased. This means that people in Poland experienced more negative health effects than those in Germany.

Similarly, mortality due to fine particulate matter ($PM_{2.5}$) was lower in Germany than that in Poland, with annual deaths per million inhabitants being lower in Germany than that in Poland. As a result, Poland had a higher rate of attributed mortality per million inhabitants than Germany. The most recent data of 2020 are not available yet; however, the study indicates that the mortality attributable to COVID-19 and environmental effects will increase. In 2019, Germany had an almost three times higher mortality rate due to exposure than Poland. In contrast, Germany's welfare cost of mortality from fine particulate exposure ($PM_{2.5}$), expressed as a percentage of GDP, was lower than that of Poland.

Moreover, mortality is a socio-economic factor associated with the concept of sustainable development. In addition, it is strictly connected to the environmental dimension of sustainable development because the state of the environment has a direct influence on the number of sick and dying people. It also generates an additional cost for the society, which has to bear these costs for the treatment of people.

Air quality and its influence on health, economically understood as both private and public goods, is the subject of the present study and discussions at different levels. The governments of Poland and Germany should take major steps toward a European green deal accord and zero-pollution policy.

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

Conceptualisation and methodology: AJ-B; analysis: AJ-B and EI; data curation: EI; writing—original draft preparation, review, and editing: AJ-B; visualisation and supervision: AJ-B. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Author EI was employed by Cognizant Technology Solutions.

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

Publisher's note

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China's air quality improvement strategy may already be having a positive effect: evidence based on health risk assessment

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Aiming to investigate the health risk impact of $PM_{2.5}$ pollution on a heavily populated province of China. The exposure response function was used to assess the health risk of $PM_{2.5}$ pollution. Results shows that the total number of premature deaths and diseases related to $PM_{2.5}$ pollution in Shandong might reach 159.8 thousand people based on the new WHO (2021) standards. The health effects of $PM_{2.5}$ pollution were more severe in men than in women. Five of the 16 cities in Shandong had higher health risks caused by $PM_{2.5}$ pollution, including LinYi, HeZe, JiNing, JiNan, and WeiFang. $PM_{2.5}$ pollution resulted in nearly 7.4 billions dollars in healthy economic cost, which accounted for 0.57% of GDP in Shandong in 2021. HeZe, LiaoCheng, ZaoZhuang, and LinYi were the cities where the health economic loss was more than 1% of the local GDP, accounted for 1.30, 1.26, 1.08, and 1.04%. Although the more rigorous assessment criteria, the baseline concentration was lowered by 30 μg/m^3 compared to our previous study, there was no significant increase in health risks and economic losses. China's air quality improvement strategy may already be having a positive effect.

KEYWORDS

health risk, economic loss, $PM_{2.5}$ pollution, exposure, prevention and control strategies

Introduction

Air pollution and population health have always been hot topics in the field of environmental research (1–4). In the past decades, air pollution has caused a series of serious health hazards to people in China (5–8). As one of the main pollutants of air pollution, fine particulate matters ($PM_{2.5}$) contains complex chemical components which including various toxic substances (9–11). Because of its diminutive size, $PM_{2.5}$ can enter in the respiratory tract and lungs (12). Once some toxic substances enter the human bloodstream, they may increase the burden on the heart (13). Long-term exposure to high concentrations of $PM_{2.5}$ will increase the health risk of the population, especially the respiratory diseases and cardiovascular diseases (14, 15). It also increases health care costs in related areas (16).

In previous studies, respiratory disease, cardiovascular disease, and lung disease were typically used as the health endpoints of health risk assessment (14–17). In some studies, asthma, acute bronchitis and chronic bronchitis are also part of the evaluation system (7, 18, 19). Some scholars use country's air quality standards as health guidelines (20). In other studies, the World Health Organization (WHO) air quality guidelines are generally used as the baseline concentration for calculation. No matter which standard is adopted, it reflects people's concern for environmental safety. That focus has been growing in recent years.

In March 2021, the "14th Five-Year Plan for National Economic and Social Development of the People's Republic of China and the Outline of Long-term Goals for 2035" offered to intensify the battle against pollution and basically eliminate heavy pollution days. In October 2021, 10 ministries and commissions including the Ministry of Ecology and Environment and the governments of seven provinces (municipalities) including Shandong jointly issued the "Plan for Comprehensive Control of Air Pollution in Autumn and Winter 2021–2022." 13 of the 16 cities in Shandong were included in the strategic control regions. In the "Action Plan for the Treatment of New Pollutants (2022)" issued by the General Office of the State Council, environmental health risk prevention has also been put at the heart of the case. Reducing the health risks and costs of $PM_{2.5}$ pollution is a growing concern. As one of the most polluted areas in North China, Shandong is still facing a severe situation of air pollution prevention and control (21, 22). And the health and economic costs caused by $PM_{2.5}$ pollution in Shandong should be made seriously.

As the third largest province in GDP in China, Shandong was plagued by air pollution (23). Although air quality in Shandong had been improving in recent years, heavy pollution events were still common in some cities (24–26). At present, only a few developed cites in Shandong have publicly reported the health risk of $PM_{2.5}$, such as Jinan and Qingdao (27, 28). There was not any accurate data on the health cost of $PM_{2.5}$ pollution for the whole Shandong Province. According to the relevant studies in key regions such as Beijing-Tianjin-Hebei, Yangtze River Delta and Pearl River Delta, the health cost of $PM_{2.5}$ pollution exposure might accounts for 0.3–1.0% of the total annual GDP (18, 29–33). In 2021, the health cost caused by $PM_{2.5}$ pollution in Shandong Province was preliminarily estimated to be about 3.86–12.88 billion dollars. On September 22, 2021, the WHO further improved the original air quality guidelines based on the conclusions of the current important reports by global scholars, and lowered the annual recommended level of $PM_{2.5}$ from 10 $\mu g/m^3$ to 5 $\mu g/m^3$. The 24-h recommended level of $PM_{2.5}$ was reduced from 25 $\mu g/m^3$ to 15 $\mu g/m^3$. The reduction in the health guideline concentration means a change in the original health risk assessment criteria for $PM_{2.5}$ exposure. It also implies that the economic cost of $PM_{2.5}$ exposure may have been underestimated.

In order to understand the $PM_{2.5}$ health risk in Shandong Province. In this study, the health and economic effects of $PM_{2.5}$ exposure in Shandong were evaluated using the new WHO guidelines as health threshold. The evaluation results were also compared with our previous study to discuss the impact of the new WHO guidelines on health risk assessment. Finally, the prevention and control strategies of air pollution in China were discussed based on the evaluation results. Therefore, this study will help clarify the health costs of $PM_{2.5}$ pollution and fill the gap on the health economic effects of $PM_{2.5}$ pollution in Shandong Province. It also provided scientific reference for the optimization of air pollution control strategy in China.

Materials and methods

Location information

Shandong Province is situated in the North China Plain, on the east coast of China. It consists of 16 cities (Figure 1). It covers an area of 158,000 square kilometers and has a population of over 101.5 millions (2021). Basic data in 16 cities of Shandong Province was shown in Table 1. The annual average concentration of $PM_{2.5}$ was 39 $\mu g/m^3$, a year-on-year improvement of 15.2% (2021). The annual average concentration of 39 $\mu g/m^3$ was well above the new health guidelines of WHO. The Ambient Air Quality Composite Index, which takes into account the concentrations of six pollutants including $PM_{2.5}$, PM_{10}, SO_2, NO_2, CO, and O_3, is used to rank the air quality of 168 key Chinese cities. In this comprehensive index ranking of 168 key cities in China, four cities including Zibo, Liaocheng, Heze and Zaozhuang were in the bottom 20. The situation of air pollution prevention and control in Shandong province was still serious.

$PM_{2.5}$ concentration data

Shandong is one of the provinces with serious air pollution in north China, especially in the western part of Shandong. According to the Bulletin of Ecological Environment of Shandong Province (BEESP 2021), only four cities had $PM_{2.5}$ concentrations that met the II-level National Guidance Standard, including Qingdao, Yantai, Weihai, and Rizhao. The remaining 12 cities had average annual concentrations of more than 35 $\mu g/m^3$. All of the 16 cities failed to meet WHO health guideline. In this study, the $PM_{2.5}$ data was obtained from the Bulletin of Ecological Environment of Shandong Province (BEESP 2021),[1] Shandong Environmental Air Quality Status Report (SEAQSR 2021),[2] and the Official website of Shandong Department of Ecology and Environment.[3]

Population health information

Since population health data were difficult to obtain, the health data used in this study mainly came from the Disease and Health Status Report of Residents in Shandong Province (DHSR 2016; it can be obtained by contacting corresponding author) and the Report on Incidence and Mortality of Key Chronic Diseases in Shandong Province (RIMKCD 2018; it can be obtained by contacting corresponding author). The health cost data was obtained from the Statistical Bulletin of Health Development of Shandong Province (SBHDSP 2021).[4] Population data were obtained from the Seventh National Census (SNC 2021)[5] published in May 2021. This study also assessed the health risks of $PM_{2.5}$ for different genders in Shandong. The Male/Female ratio was from the public security household

1 http://xxgk.sdein.gov.cn/xxgkml/hjzkgb/202206/P020220607364593369389.pdf

2 http://www.shandong.gov.cn/art/2022/1/24/art_305267_10331968.html?xxgkhide=1

3 http://sthj.shandong.gov.cn/zwgk/sqcspm/

4 http://www.shandong.gov.cn/art/2023/1/10/art_305258_10333917.html

5 http://tjj.shandong.gov.cn/art/2021/5/21/art_156112_10287516.html

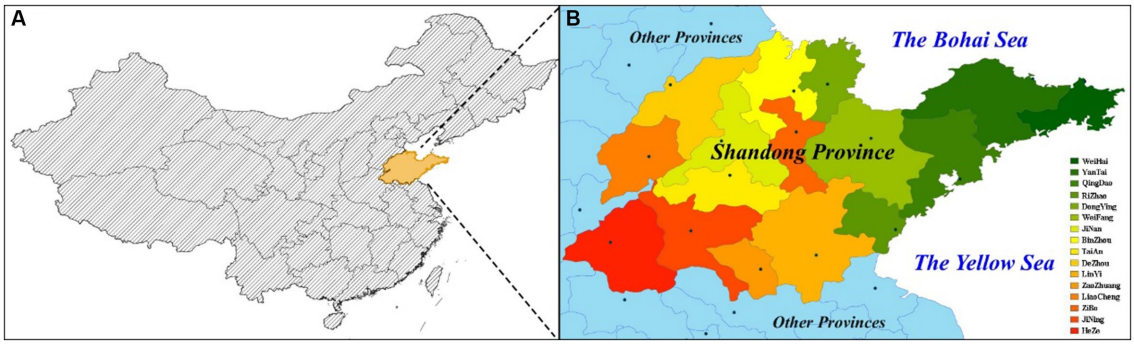

FIGURE 1
(A) Shandong Province within China; **(B)** Cities in Shandong Province.

registration statistics in Shandong Statistical Yearbook (SSY 2022).[6] Area data was drawn from government portals.

$PM_{2.5}$ health effect assessment

To assess the health risks of $PM_{2.5}$ exposure, the first step should be to correlate $PM_{2.5}$ concentrations with population health. Therefore, it is a critical step to determine the exposure response coefficients used in this work. In this study, all exposure response coefficients were referenced from our earlier studies and other recent relevant studies in China (18, 27, 34–36). Table 2 presents the baseline incidence for six health endpoints in Shandong Province.

In a large population, the occurrence of disease can be regarded as a low probability event (18, 27). Therefore, its probability of occurrence should conform to the Poisson distribution (34). In this study, the health risk was calculated with the PM exposure response function which was the WHO recommended model for health effect estimation in high PM concentration area (WHO, 2006). There are four major factors in the Equations (1) and (2), which including population size, $PM_{2.5}$ concentration, exposure response coefficient, and the baseline incidence of health endpoint.

$$E_i = E_0 \exp\left[\beta_i \left(C - C_0\right)\right] \tag{1}$$

$$\Delta E = P\left(E_i - E_0\right) = P\left\{1 - \frac{1}{\exp\left[\beta_i \left(C - C_0\right)\right]}\right\} E_i \tag{2}$$

Here, E_0 is baseline incidence of a disease, E_i is the estimated incidence of health endpoint i under $PM_{2.5}$ concentration C, C_0 is the baseline concentration of $PM_{2.5}$ (set as 5 μg/m^3, the new WHO annual guideline concentration), C is the exposure concentration of $PM_{2.5}$, β_i is the exposure response coefficient. P is the population size, ΔE is for population health risks associated with $PM_{2.5}$ pollution. In this study, C_0 refers to the new WHO standards.

6 http://tjj.shandong.gov.cn/tjnj/nj2022/zk/zk/indexch.htm

TABLE 1 Basic data in 16 cities of Shandong Province.

Districts	$PM_{2.5}$ annual average concentration (μg/m^3)	Residents (million people)	Male/female ratio	Area (Km^2)
WeiHai	24	2.907	0.978	5,799
YanTai	27	7.102	0.985	13,864
QingDao	28	10.072	0.973	11,293
Rizhao	31	2.968	1.034	5,358
DongYing	36	2.194	0.986	8,243
WeiFang	38	9.387	1.015	16,167
JiNan	40	9.202	0.982	10,244
BinZhou	40	3.929	1.018	9,660
TaiAn	42	5.472	1.020	7,762
DeZhou	42	5.611	1.028	10,356
LinYi	43	11.018	1.071	17,191
ZaoZhuang	45	3.856	1.098	4,564
LiaoCheng	46	5.952	1.058	8,628
ZiBo	47	4.704	0.985	5,965
JiNing	47	8.358	1.064	11,187
HeZe	48	8.796	1.093	12,239

$PM_{2.5}$ economic effect assessment

In this study, health economic losses were estimated using health risk assessment results and average disease costs. The economic effect of $PM_{2.5}$ was assessed with the following equation:

$$EC_i = \Delta E \cdot \cos t_i \tag{3}$$

where EC_i is the total cost of health endpoint i; $Cost_i$ is the cost per case.

Here, the health economic effect of hospitalization was estimated using the cost of illness (COI) method (7, 18, 27). Hospitalization costs were obtained from the SBHDSP 2021. Premature death cost was estimated using the method of value of

statistical life (VSL) (37). VSL refers to the willingness-to-pay of patients to avoid risk of death. Since willingness-to-pay usually increases with people's income, a adjusted equation was utilized to correct VSL in this study (27). The *per capita* income was obtained from Shandong Statistical Yearbook. The adjusted equation of VSL as following:

$$VSL_{now} = VSL_{past}\left(\frac{Income_{now}}{Income_{past}}\right)^{e} \quad (4)$$

where VSL_{now} and VSL_{past} refers to current and past willingness to pay; $Income_{now}$ and $Income_{past}$ represents current and past *per capita* income; e is an elastic coefficient of willingness-to-pay assumed to be 0.8. In this study, VSL was adjusted twice because it lacked a reliable reference value in Shandong. Firstly, it was adjusted to get VSL_{2021} based on VSL_{2016} in Jinan. Then, it was adjusted again to get $VSL_{Shandong}$ based on the VSL_{Jinan} in 2021.

Results and discussion

$PM_{2.5}$ concentration status report

Pollutant concentration is one of the important factors affecting health risk assessment results (38–40). High levels of $PM_{2.5}$ exposure will increase the risk of some health endpoints such as respiratory, cardiovascular and lung diseases (41–43). As shown in Figure 2, the $PM_{2.5}$ concentration was relatively low in the area of Shandong Peninsula. While it had a high concentration in the western area of Shandong province. Industrial distribution and regional differences, as well as unbalanced economic development, might lead to the spatial differences in $PM_{2.5}$ concentration in Shandong. The $PM_{2.5}$ concentrations of 16 cities in Shandong Province have been provided in Table 1. Therefore, the health effects of $PM_{2.5}$ pollution were likely to be greater in the western area of Shandong province without considering the influence of population density factor. $PM_{2.5}$ pollution might have great impact on the four cities including Heze, Jining, Zibo, and Liaocheng.

TABLE 2 Baseline incidences and exposure-response coefficients associated with 10 μg m^{-3} increment of $PM_{2.5}$.

Health endpoints	Incidence			Coefficients β_i (95% CI)	References
	Male	Female	All		
All-cause mortality	0.0081804	0.0064967	0.0073556	0.0090 (0, 0.0180) (35)	RIMKCD (2018)
Cardiovascular mortality	0.0021664	0.0022355	0.0022003	0.0053 (0.0085, 0.0201) (34)	RIMKCD (2018)
Respiratory mortality	0.0006453	0.0005697	0.0006078	0.0143 (0.0085, 0.0201) (34)	DHSR (2016)
Lung-cancer mortality	0.0008456	0.0004147	0.0006345	0.0340 (0, 0.0710) (34)	RIMKCD (2018)
Cardiovascular hospital admission	0.0154545	0.0185454	0.017	0.0068 (0.0043, 0.0093) (18)	CHSY (2021)
Respiratory hospital admission	0.0199091	0.0238909	0.0219	0.0109 (0, 0.0221) (18)	CHSY (2021)
Lung-cancer morbidity	0.0009505	0.0005583	0.0007554	0.0340 (0, 0.0710) (27)	RIMKCD (2018)

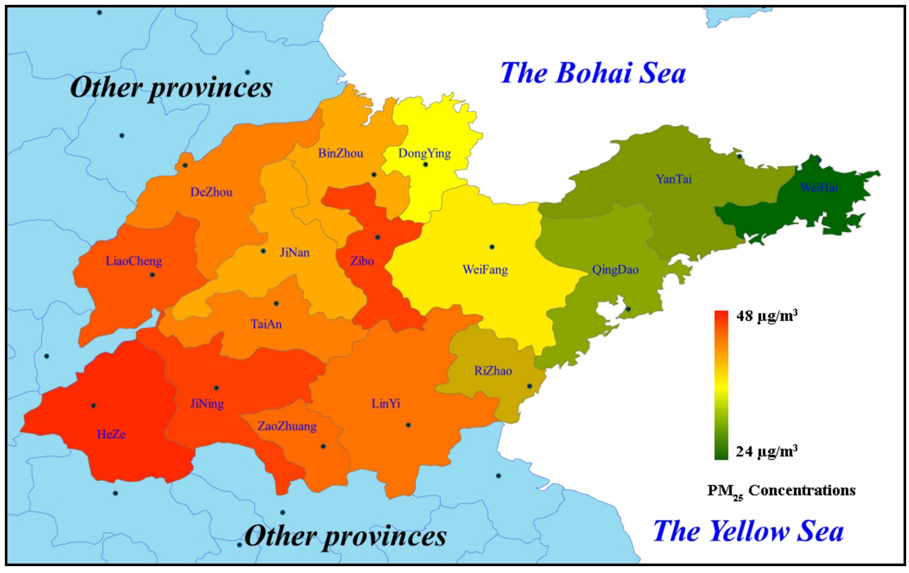

FIGURE 2
$PM_{2.5}$ concentrations in 16 cities of Shandong Province in 2021.

TABLE 3 Health effect of $PM_{2.5}$ in Shandong in 2021.

Gender	Health endpoints	WeiHai	YanTai	QingDao	Rizhao	DongYing	WeiFang	JiNan	BinZhou	TaiAn	DeZhou	LinYi	ZaoZhuang	LiaoCheng	ZiBo	JiNing	HeZe	Sum.	Annual %**
Male	All-cause mortality	203	577	850	292	252	1,166	1,194	519	765	788	1,622	605	941	736	1,358	1,483	13,349	1.79
	Cardiovascular mortality	*32*	*90*	*132*	*45*	*39*	*181*	*185*	*80*	*119*	*122*	*251*	*94*	*146*	*114*	*210*	*229*	*2,068*	*0.93*
	Respiratory mortality	*26*	*73*	*107*	*37*	*32*	*147*	*151*	*66*	*97*	*100*	*205*	*77*	*119*	*93*	*172*	*188*	*1,689*	*2.74*
	Lung-cancer mortality	*81*	*231*	*342*	*118*	*102*	*475*	*487*	*212*	*313*	*322*	*665*	*249*	*387*	*303*	*559*	*611*	*5,458*	*8.47*
	Cardiovascular hospital admission	289	821	1,210	416	359	1,658	1,697	738	1,088	1,120	2,305	860	1,337	1,045	1,929	2,106	18,978	1.10
	Respiratory hospital admission	599	1,703	2,511	863	745	3,448	3,530	1,534	2,264	2,330	4,797	1,790	2,784	2,177	4,018	4,388	39,483	1.78
	Lung-cancer morbidity	91	260	384	133	115	534	548	238	352	362	747	279	435	341	629	687	6,135	8.00
Female	All-cause mortality	165	465	694	224	203	912	965	405	596	609	1,203	438	706	593	1,013	1,077	10,268	1.37
	Cardiovascular mortality	*33*	*94*	*140*	*45*	*41*	*184*	*194*	*81*	*120*	*122*	*242*	*88*	*142*	*119*	*204*	*217*	*2,067*	*0.93*
	Respiratory mortality	*23*	*65*	*97*	*31*	*29*	*128*	*136*	*57*	*84*	*86*	*169*	*62*	*99*	*84*	*143*	*152*	*1,444*	*2.34*
	Lung-cancer mortality	*41*	*115*	*172*	*56*	*51*	*229*	*243*	*102*	*151*	*154*	*304*	*111*	*179*	*151*	*258*	*274*	*2,592*	*4.02*
	Cardiovascular hospital admission	354	1,000	1,492	483	436	1,961	2,074	870	1,280	1,307	2,583	940	1,516	1,273	2,176	2,313	22,058	1.28
	Respiratory hospital admission	735	2,075	3,096	1,002	907	4,076	4,313	1,809	2,663	2,720	5,375	1,957	3,158	2,652	4,532	4,818	45,889	2.06
	Lung-cancer morbidity	55	155	232	75	69	309	328	137	203	207	410	149	242	203	347	369	3,489	4.55
All	All-cause mortality	369	1,045	1,550	517	457	2,081	2,166	925	1,363	1,398	2,820	1,040	1,646	1,333	2,368	2,553	23,628	3.16
	Cardiovascular mortality	*65*	*183*	*272*	*91*	*80*	*364*	*379*	*162*	*238*	*244*	*493*	*182*	*288*	*233*	*414*	*446*	*4,134*	*1.85*
	Respiratory mortality	*49*	*138*	*205*	*68*	*60*	*276*	*287*	*123*	*181*	*185*	*374*	*138*	*218*	*177*	*314*	*339*	*3,132*	*5.08*
	Lung-cancer mortality	*123*	*350*	*520*	*174*	*155*	*707*	*738*	*315*	*465*	*477*	*964*	*356*	*565*	*458*	*814*	*879*	*8,061*	*12.51*
	Cardiovascular hospital admission	643	1,820	2,699	900	795	3,621	3,768	1,609	2,370	2,430	4,903	1,807	2,861	2,317	4,116	4,437	41,096	2.38
	Respiratory hospital admission	1,332	3,775	5,600	1,868	1,651	7,529	7,837	3,346	4,932	5,057	10,204	3,763	5,957	4,826	8,574	9,244	85,496	3.85
	Lung-cancer morbidity	147	417	619	207	184	842	878	375	554	568	1,148	424	673	545	969	1,046	9,597	12.51
	Sum.*	2,490	7,056	10,467	3,493	3,087	14,074	14,649	6,255	9,219	9,453	19,075	7,035	11,136	9,021	16,028	17,279	159,817	/

Male + Female≠All. Baseline incidence was calculated separately, which caused this error (<3%).

*Sum = *All cause mortality + Respiratory hospital admission + Cardiovascular hospital admission + Lung-cancer morbidity*.

**Cases caused by $PM_{2.5}$/annual cases of this health endpoint.

Italics: All-cause mortality including Cardiovascular mortality, Respiratory mortality, and Lung-cancer mortality.

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$PM_{2.5}$ health risk assessment

As shown in Table 2, the baseline incidences of health endpoints were provided. The incidences of cardiovascular and respiratory diseases were obtained from China Health Statistics Yearbook (CHSY, 2021)[7] Male/Female incidences were calculated based on the hospitalization rate of residents and the sex ratio of hospitalized patients in the national survey data in 2018. Due to the exposure-response coefficient of lung cancer morbidity cannot be obtained, its coefficient referred to lung-cancer mortality in this work.

The evaluation result showed that the premature death related to $PM_{2.5}$ pollution contributed 3.16% of all-cause deaths (shown in Table 3). Among them, the proportion of male was 1.79%, and the proportion of female was 1.37%. Cardiovascular mortality, respiratory mortality, and lung-cancer mortality related to $PM_{2.5}$ pollution contributed 1.85, 5.08, and 12.51%, respectively, to annual cases of these health endpoints. Cardiovascular hospital admission, respiratory hospital admission, and lung-cancer morbidity related to $PM_{2.5}$ pollution contributed 2.38, 3.85, and 12.51% to yearly cases of these health endpoints. The four health endpoints related to $PM_{2.5}$ pollution including all-cause mortality, respiratory mortality, lung-cancer mortality, and lung-cancer morbidity in male were higher than those in female. The contribution of cardiovascular mortality in male and female was roughly equal. The contributions of cardiovascular and respiratory hospital admission in female were higher than those in male. This result was consistent with the findings reported by Bell et al. (44) and Sang et al. (45). Bell et al. (44) pointed out that women might be more susceptible to $PM_{2.5}$-related hospitalizations for some respiratory and cardiovascular causes. Sang et al. (45) suggested that global ambient $PM_{2.5}$ pollution caused more premature deaths and consumption in men than in women. Therefore, $PM_{2.5}$ pollution had a greater impact on respiratory mortality and lung-cancer mortality and morbidity in male. And it also made a significant contribution to all-cause premature deaths in male. While it played an import role on cardiovascular and respiratory hospital admission in female. As a whole, the health consequences of $PM_{2.5}$ pollution appeared to be more severe in male than in female. For male, more attention should be paid to daily physical examination to reduce the premature death risk from diseases related to $PM_{2.5}$ pollution, especially respiratory system examination including lungs and respiratory tract.

Based on the evaluation results of this study, the number of premature deaths and illnesses related to $PM_{2.5}$ pollution in Shandong Province reached 159,817 in 2021. Without considering population density, LinYi, HeZe, JiNing, JiNan and WeiFang had higher health risks caused by $PM_{2.5}$ pollution. In each of these cities, more than 14,000 people experienced premature death or morbidity due to $PM_{2.5}$ pollution. Only three cities, WeiHai, DongYing and Rizhao, were less impacted by $PM_{2.5}$ pollution in terms of health risk. The number of premature deaths and illnesses affected by $PM_{2.5}$ in each of these areas was less than 5,000. Therefore, further strengthening the control of $PM_{2.5}$ emission will have a positive effect on population health, especially in areas with high health risks.

$PM_{2.5}$ health economic costs

Health economic effect assessment is an important means to evaluate the economic burden of environmental pollution to a city (46–49). The value of statistical life (VSL) method was a common method to assess the health cost of premature death in previous studies (34). The occurrence of respiratory and cardiovascular diseases is closely related to PM pollution, which has been confirmed in many previous studies (50–54). Therefore, the hospitalization costs for respiratory and cardiovascular diseases were also assessed in addition to premature death endpoint in this study. Since the exact cost of each disease could not be obtained, the mean hospitalization cost was selected as the reference value for calculation in this work. Owing to the high mortality rate of lung-cancer, its health cost was estimated using VSL method in this study. The costs of premature death and hospitalization were shown in Table 4. Finally, the economic effect related to $PM_{2.5}$ pollution was assessed based on the result of health risk assessment.

Some scholars suggested that the health economic costs caused by $PM_{2.5}$ pollution could be around 1% of GDP (7, 22). As shown in Table 5, the health economic loss of each heath endpoint related to $PM_{2.5}$ pollution was estimated. It resulted in nearly 7.4 billions dollars in healthy economic cost, which accounted for 0.57% of GDP in Shandong in 2021. This result was basically consistent with our previous study in Beijing. It accounted for 0.87, 0.54, and 0.45% of GDP in Beijing during 2014–2016, respectively (34). The percentage of health economic loss in GDP was lower than other long-term exposure studies in China (18, 27, 35). It may be due to the failure to account for outpatient costs, such as asthma, acute bronchitis and chronic bronchitis. In addition, the reduction of air pollution in China may also be a factor in the falling economic costs of health (34, 55, 56).

Overall, the health economic effects were higher for male than for female in Shandong. The health economic costs of male and female accounted for 0.336 and 0.239% of GDP, respectively. In terms of the health effects in cities, LinYi, HeZe, JiNing, JiNan, WeiFang, and LiaoCheng were the cities where the health economic cost was more than 500 millions. For the proportion of health economic cost, HeZe, LiaoCheng, ZaoZhuang, and LinYi were the cities where it was more than 1% of GDP, accounted for 1.30, 1.26, 1.08, and 1.04% of the GDP in local areas. On the whole, the

7 https://www.doc88.com/p-11461558491027.html

TABLE 4 Health cost situation.

Health endpoints	Costs (US$)				Approach	References
	Hospital	Community health center	Town and township hospital	Mean		
Mortality	/	/	/	219,000	VSL	Yin et al. (35)
Hospital admission	1,753	607	450	937	COI	SBHDSP (2021)

TABLE 5 Health economic effect of $PM_{2.5}$ exposure in Shandong in 2021 (million US$).

Gender	Health endpoints	WeiHai	YanTai	QingDao	Rizhao	DongYing	WeiFang	JiNan	BinZhou	TaiAn	DeZhou	LinYi	ZaoZhuang	LiaoCheng	ZiBo	JiNing	HeZe	Sum.	EC_i/GDP (%)**
Male	All-cause mortality	44.5	126.4	186.2	63.9	55.2	255.4	261.5	113.7	167.5	172.6	355.2	132.5	206.1	161.2	297.4	324.8	2923.9	0.227
	Cardiovascular mortality	*7.0*	*19.7*	*28.9*	*9.9*	*8.5*	*39.6*	*40.5*	*17.5*	*26.1*	*26.7*	*55.0*	*20.6*	*32.0*	*25.0*	*46.0*	*50.2*	*453.1*	*0.035*
	Respiratory mortality	*5.7*	*16.0*	*23.4*	*8.1*	*7.0*	*32.2*	*33.1*	*14.5*	*21.2*	*21.9*	*44.9*	*16.9*	*26.1*	*20.4*	*37.7*	*41.2*	*370.1*	*0.029*
	Lung-cancer mortality	*17.7*	*50.6*	*74.9*	*25.8*	*22.3*	*104.0*	*106.7*	*46.4*	*68.5*	*70.5*	*145.6*	*54.5*	*84.8*	*66.4*	*122.4*	*133.8*	*1195.1*	*0.093*
	Cardiovascular hospital admission	0.3	0.8	1.1	0.4	0.3	1.6	1.6	0.7	1.0	1.0	2.2	0.8	1.3	1.0	1.8	2.0	17.8	0.001
	Respiratory hospital admission	0.6	1.6	2.4	0.8	0.7	3.2	3.3	1.4	2.1	2.2	4.5	1.7	2.6	2.0	3.8	4.1	37.0	0.003
	Lung-cancer morbidity	19.9	56.9	84.1	29.1	25.2	116.9	120.0	52.1	77.1	79.3	163.6	61.1	95.3	74.7	137.8	150.5	1343.6	0.104
Female	All-cause mortality	36.1	101.8	152.0	49.1	44.5	199.7	211.3	88.7	130.5	133.4	263.5	95.9	154.6	129.9	221.8	235.9	2248.7	0.175
	Cardiovascular mortality	*7.2*	*20.6*	*30.7*	*9.9*	*9.0*	*40.3*	*42.5*	*17.7*	*26.3*	*26.7*	*53.0*	*19.3*	*31.1*	*26.1*	*44.7*	*47.5*	*452.5*	*0.035*
	Respiratory mortality	*5.0*	*14.2*	*21.2*	*6.8*	*6.4*	*28.0*	*29.8*	*12.5*	*18.4*	*18.8*	*37.0*	*13.6*	*21.7*	*18.4*	*31.3*	*33.3*	*316.5*	*0.025*
	Lung-cancer mortality	*9.0*	*25.2*	*37.7*	*12.3*	*11.2*	*50.2*	*53.2*	*22.3*	*33.1*	*33.7*	*66.6*	*24.3*	*39.2*	*33.1*	*56.5*	*60.0*	*567.4*	*0.044*
	Cardiovascular hospital admission	0.3	0.9	1.4	0.5	0.4	1.8	1.9	0.8	1.2	1.2	2.4	0.9	1.4	1.2	2.0	2.2	20.7	0.002
	Respiratory hospital admission	0.7	1.9	2.9	0.9	0.8	3.8	4.0	1.7	2.5	2.5	5.0	1.8	3.0	2.5	4.2	4.5	43.0	0.003
	Lung-cancer morbidity	12.0	33.9	50.8	16.4	15.1	67.7	71.8	30.0	44.5	45.3	89.8	32.6	53.0	44.5	76.0	80.8	764.3	0.059
All	All-cause mortality	80.8	228.9	339.5	113.2	100.1	455.7	474.4	202.6	298.5	306.2	617.6	227.8	360.5	291.9	518.6	559.1	5175.2	0.402
	Cardiovascular mortality	*14.2*	*40.1*	*59.6*	*19.9*	*17.5*	*79.7*	*83.0*	*35.5*	*52.1*	*53.4*	*108.0*	*39.9*	*63.1*	*51.0*	*90.7*	*97.7*	*905.3*	*0.070*
	Respiratory mortality	*10.7*	*30.2*	*44.9*	*14.9*	*13.1*	*60.4*	*62.9*	*26.9*	*39.6*	*40.5*	*81.9*	*30.2*	*47.7*	*38.8*	*68.8*	*74.2*	*685.9*	*0.053*
	Lung-cancer mortality	*26.9*	*76.7*	*113.9*	*38.1*	*33.9*	*154.8*	*161.6*	*69.0*	*101.8*	*104.5*	*211.1*	*78.0*	*123.7*	*100.3*	*178.3*	*192.5*	*1765.1*	*0.137*
	Cardiovascular hospital admission	0.6	1.7	2.5	0.8	0.7	3.4	3.5	1.5	2.2	2.3	4.6	1.7	2.7	2.2	3.9	4.2	38.5	0.003
	Respiratory hospital admission	1.2	3.5	5.2	1.8	1.5	7.1	7.3	3.1	4.6	4.7	9.6	3.5	5.6	4.5	8.0	8.7	80.1	0.006
	Lung-cancer morbidity	32.2	91.3	135.6	45.3	40.3	184.4	192.3	82.1	121.3	124.4	251.4	92.9	147.4	119.4	212.2	229.1	2101.5	0.163
	Sum.*	114.9	325.4	482.8	161.1	142.7	650.6	677.5	289.3	426.7	437.6	883.1	325.8	516.1	418.0	742.7	801.0	7395.3	0.574
	EC_{city}/GDP_{city}(%)#	0.21	0.24	0.22	0.47	0.27	0.60	0.38	0.65	0.92	0.81	1.04	1.08	1.26	0.64	0.95	1.30	0.57	/

*Sum = All cause mortality + Respiratory hospital admission + Cardiovascular hospital admission + Lung-cancer morbidity.

**Economic costs caused by health endpoint *i*/the GDP in Shandong in 2021.

Economic costs caused by PM2.5/the local GDP in 2021.

Italics: All-cause mortality including Cardiovascular mortality, Respiratory mortality, and Lung-cancer mortality.

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economic cost of health in highly polluted and densely populated areas in Shandong was higher than that in other cities. It also led to a heavier fiscal burden for these areas.

Policies implication

Since the publication of the WHO Air Quality Guidelines - Global Update 2005 (AQG2005), it has had a positive impact on air pollution control policies around the world (57, 58). AQG2005 provided the first globally referenced framework for air pollution control targets and established transitional targets based on the potential risk of death from long-term exposure to each pollutant (59–61). It was then adopted by many highly polluted regions and countries as progressive targets for the gradual reduction of air pollution (62). China also updated its Air Quality Standards in 2012, and included $PM_{2.5}$ and O_3 in monitoring projects for the first time (63). With the progress of science, the monitoring capabilities of environmental and health and the level of exposure and risk assessment had gradually improved (64). It led a significant increase in scientific evidence of the health hazards of air pollution (65, 66). Finally, WHO updated the AQG again in September 2021 on the basis of comprehensive analysis and scientific assessment of the literature and results over the past 15 years. Air quality standards have become more stringent.

As air quality standards have been ever more stringent, $PM_{2.5}$ health guideline has also been changed and further reduced. Population health risks and economic effects assessed based on the new WHO standards should be higher than that using the previous air quality standards. However, the increase of health risks and economic costs related to $PM_{2.5}$ pollution was not very significant compared with our previous study. Considering these differences in population, economy, and environment, making a direct comparison between Shandong and Beijing may not be entirely appropriate. The total health effects and economic losses caused by $PM_{2.5}$ pollution may vary greatly in the two regions. Therefore, in order to reduce the uncertain impact of these factors, this study only compared the proportion of $PM_{2.5}$ pollution-related health endpoints and the proportion of economic loss in local GDP between the two regions. Finally, whether it was the proportion of affected population or the proportion of health economic costs, the results of this study were comparable to our previous assessment of Beijing in 2015 (34). In our previous study of Beijing, it was the Class II limit values of the National Ambient Air Quality Standard (35 $\mu g/m^3$) that used as the baseline concentration to complete the health risk assessment work. It was a full 30 $\mu g/m^3$ higher than the baseline concentration used in this study. The fact that the health and economic effects related to $PM_{2.5}$ did not increase significantly under the stricter standards can only be attributed to the possibility that China's air pollution control measures were having a positive effect. The annual $PM_{2.5}$ concentration assessed in this study should be at least 30 $\mu g/m^3$ lower than that in Beijing in 2015. In fact, the $PM_{2.5}$ concentration in Beijing was 80.6 $\mu g/m^3$ in 2015, while it was 39 $\mu g/m^3$ in Shandong in 2021. Therefore, with the positive effect of China's air pollution control measures, the nationwide decrease in $PM_{2.5}$ concentration was the main reason why the health and economic effects related to $PM_{2.5}$ pollution had not increased substantially in this study. China's air quality improvement strategy had started to pay off, which was confirmed in this study from the perspective of health risk assessment.

Although the results of this study were mainly based on the analysis of $PM_{2.5}$ pollution in Shandong Province, they still provided side evidence for the positive effects of air quality improvement strategies in China. In the follow-up studies, strengthening regional difference analysis and long-term assessment may be more valuable for evaluating China's air quality prevention and control strategies. In addition, how to tailor the prevention and control strategies of different regions according to the health risks of regional populations should also attract the attention of decision-making departments. Reducing population health risks should be the ultimate goal of improving air quality.

Conclusion

In this study, the exposure response function was used to assess the health risks of $PM_{2.5}$ pollution in Shandong Province. The cost of illness (COI) method and value of statistical life (VSL) method were used to estimate the health economic losses associated with $PM_{2.5}$ pollution. The new WHO (2021) Health Guidelines were used as the $PM_{2.5}$ baseline concentration in this study. The health risks and economic effects of $PM_{2.5}$ exposure in 16 cities in Shandong Province were assessed separately. Results showed that despite a 30 $\mu g/m^3$ reduction in $PM_{2.5}$ baseline concentration compared to our previous study, there was no significant increase in health risks and economic losses. About 159.8 thousand people died or became ill prematurely due to $PM_{2.5}$ pollution, which caused a health economic loss of about 7.4 billion dollars in Shandong. The health economic cost accounted for about 0.57% of GDP in Shandong in 2021. It was similar to our previous assessment of the economic effects of $PM_{2.5}$ pollution in Beijing in 2015. Therefore, under the more stringent criteria, there was no qualitative change in the assessment of health risks and economic losses, which proved that China's air pollution prevention and control strategy might already be having a positive effect.

Data availability statement

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

Author contributions

XX: Writing – review and editing, Conceptualization, Methodology, Project administration. WZ: Writing – review and editing. XS: Review and editing. ZS: Writing – review and editing, Formal Analysis. WC: Review and editing. YW: Writing – review and editing. HM: Writing – review and editing. TL: Writing – review and editing. ZW: Review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Effects of air pollution on emergency visits for acute otitis media among children: a case-crossover study in Chongqing, China

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Background: Many epidemiological studies have demonstrated the short-term effects of air pollution on acute otitis media (AOM) in children, but few studies have explored the association between AOM and air pollution in Chinese children. This study aimed to analyze the effects of air pollution on emergency visits for AOM among children through a time-stratified case-crossover design in Chongqing, China.

Methods: The outpatient medical records of children from nine main urban districts who presented with AOM between December 22, 2018 and December 21, 2021 were collected from the Children's Hospital of Chongqing Medical University. Data for air pollution variables, including the air quality index (AQI), particulate matter $\leq 10\,\mu m$ (PM_{10}), $PM_{2.5}$, SO_2, CO, NO_2 and O_3 from 17 monitoring sites were collected. Data for meteorological factors as confounding variables also were collected. Conditional logistic regression was used to analyze the data with single-pollutant models, multi-pollutant models, and stratified analyses.

Results: Increases in AQI, PM_{10}, $PM_{2.5}$, SO_2, CO and NO_2 were positively associated with emergency visits for AOM among children in single-pollutant models and stratified analyses. Increases in PM_{10}, SO_2, CO and NO_2 were positively associated with emergency visits for AOM among children in multi-pollutant models. NO_2 had the most statistically significant OR values in all models, whereas significant effects of O_3 were observed only in seasonal stratification. In single-pollutant models, we found that the best lag periods were lag 0–7 for air pollution variables except for O_3 and the largest OR values were 1.185 (95%CI: 1.129–1.245) for SO_2 in single-pollutant models. In stratified analyses, there were no difference between groups in these statistically significant OR values through gender and age stratification, while the differences between seasons in these OR values of PM_{10}, SO_2, CO, NO_2 and O_3 were statistically significant. Children aged 0 years and 3–5 years represented the most susceptible population, and among the seasons, susceptibility was greater during Winter and Spring.

Conclusion: Short-term exposure to air pollution can increase emergency visits for AOM among children in Chongqing, China.

KEYWORDS

air pollution, air quality index, particulate matter, acute otitis media, children, case-crossover

1. Introduction

Acute otitis media (AOM) is one of the most common emergencies encountered in pediatrics and otolaryngology departments. It is an acute infectious inflammation of the mucous membrane of the middle ear, with sudden earache as the main manifestation, and in some children, AOM may be accompanied by tinnitus, hearing loss, ear discomfort, and ear discharge. If timely treatment is not administered, AOM can cause tympanic membrane perforation, hearing loss, or even chronic suppurative otitis media, which can create heavy burden for children and their families (1). The anatomical structure of children's middle ears is smaller and shorter than that of adults, and the Eustachian tube is more neatly arranged horizontally. Accordingly, the incidence of AOM is higher in children than in adults (2). Globally, more than 80% of children under the age of 3 years have suffered from otitis media, and 30%–45% of them have experienced two or more episodes of AOM (3).

Otitis media is a multifactorial disease, with known risk factors including infection, Eustachian tube dysfunction, allergies, immunological disorders, gastroesophageal reflux, and various environmental factors. However, due to their immature immune system and lungs, children have a higher respiratory rate and spend more time breathing through their mouths than adults (4). These factors combined with their participation in more outdoor activities make them more sensitive to air pollution exposure. Indeed, the effects of air pollution on children's otitis media have received increasing attention from researchers. One pathogenic mechanism involves interaction of pollutants with the Eustachian tube epithelium upon entry into the nasopharynx, which can directly cause swelling of the Eustachian tube mucosa, resulting in Eustachian tube stenosis (5). Second, pollutants may interfere with the clearance of mucocilia, which also can lead to Eustachian tube dysfunction (6). Eustachian tube dysfunction and stenosis ultimately lead to middle ear infection and effusion (7, 8).

Many epidemiological studies around the world have demonstrated the short-term and long-term effects of air pollution on AOM in children (9–13). However, few studies have explored the association between AOM and air pollution in Chinese children. Two birth cohort studies conducted in Changsha, China confirmed the effects of NO_2, particulate matter ≤10 μm (PM_{10}) and SO_2 on the onset of early AOM in children (14, 15). Additionally, a limited number of Chinese reports describe analyses of the short-term correlation between air pollution and AOM in China through simple cross-sectional studies (16–18). However, these studies did not control for confounding factors such as meteorological factors and personal characteristics, nor did they consider lag effects. Therefore, the present study aimed to analyze the effects of air pollution on emergency visits for AOM among children after controlling for meteorological factors and personal characteristics through a case-crossover design.

2. Materials and methods

2.1. Study region

Chongqing is located in southwest China and is one of the four municipalities directly under the Central Government of China. As an important industrial city in the upper reaches of the Yangtze River, it is among the most heavily polluted cities in the country. Starting in 2013, Chongqing become one of the first 74 cities to implement the new air quality standard in China. The monitoring sites in Chongqing could real-time monitor the concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, and CO.

At present, Chongqing has nine main urban districts, including the Yuzhong District, Dadukou District, Jiangbei District, Shapingba District, Jiulongpo District, Nanan District, Beibei District, Yubei District, and Banan District. The Children's Hospital of Chongqing Medical University is the only public children's hospital in Chongqing and is currently the third ranked children's hospital in China. It has two hospital locations in Yubei District and Yuzhong District in Chongqing, and the average number of outpatient visits in the otolaryngology department daily ranges from 900 to 1,100. Because this hospital is the most popular choice for the treatment of children with AOM in this urban area, a large sample of cases treated at this hospital can be considered representative.

2.2. AOM visits

The outpatient medical records of children treated for AOM between December 22, 2018 and December 21, 2021 were collected from the Children's Hospital of Chongqing Medical University. Children from all nine main urban districts of Chongqing were included according to the following criteria: (1) age 0–18 years; (2) main complaint of ear pain, ear discharge, ear tightness, ear discomfort, hearing loss or other related symptoms; (3) residential address in one of the nine main urban districts; (4) diagnosis of AOM according to the 10th edition (ICD-10) codes H65.0 (acute serous otitis media), H65.1 (other acute nonsuppurative otitis media), or H66.0 (acute suppurative otitis media); and (5) first visit for AOM was in our hospital. Because the course of AOM is 1–2 weeks, review within 2 weeks or multi-department visits for the same disease was only counted as one visit, and the first visit date was taken as the basis.

The following exclusion criteria were applied: (1) prior treatment of AOM in another hospital, or only review in our hospital; (2) absence of symptoms related to AOM, with otitis media found incidentally during physical examination or for another reason; or (3) AOM referred to as previous disease during hospital visit. These types of cases were excluded due to the inaccuracy of the onset date, which could affect the results of the study.

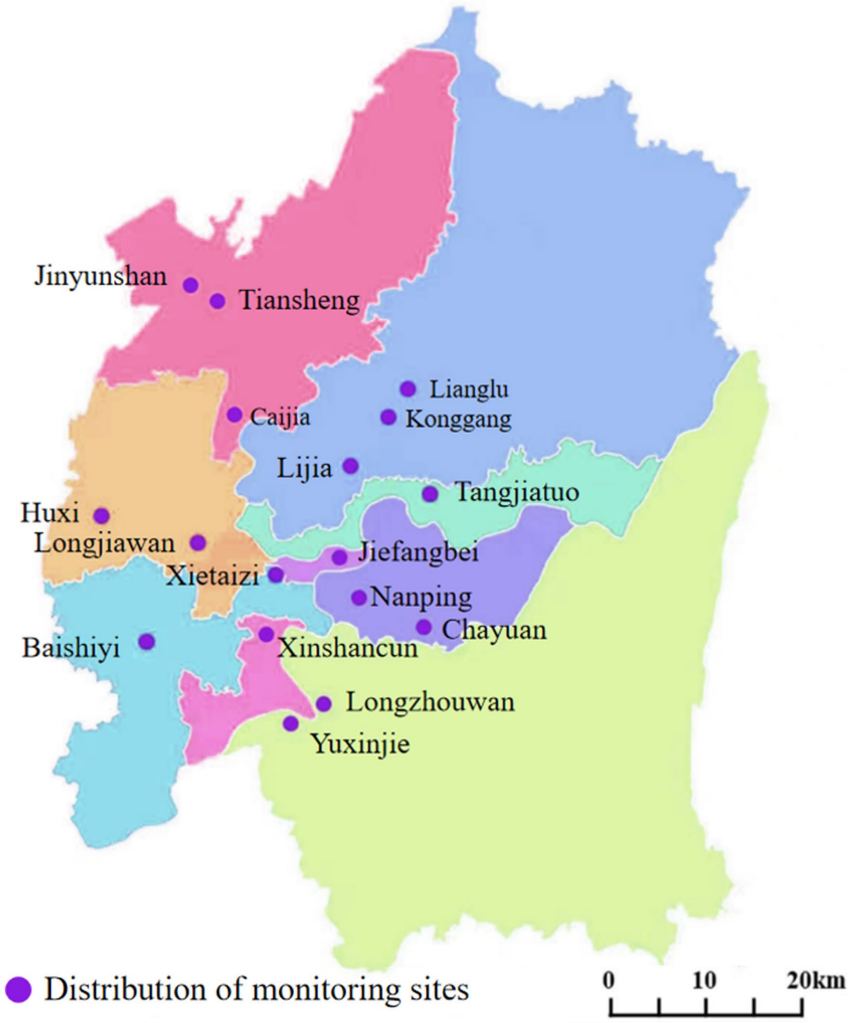

FIGURE 1
Locations of air quality-monitoring stations in the main urban areas of Chongqing.

The following data were collected for each included case: patient serial number, sex, date of birth, date of visit, residential address, and chief complaint. The total number of daily cases was calculated.

The research protocol was approved by the Medical Ethics Committee of our hospital, and the research team was committed to protecting patient privacy. Because this study retrospectively collected data from medical records, consent from the patients' guardians was not required.

2.3. Pollution and meteorological data

The data for air pollutant levels in the main urban area of Chongqing were obtained from a report issued by the Environmental Protection Bureau. The time period was from December 22, 2018 to December 21, 2021. The report included data from the following 17 monitoring sites in the main urban area. The specific locations of the monitoring sites are shown in Figure 1. The average daily AQI and daily concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, CO and O_3 were collected. AQI is a dimensionless index that is determined by taking the maximum values for air quality sub-indexes of PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, and CO from the Technical Regulation on Ambient Air Quality Index of China (NO: HJ633-2012) (19). The PM_{10}, $PM_{2.5}$, SO_2, NO_2, and O_3 levels were reported in units of $\mu g/m^3$, and the CO level as mg/m^3. The average concentrations of PM_{10}, $PM_{2.5}$, SO_2, NO_2, and CO were obtained by averaging the hourly concentrations sampled 24 times a day. For O_3, the 8-h maximum average in a day was used.

The meteorological data for Chongqing were collected between December 22, 2018 and December 21, 2021 from the China Meteorological Data Sharing Service System with a spatial resolution of $0.0625° \times 0.0625°$.[1] The collected data included the daily average values for temperature, relative humidity, atmospheric pressure, and wind speed.

1 http://data.cma.cn/

2.4. Study design and statistical analyses

The study employed a time-stratified, case-crossover design and can be viewed as a special case–control study. In this design, each case serves as its own control to control for the potential confounding influence of individual characteristics, such as age, sex, and family economic conditions. This method has been widely used in epidemiological studies to explore the risks of acute events (20). Considering that the medication period for AOM is 1–2 weeks after diagnosis, children will not seek treatment again even if air pollution levels increase during this time. As a result, we selected three control time points for each case of 2 weeks after and 1 and 2 weeks before the day of the emergency visit.

SPSS 23 software was used for statistical analyses of the case characteristics, air pollution variables, and meteorological variables. Correlation analysis was conducted between meteorological variables and air pollution variables. Pearson correlation test was used for data that followed a normal distribution, and Spearman test was used for data not consistent with a normal distribution. Then, a conditional logistic regression method was used with the daily number of patients as the weight through the Cox regression module in the SPSS software (21). Meteorological factors that could affect AOM visits and levels of air pollution variables were viewed as control variables in the model. The model was as follows:

$$\ln\left(h\left(t,X\right)\right) = \ln\left(h_{0i}\left(t\right)\right) + T\beta_1 + RH\beta_2 + AP\beta_3 + WS\beta_4 + C\left(AQI\right)\beta_5 + C\left(PM_{10}\right)\beta_6 + C\left(PM_{2.5}\right)\beta_7 + C\left(SO_2\right)\beta_8 + C\left(CO\right)\beta_9 + C\left(NO2\right)\beta_{10} + C\left(O_3\right)\beta_{11}$$

where, "t" refers to the day; "X" refers to the emergency visit; "ln (h (t, X))" refers to the risk function; "ln (h0i (t))" refers to the baseline risk function; "T, RH, AP and WS" refer to the temperature, relative humidity, atmospheric pressure and wind speed, respectively; "C (AQI), C (PM_{10}), C ($PM_{2.5}$), C (SO_2),C (CO), C (NO_2), C (O_3)" are the corresponding values of AQI or the concentrations of air pollutants; and "β_1-β_{11}" refers to the coefficient for each covariate. Results were represented by the percentage change in the number of daily visits caused by an increase in AQI and air pollutant concentrations, in the form of odds ratios (ORs) and the corresponding 95% confidence intervals (CIs).

The health effects of air pollutants have a lag effect, and Wong et al. (22) reported that a single lag model may underestimate the health impact of air pollutants. Therefore, the present study used a lag model that included single-day lags from lag 0 to lag 7 and multi-day lags from lag 0–1 to lag 0–7. Lag 0 referred to the day on which AOM was diagnosed, and lag 1 corresponded to the previous day, up to lag 7. Lag 0–1 referred to the 2-day mean for the same day and previous day, and lag 0–7 referred to the 8-day mean for the same day and all days to 7 days before. The meteorological variables were also lagged when the pollution data lagged in a lagged model. In addition, the best lag periods for air pollution variables were determined according to the maximum values of odds ratios (ORs) in the single-pollutant model.

To adjust for the potential effect of modification such as gender, age and season on the results, cases in this study were stratified according to gender (male and female), age group (0, 1–2, 3–5, and 6–17 years), and season (Spring, Summer, Autumn, and Winter). The health effect values for air pollution variables were analyzed with stratification. The differences were tested for statistical significance by calculating 95% CIs based on the following formula:

$$\left(\hat{Q}_1 - \hat{Q}_2\right) \pm 1.96\sqrt{\left(S\hat{E}_1\right)^2 + \left(S\hat{E}_2\right)^2}$$

where $\hat{Q}_1$ and $\hat{Q}_2$ are the effect estimates for the two categories, and $S\hat{E}_1$ and $S\hat{E}_2$ are their respective standard errors (23).

3. Results

3.1. Characteristics of pediatric patients with AOM

A total of 21,416 children were included in this study, with a male to female ratio of 1.12:1 (11,329:10087). The median age at onset was 4.410 years (3.360 years, 6.015 years). Figure 2A shows the number of cases according to different ages. The 3- to 5-year age range included the largest number of patients, accounting for 57.49% of all patients (n = 12,311). Figure 2B shows the number of cases diagnosed in each month. The month in which the highest number of cases presented was December followed by November and then January.

3.2. Summary statistics for air pollution and meteorological variables

Table 1 shows the summarized data for air pollution variables (AQI, PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, and CO) and meteorological

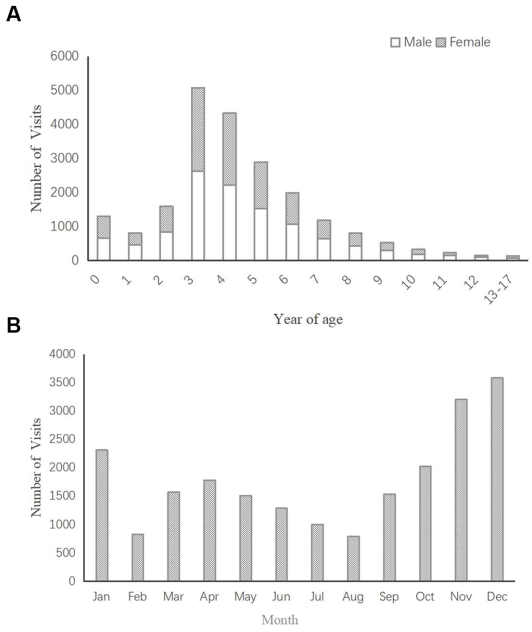

FIGURE 2
(A) Distribution of AOM visits by age (n = 21,416). **(B)** Distribution of AOM visits by month (n = 21,416).

TABLE 1 Summary statistics for air pollution and meteorological variables (AQI is unitless; CO concentration is reported as mg/m^3; and PM_{10}, $PM_{2.5}$, SO_2, NO_2 and O_3 concentrations are reported as μg/m^3).

Variables	All				Spring	Summer	Autumn	Winter
	Min	Max	Mean ± SD	IQR	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
AQI	21.00	203.00	66.69 ± 29.25	38.00	62.39 ± 23.47	68.79 ± 35.26	56.56 ± 21.05	79.12 ± 30.04
PM_{10}	14.00	198.00	54.74 ± 38.52	35.75	54.58 ± 18.45	36.83 ± 13.27	48.07 ± 25.13	79.89 ± 33.45
$PM_{2.5}$	8.00	143.00	34.96 ± 21.02	24.00	32.61 ± 11.15	20.78 ± 7.52	29.24 ± 15.93	57.56 ± 24.31
SO_2	1.00	17.00	8.13 ± 2.28	3.00	8.11 ± 2.13	7.39 ± 1.85	8.13 ± 2.35	8.91 ± 2.47
CO	0.30	1.70	0.79 ± 0.178	0.20	0.75 ± 0.13	0.71 ± 0.12	0.76 ± 0.16	0.93 ± 0.20
NO_2	9.00	76.00	36.32 ± 11.58	15.00	38.61 ± 10.67	30.22 ± 8.33	36.53 ± 12.17	39.97 ± 12.22
O_3	5.00	277.00	72.27 ± 50.14	68.00	84.07 ± 45.25	111.95 ± 50.19	56.85 ± 41.00	35.36 ± 21.61
Temp	4.20	35.60	19.31 ± 7.58	13.58	19.29 + 4.57	28.18 ± 3.41	19.33 ± 5.55	10.28 ± 2.46
RH	39.80	97.00	75.80 ± 10.83	15.20	73.84 ± 10.37	72.52 ± 12.62	79.72 ± 10.11	77.19 ± 8.16
AP	965.00	1005.10	983.12 ± 8.87	15.40	981.85 ± 6.34	972.81 ± 3.21	986.38 ± 6.71	991.62 ± 5.34
WS	0.00	3.70	1.21 ± 0.42	0.50	1.29 ± 0.45	1.29 ± 0.45	1.12 ± 0.37	1.11 ± 0.36

Spring refers to March, April, and May; Summer refers to June, July, and August; Autumn refers to September, October, and November; and Winter refers to December, January, and February. Temp, temperature; RH, relative humidity; AP, atmospheric pressure; WS, wind speed.

TABLE 2 Spearman correlation coefficients for correlations between air pollution variables and meteorological variables.

	AQI	PM_{10}	$PM_{2.5}$	SO_2	CO	NO_2	O_3	Temp	RH	AP	WS
AQI	1										
PM_{10}	0.743**	1									
$PM_{2.5}$	0.646**	0.965**	1								
SO_2	0.543**	0.617**	0.531**	1							
CO	0.507**	0.653**	0.673**	0.264**	1						
NO_2	0.576**	0.729**	0.657**	0.451**	0.691**	1					
O_3	0.262**	−0.155**	−0.273**	0.060*	−0.264**	−0.153**	1				
Temp	0.005	−0.437**	−0.560**	−0.092**	−0.355**	−0.303**	0.760**	1			
RH	−0.514**	−0.274**	−0.134**	−0.470**	0.038	−0.163**	−0.629**	−0.344**	1		
AP	0.015	0.386**	0.474**	0.126**	0.255**	0.308**	−0.656**	−0.873**	0.267**	1	
WS	−0.099**	−0.145**	−0.157**	−0.225**	−0.116**	−0.126**	0.130**	0.119**	−0.126**	−0.158**	1

Temp, temperature; RH, relative humidity; AP, atmospheric pressure; WS, wind speed. *$p < 0.05$, **$p < 0.01$.

variables (mean temperature, relative humidity, atmospheric pressure, and wind speed) during the study period. The results show that the AQI value, the concentrations of PM_{10}, $PM_{2.5}$, CO, SO_2, CO and NO_2 were highest in Winter, whereas the highest concentrations of O_3 occurred in Summer. Because these variables were not normally distributed, the Kruskal Wallis test was used to compare the values of variables among different seasons, and the results suggested that all observed group differences were statistically significant.

3.3. Correlations between air pollution variables and meteorological variables

The Spearman test was used to identify correlations between different air pollution variables and meteorological variables. As shown by the data in Table 2, PM_{10} and $PM_{2.5}$ were most strongly correlated (correlation coefficient = 0.965, $p < 0.01$).

3.4. Single-pollutant models for the associations between air pollution variables and emergency visits for AOM in children

Table 3 shows the results from the single-pollutant models for air pollution variables after controlling for the meteorological factors. Increases in AQI and the concentrations of PM_{10}, $PM_{2.5}$, SO_2, CO and NO_2 were significantly associated with an increased risk for emergency visits for AOM, while no significant association was detected for changes in the concentrations of O_3. The strongest effect on emergency visits was observed on the lag 0–7 model except for O_3, and the largest OR was 1.185 (95% CI, 1.129–1.245) for SO_2.

3.5. Multi-pollutant models for associations between air pollution variables and emergency visits for AOM in children

AQI is not one pollutant as PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, or CO. It is the maximum value reflecting the air quality sub-indexes for six

TABLE 3 Associations between air pollution variables (per IQR increase in AQI and the concentrations of air pollutants) and emergency visits for AOM in children: single-pollutant models.

	AQI	PM_{10}	$PM_{2.5}$	SO_2	CO	NO_2	O_3
L0	1.000 (0.975–1.025)	1.006 (0.984–1.028)	1.001 (0.980–1.022)	1.010 (0.983–1.038)	1.019 (0.997–1.041)	1.031* (1.004–1.057)	0.980 (0.935–1.028)
L1	1.018 (0.993–1.044)	1.019 (0.996–1.042)	1.015 (0.993–1.037)	1.017 (0.990–1.045)	1.021 (1.000–1.044)	1.049** (1.022–1.076)	0.968 (0.923–1.015)
L2	1.027* (1.002–1.053)	1.035** (1.012–1.058)	1.031** (1.009–1.053)	1.031* (1.003–1.059)	1.020 (0.999–1.042)	1.054** (1.028–1.082)	0.962 (0.918–1.009)
L3	1.063** (1.038–1.089)	1.059** (1.037–1.083)	1.057** (1.035–1.079)	1.072** (1.043–1.101)	1.047** (1.025–1.069)	1.080** (1.052–1.108)	1.017 (0.970–1.066)
L4	1.056** (1.031–1.082)	1.065** (1.042–1.089)	1.060** (1.039–1.083)	1.077** (1.049–1.107)	1.062** (1.040–1.085)	1.087** (1.060–1.116)	0.976 (0.931–1.023)
L5	1.071** (1.046–1.097)	1.074** (1.050–1.097)	1.072** (1.050–1.094)	1.088** (1.059–1.118)	1.065** (1.043–1.088)	1.097** (1.069–1.126)	0.971 (0.926–1.018)
L6	1.081** (1.055–1.107)	1.077** (1.053–1.101)	1.075** (1.053–1.098)	1.081** (1.052–1.111)	1.064** (1.041–1.086)	1.097** (1.069–1.126)	1.003 (0.957–1.050)
L7	1.092** (1.066–1.119)	1.084** (1.061–1.108)	1.081** (1.059–1.104)	1.085** (1.056–1.115)	1.065** (1.043–1.088)	1.111** (1.083–1.140)	0.985 (0.940–1.032)
L0-1	1.011 (0.983–1.038)	1.014 (0.989–1.038)	1.008 (0.986–1.032)	1.017 (0.985–1.050)	1.023 (0.999–1.048)	1.048** (1.019–1.078)	0.968 (0.915–1.024)
L0-2	1.020 (0.990–1.050)	1.024 (0.998–1.051)	1.018 (0.994–1.043)	1.029 (0.993–1.067)	1.025 (0.999–1.051)	1.060** (1.029–1.092)	0.954 (0.894–1.018)
L0-3	1.044** (1.012–1.077)	1.044** (1.016–1.072)	1.037** (1.011–1.064)	1.064** (1.024–1.107)	1.040** (1.012–1.068)	1.083** (1.049–1.117)	0.976 (0.908–1.050)
L0-4	1.059** (1.025–1.095)	1.059** (1.029–1.089)	1.037** (1.011–1.064)	1.095** (1.050–1.141)	1.040** (1.012–1.068)	1.102** (1.066–1.139)	0.973 (0.900–1.053)
L0-5	1.079** (1.043–1.116)	1.076** (1.044–1.108)	1.068** (1.039–1.098)	1.128** (1.080–1.179)	1.071** (1.040–1.103)	1.122** (1.085–1.161)	0.971 (0.892–1.056)
L0-6	1.097* (1.059–1.136)	1.089** (1056–1.123)	1.081** (1.050–1.112)	1.152** (1.100–1.206)	1.081** (1.049–1.115)	1.137** (1.097–1.177)	0.971 (0.892–1.056)
L0-7	1.123** (1.082–1.165)	1.107** (1.072–1.143)	1.098** (1.065–1.132)	1.185** (1.129–1.245)	1.097** (1.062–1.133)	1.159** (1.117–1.202)	0.971 (0.892–1.056)

L, lag. L0 refers to day of AOM diagnosis, and L1 corresponds to the previous day, up to L7. L0-1 refers to the 2-day mean for the same day and previous day, and L0-X refers to the X + 1-day mean for the same day and all days to X days before. *$p < 0.05$, **$p < 0.01$ adjusted for temperature, relative humidity, atmospheric pressure, and wind speed.

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TABLE 4 Associations between air pollution variables (per IQR increase in AQI and the concentrations of air pollutants) and emergency visits for AOM in children: multi-pollutant models.

	PM_{10} (lag 0–7)	SO_2 (lag 0–7)	CO (lag 0–7)	NO_2 (lag 0–7)	O_3 (lag 3)
Adjusted for PM_{10}	/	1.131** (1.049–1.219)	1.035 (0.985–1.087)	1.168** (1.097–1.243)	1.014 (0.967–1.063)
Adjusted for SO_2	1.041 (0.991–1.094)	/	1.038 (0.997–1.082)	1.125** (1.066–1.187)	1.018 (0.971–1.068)
Adjusted for CO	1.079* (1.028–1.133)	1.145** (1.076–1.218)	/	1.171** (1.108–1.237)	1.010 (0.963–1.059)
Adjusted for NO_2	0.992 (0.939–1.047)	1.056 (0.982–1.135)	0.988 (0.941–1.038)	/	0.999 (0.953–1.048)
Adjusted for O_3	1.109** (1.074–1.146)	1.188** (1.131–1.248)	1.099** (1.064–1.136)	1.167** (1.124–1.211)	/
Adjusted for the other four pollutants	0.973 (0.912–1.037)	1.069 (0.988–1.158)	0.991 (0.940–1.045)	1.162** (1.082–1.247)	1.005 (0.958–1.055)

*$p < 0.05$, **$p < 0.01$ adjusted for temperature, relative humidity, atmospheric pressure and wind speed.

pollutants. If we include AQI in multi-pollutant models, there might be overlapping effects. So we did not include the AQI in the multi-pollutant models. Table 2 shows the correlation coefficient for PM_{10} and $PM_{2.5}$ was 0.965, and Table 3 shows PM_{10} had a higher OR value for influencing emergency visits for AOM. Therefore, we included PM_{10} and excluded $PM_{2.5}$ in the multi-pollutant models, consistent with the approach used by Ding et al. and Ko et al. (24, 25). Table 4 shows that in the multi-pollutant models, most OR values for PM_{10}, SO_2, CO and NO_2 were statistically significant. We found the statistically significant OR_S values for PM_{10} became smaller after adjusting for CO and became slightly bigger after adjusting for O_3. For the statistically significant OR values for SO_2, the ORs became smaller after adjusting for PM_{10} and CO, and the OR became slightly bigger after adjusting for O_3. Also, the statistically significant OR values for CO became slightly bigger after adjusting for O_3. For the statistically significant OR values for NO_2, all the ORs became bigger except after adjusting for SO_2. The OR values for NO_2 were significant in all the multi-pollutant models and the OR values for O_3 were not significant in any of the multi-pollutant models.

3.6. Stratified analyses of the associations between air pollution variables and emergency visits for AOM in children

Table 5 shows the results of stratified analyses according to gender, age and season. The OR values for associations between O_3 and AOM were not statistically significant with any gender and age stratification. With gender stratification, the OR values for the effects of increases in AQI, PM_{10}, $PM_{2.5}$, CO and NO_2 on emergency visits for AOM were greater for male patients than for female patients, and the OR values for increases in SO_2 were greater for female patients than for male patients. With age stratification, the statistically significant OR values for the effects of increases in AQI, PM_{10}, SO_2, and NO_2 on emergency visits for AOM were greatest for patients aged 3–5 years, while the greatest OR values for $PM_{2.5}$ and CO were observed for the groups aged 0 years, respectively. However, there was no difference between groups in these statistically significant OR values through gender and age stratification. With season stratification, the statistically significant OR values for AQI, $PM_{2.5}$ and CO were highest in Winter, the statistically significant OR values for PM_{10}, SO_2 and NO_2 were highest in Spring; and the statistically significant OR values for O_3 were highest in Summer. Notably, the differences between seasons in these statistically significant OR values of PM_{10}, SO_2, CO, NO_2 and O_3 were statistically significant.

4. Discussion

In one of the first studies on this topic in Asia, the present study analyzed the short-term effects of air pollution on pediatric emergency visits for AOM by collecting data for seven air pollutant variables from 17 monitoring sites in Chongqing, China. Data for a total of 21,416 children aged 0–17 years were collected for this study, representing the largest sample size among the relevant published studies from a single center. A 1:3 case-crossover design was used to control individual characteristics. Additionally, data for meteorological variables were collected as confounding factors.

The results of this study found that in the single-pollutant and stratified analyses increases in the AQI as well as the concentrations of PM_{10}, $PM_{2.5}$, SO_2, CO and NO_2 led to statistically significant increases in the number of pediatric AOM cases, and in multi-pollutant models, increases in the concentrations of PM_{10}, SO_2, CO and NO_2 led to statistically significant increases in the number of pediatric AOM cases. These findings are consistent with most epidemiological studies (12, 26–31). However, a few studies did not find short-term associations between these air pollution variables and AOM. Although a case-crossover study from Windsor, Ontario, Canada reported a significant association between $PM_{2.5}$ and emergency department visits for AOM in children, they found no significant association between SO_2, CO and NO_2 levels and AOM presentations (32). Strickland et al. (33) did not find significant associations between emergency department visits for AOM and same-day and previous-day $PM_{2.5}$ concentrations through time-stratified case-crossover models stratified by ZIP code, year, and month. Moreover, another Canadian study analyzing data collected over 10 years also used a case-crossover design to explore the association between emergency department visits for OM and air pollution through a sample of 14,527 children aged 1–3 years (13). In their study, the ORs for PM_{10}, CO, NO_2 and O_3 were positive statistically significant, while those for SO_2 and $PM_{2.5}$ were not positive statistically significant.

In the present study, no significant associations were found between increases in O_3 concentrations and the number of patients with AOM in the single-pollutant model and multi-pollutant models. Similarly, a time series study from Lanzhou, China analyzed the correlation between environment-meteorological factors and patients

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TABLE 5 Associations between air pollution variables (per IQR increase in AQI and the concentrations of air pollutants) and emergency visits for AOM in children upon stratification by patient characteristics.

	AQI	PM_{10}	$PM_{2.5}$	SO_2	CO	NO_2	O_3
Sex							
Male	1.135** (1.078–1.195)	1.115** (1.067–1.165)	1.100** (1.055–1.147)	1.181** (1.104–1.263)	1.109** (1.061–1.160)	1.186** (1.127–1.247)	1.019 (0.955–1.086)
Female	1.109** (1.051–1.171)	1.098** (1.048–1.151)	1.096** (1.049–1.145)	1.190** (1.108–1.278)	1.082** (1.033–1.135)	1.130** (1.071–1.192)	1.015 (0.947–1.089)
Age (years)							
0	1.133 (0.975–1.316)	1.144 (1.000–1.309)	1.159* (1.021–1.317)	1.206 (0.974–1.492)	1.155* (1.007–1.325)	1.112 (0.962–1.286)	1.058 (0.891–1.257)
1–2	1.052 (0.944–1.173)	1.083 (0.985–1.190)	1.061 (0.971–1.159)	1.206* (1.039–1.401)	1.104* (1.004–1.215)	1.127* (1.014–1.253)	0.985 (0.857–1.132)
3–5	1.133** (1.079–1.190)	1.112** (1.066–1.159)	1.102** (1.059–1.146)	1.207** (1.133–1.286)	1.094** (1.049–1.141)	1.186** (1.130–1.245)	1.063 (0.996–1.135)
6–17	1.129** (1.049–1.215)	1.108** (1.037–1.184)	1.099** (1.033–1.169)	1.134* (1.025–1.253)	1.090* (1.020–1.166)	1.140** (1.057–1.229)	0.936 (0.856–1.024)
Season							
Spring	0.889 (0.763–1.036)	1.400** (1.215–1.613)	1.053 (0.899–1.235)	1.500** (1.261–1.785)	0.825** (0.715–0.953)	1.556** (1.387–1.746)	1.099 (0.994–1.215)
Summer	1.139 (0.968–1.341)	1.037 (0.782–1.376)	0.902 (0.666–1.222)	1.413** (1.116–1.790)	0.950 (0.789–1.144)	1.272* (1.025–1.577)	1.167** (1.060–1.285)
Autumn	0.908 (0.817–1.010)	1.127** (1.046–1.214)	1.008 (0.937–1.085)	1.039 (0.938–1.152)	1.045 (0.973–1.123)	1.392** (1.293–1.498)	1.010 (0.926–1.102)
Winter	1.175** (1.120–1.233)	1.115** (1.071–1.161)	1.154** (1.112–1.197)	1.306** (1.224–1.393)	1.283** (1.230–1.338)	1.147** (1.090–1.208)	0.795** (0.693–0.911)

*$p<0.05$, **$p<0.01$ adjusted for temperature, relative humidity, atmospheric pressure and wind speed.

with AOM in entire population (34). The results showed that $PM_{2.5}$, PM_{10}, NO_2, SO_2, and CO are positively correlated with daily visits to AOM, whereas O_3 is not. Surprisingly, we found that the OR values for O_3 were statistically significant upon seasonal stratification. However, several other studies did report significant ORs for the effects of O_3 concentrations on AOM (12, 13, 27, 32). Therefore, the associations of O_3 with AOM need to be confirmed by more epidemiological studies, and seasonal stratification should be carried out if necessary.

In our single pollutant models, we found that the best lag periods were lag 0–7 for air pollution variables except O_3. This best period was later than other best periods in some studies (13, 28, 32, 34). One possible reason is that most of these studies did not use cumulative lags, which are more robust and significant than individual lags (13, 28, 32). Another possible reason is that otitis media is often secondary to upper respiratory infection (URI) (31), and thus, the best lag period may be late. However, since the effects would be overlapping and mixed, we did not continue to analyze the effect values after lag 7 and lag 0–7. More studies are needed to explore the best lag periods for air pollution effecting emergency visits for AOM.

Although the results of multi-pollutant models showed that PM_{10}, SO_2, CO and NO_2 were positively correlated with emergency visits to AOM after controlling some air pollution variables, only the OR values for NO_2 were statistically significant in each multi-pollutant model. Also, NO_2 had the most statistically significant OR values in the single-pollutant models and stratified analyses. These results indicate that NO_2 is the most significant pollutant variable in our study. NO_2 was associated with the visits for OM in other studies, but it has not had the most significant OR values (13, 27). In the largest birth cohort studies involving 10 European birth cohorts, a significant positive association was found between NO_2 and OM, while no significant association was found between PM_{10}, $PM_{2.5}$ and OM (9). These results indicate that NO_2 has more robust effects on OM than PM_{10} and $PM_{2.5}$. The reason maybe NO_2 can impair the mucociliary clearance of the upper respiratory tract and middle ear and alter the inflammatory response to infections, possibly resulting in an increased number of visits for URI and OM (30, 35, 36).

The distribution of patients according to age (Figure 2A) showed that the peak incidence of AOM occurred in preschool children aged 3–5 years, which is not completely consistent with other studies (5, 17). With age stratification, our results showed that the highest OR values were aged 0 years or 3–5 years or for air pollution variables. These results indicate that children aged 0 years and 3–5 years may be the most susceptible group to air pollution. One possible explanation is that the immunity of children less than 5 years of age is weaker than that of older children. Another possible reason is that these children may spend more time outdoors, leading to more chances for inhalation of air pollutants. Lastly, children less than 5 years old have the peak incidence of URI, and air pollution can increase the incidence of URI (37, 38). Approximately 35% of pediatric cases of URI are complicated by OM (39, 40). Finally, air pollution indirectly increases the incidence of AOM in children less than 5 years old.

In the present study, November, December and January had the highest AOM incidence (Figure 2B), which is similar to the results of most previous epidemiological studies (27, 41). November in within Autumn, and December and January are in Winter in Chongqing. Our seasonal stratification results showed that the positive significant OR values for AQI, PM_{10}, $PM_{2.5}$, SO_2, CO and NO_2 were highest in Winter

or Spring. The results indicate that children are most affected by air pollution during Winter and Spring. One explanation may be that heavy pollution combined with the low temperatures lead to the highest incidence of respiratory infection, which is an important cause of AOM in children.

As an environmental epidemiological study, the present study still has some limitations. First, the pollution concentrations we studied came from areas of children's residences. Although children spend much time in school, China has the policy of going to school near to one's residence, and thus, children will go to the school that the closest to their home, making the error between the pollution concentrations at their school and residence extremely small. However, the children's actual exposure levels to air pollution likely differ from the measured pollution concentrations due to differences in indoor environments, personal outdoor activity habits, and so on. Therefore, there is deviation between the exposure level, and it is difficult to estimate the magnitude and direction of this deviation. Second, due to technical limitations and the small area of Chongqing's main urban area, which is only 4,779 km^2, the data for air pollution variables were averaged from 17 fixed monitoring stations. The results would be more accurate if concentrations of air pollutants could be obtained according the children's specific residential locations. For example, Xiao et al. (12) used CMAQ model simulations and ground-based measurements to estimate the concentrations of air pollutants, and Ko et al. (25) modeled the concentration $PM_{2.5}$ through satellite, remote sensing, meteorological and land use data. In addition, compared with other multi-center or national studies in developed countries, this study was only a single-center study. Our findings may not be applicable to other cities and populations.

In conclusion, increases in the AQI and the concentrations of PM_{10}, $PM_{2.5}$, SO_2, CO and NO_2 were positively associated with emergency visits for AOM by children. However, increases in O_3 showed effects on AOM visits just in summer. We found that the best lag periods were lag 0–7 for air pollution variables except O_3 in single pollutant models. As NO_2 had the most statistically significant OR values in all models of our study, we need to control car exhaust to reduce NO_2. Children aged 0 years and 3–5 years were most susceptible to the effects of air pollution on the occurrence of AOM, and Winter and Spring were the seasons when air pollutant levels had the most positive significant effects on AOM visits. These findings can provide a basis for the early prevention in Winter and Spring and for susceptible children to prevent the occurrence of AOM. Further multi-center studies are needed, particularly using more accurate measurement of exposure levels, to explore the effects of air pollution on AOM.

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 research protocol was approved by the Medical Ethics Committee of the Children's Hospital of the Chongqing Medical University. Informed consent was obtained from all individual participants and/or their legal guardians included in the study.

Author contributions

LX collected data and wrote the paper. SS finished statistical analysis. CC and HY continued to check data and paper, and LD proposed ideas and finished project administration. 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.

Publisher's note

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Kitchen fine particulate matter ($PM_{2.5}$) concentrations from biomass fuel use in rural households of Northwest Ethiopia

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Background: Combustion of solid biomass fuels using traditional stoves which is the daily routine for 3 billion people emits various air pollutants including fine particulate matter which is one of the widely recognized risk factors for various cardiorespiratory and other health problems. But, there is only limited evidences of kitchen $PM_{2.5}$ concentrations in rural Ethiopia.

Objective: This study is aimed to estimate the 24-h average kitchen area concentrations of $PM_{2.5}$ and to identify associated factors in rural households of northwest Ethiopia.

Method: The average kitchen area $PM_{2.5}$ concentrations were measured using a low-cost light-scattering Particle and Temperature Sensor Plus (PATS+) for a 24-h sampling period. Data from the PATS+ was downloaded in electronic form for further analysis. Other characteristics were collected using face-to-face interviews. Independent sample t-test and one-way analysis of variance were used to test differences in $PM_{2.5}$ concentrations between and among various characteristics, respectively.

Result: Mixed fuels were the most common cooking biomass fuel. The 24-h average kitchen $PM_{2.5}$ concentrations was estimated to be 405 $\mu g/m^3$, ranging from 52 to 965 $\mu g/m^3$. The average concentrations were 639 vs. 336 $\mu g/m^3$ ($p < 0.001$) in the thatched and corrugated iron sheet roof kitchens, respectively. The average concentration was also higher among mixed fuel users at 493 vs. 347 $\mu g/m^3$ ($p = 0.042$) compared with firewood users and 493 vs. 233 $\mu g/m^3$ ($p = 0.007$) as compared with crop residue fuel users. Statistically significant differences were also observed across starter fuel types 613 vs. 343 $\mu g/m^3$ ($p = 0.016$) for kerosene vs. dried leaves and Injera baking events 523 vs. 343 $\mu g/m^3$ ($p < 0.001$) for baked vs. not baked events.

Conclusion: The average kitchen $PM_{2.5}$ concentrations in the study area exceeded the world health organization indoor air quality guideline value of 15 $\mu g/m^3$ which can put pregnant women at greater risk and contribute to poor pregnancy outcomes. Thatched roof kitchen, mixed cooking fuel, kerosene fire starter, and Injera baking events were positively associated with high-level average kitchen $PM_{2.5}$ concentration. Simple cost-effective interventions like the use of chimney-fitted improved stoves and sensitizing women about factors that aggravate kitchen $PM_{2.5}$ concentrations could reduce kitchen PM $_{2.5}$ levels in the future.

KEYWORDS
biomass fuel, kitchen concentration, fine particle, cooking, Ethiopia

Introduction

Every day, nearly 3 billion people rely on solid biomass fuels (wood, dung, plant leaves, and charcoal) to cook their foods and to provide heat and light (1–3). Burning of these solid biomass fuels with open fires or inefficient stoves results in large amounts of health-damaging pollutants including a multitude of complex particulate matter and carbon monoxide (4–6) that exceed world health organization (WHO) air quality guidelines (24-h mean $PM_{2.5}$ concentrations of 15 μg/m^3) (7). Based on WHO report, in regions where solid biomass fuels are widely used, average levels of $PM_{2.5}$ were very high in kitchens 972 μg/m^3 and for personal exposure of women 267 μg/m^3 (8). In Africa, especially in the east, west, central, and southern parts of the continent, an estimated three-fourths of the population relies on solid biomass fuels for cooking and is exposed to high concentrations of harmful pollutants at home every day (3, 9).

In Ethiopia, more than 95% of the population used solid biomass fuels for cooking and were exposed to kitchen smoke which is typical for low-income countries (10, 11). Evidences from rural Ethiopia showed that women, girls, and children at early age were exposed to extremely high levels of $PM_{2.5}$ (12–14). Previous studies also reported 24-h average particulate matter concentrations of 818 ug/m^3 in slum areas of Addis Ababa, 1,297 ug/m^3 in three regions (Amhara, Oromia, and South Nation Nationalities and People) of Ethiopia, 772 μg/m^3 in Wolaita Sodo town and 410 ug/m^3 in Butajira town (13–16) all exceeded 24-h WHO safety level (17). As previously reported, these differences in concentrations may be due to differences in fuel and kitchen types, measuring devices, sampling seasons, and cooking patterns within households (13, 18–20).

Epidemiological studies are also increasingly showing that exposure to high levels of indoor air pollution from biomass fuel use kills millions and is a major contributor to global climate change (4–6). Household air pollution (HAP) contributed to more than 3.2 million annual premature deaths and 91.5 million disability-adjusted life years (DALYs) worldwide with a clear geographical variation where the majority of the burden is found in southeast Asia and sub-Saharan Africa (21–23). In 2019, air pollution was responsible for 1.1 million deaths across Africa, with more than half of those fatalities associated with household pollutants (24). Pneumonia and stroke are the leading causes of premature death due to HAP (3, 22, 23). About 400,000 children under 5 years old die each year as a result of HAP, primarily in sub-Saharan Africa and Asia (25).

In addition to detrimental cardiovascular effects, growing evidence shows potential perinatal risks associated with solid biomass burning (26–28). Adverse pregnancy outcomes such as low birth weight (LBW), pre-term birth (PTB), intrauterine growth restriction, and post-neonatal infant mortality are associated with biomass fuel smoke exposure (29). Fetuses are the most vulnerable stage to air pollution due to susceptibility at early ages (30, 31). In 2019, more than 100,000 deaths and 11.3 million DALYs related to preterm birth worldwide (66% in western sub-Saharan Africa and south Asia) were caused by excess $PM_{2.5,}$ of which nearly two-thirds of them were attributable to household particulate matters $PM_{2.5}$ (32).

According to the local burden of disease estimate in Ethiopia, exposure to HAP from solid biomass fuel use was the second highest risk factor for child pneumonia deaths next to child malnutrition (33). The available local epidemiological studies have reported strong correlations between elevated $PM_{2.5}$ levels and acute respiratory infections (ARIs) among under-five children (16, 34–36). In Adama (southeast Ethiopia), HAP causes premature death and a significant number of DALYs due to biomass fuel use among women (37). Other existing evidences in Ethiopia revealed that the prevalence of acute respiratory infection including pneumonia among under-five children in households using solid biomass fuel remains high, ranging from 8 to 30 percent (34, 38–40).

Research on kitchen area concentration of particulate matter is limited in Ethiopia. Even the available evidences reported different results due to differences in the technologies used in the measurements, the sampling period, the study area (urban vs. rural), the season of measurements (dry vs. wet), the fuel and kitchen types, housing conditions, and other characteristics. Therefore, measuring local kitchen $PM_{2.5}$ concentrations and understanding different factors that influence kitchen particle concentration can inform measures to maximize the effectiveness of various interventions.

Methods and materials

Study setting

This study was conducted in a low-income rural community of the south Gondar zone, northwest Ethiopia as part of the ongoing stove intervention study. Pregnant women were recruited from six kebeles (the smallest administrative unit) of the Guna–Tana integrated field research and development center catchment area. The field research center was established in 2013 by Debre Tabor University to integrate education, research, and community services. It is located 650 km away from the capital city of Ethiopia, Addis Ababa, toward northwest Ethiopia and 105 km far away from the capital city of Amhara regional state, Bahir Dar. Solid biomass fuel is exclusively a household energy source for cooking with traditional three-stone stoves in the study area. Kebeles in the two ecological zones (cold and temperate) were included to represent a diversity of characteristics expected to influence kitchen concentration of particulate matter including altitude, cooking practices, fuel types, and socioeconomic conditions. Tobacco smoking is uncommon and vehicle emission is almost negligible in the study community.

Study design and population

A cross-sectional data was analyzed using the baseline measurements from an ongoing improved stove randomized controlled

FIGURE 1
Small thatched roof kitchen near the main house.

FIGURE 2
Small corrugated iron sheet roof kitchen near the main house.

field trial study[1] to estimate $PM_{2.5}$ concentrations in kitchens of pregnant women cooking with solid biomass fuel in traditional stoves. The study participants who fulfilled the eligibility criteria were randomly selected and recruited from households in the stove trial project. To be eligible and participate in this study, a pregnant woman must meet the following inclusion criteria: Aged 18–38 years, being the primary cook of the household, in her first or second-trimester gestation (gestational age ≤ 24 weeks), exclusively using the traditional biomass-fueled stove or locally modified mud stove and having enclosed cooking area separated from or attached to the main house. But, pregnant women who had the plan to move permanently outside the study area in the next 12 months and who are engaged in local alcohol production activities were excluded from the study.

Sample size

The number of households with eligible pregnant women for kitchen $PM_{2.5}$ concentration measurement was determined based on standard conventional power calculations in the HAP intervention studies (41). These standard conventions include achieving a statistical power of 0.80, a value of p of 5% in two-tailed tests, and detecting a 64% HAP reduction due to an improved stove from a previous study (14). But, a reliable Ethiopia-based estimate of the coefficient of variation in HAP reduction was not available before our study to compute the minimum sample size. Therefore, a conservative COV estimate of 0.7 (41) was used which gave a minimum sample size of 43 households in each arm (a total of 86 households with pregnant women). Hence, all the baseline data collected from the upcoming stove trail study were analyzed for 86 randomly selected households.

Variable definitions and measurements

Kitchen

In this study, the kitchen is used to indicate all enclosed cooking spaces separated from or attached to the main house in rural households.

Kitchen types

There were two main kitchen types included in this study. The first one is a small thatched-roof kitchen near the main house. This type of kitchen had low-lying ceilings and very tightly enclosed walls resulting in the accumulation of dense biomass smoke during meal cooking due to the lack of an outlet at the highest part of the roof (Figure 1). The second kitchen is the small congrugated iron sheet(CIS) roof-enclosed kitchen with outlets between the wall and the roof for smoke removal (Figure 2).

$PM_{2.5}$ concentrations

It is the daily average concentrations of $PM_{2.5}$ calculated for the 24-h sampling period. Continuous $PM_{2.5}$ measurements were done using PATS+ following standard protocol. In this study, the device logged particle concentration with a logging interval of 1 min.

Biomass fuel

Any plant or animal matter which when burned provide heat or light. The type of cooking fuel was re-categorized into three classes; (a) firewood (b) cow dung (c) agricultural residue and (d) mixed fuels (using two or more biomass fuels together).

Primary biomass fuel

It is the first fuel choice that is usually cheap and easily available in villages. It's the primary practical option for rural households.

Family size

The total number of individuals permanently living in the household was assessed by recording all individuals (male, female,

1 https://pactr.samrc.ac.za/; Identifier: ACTR202111534227089.

under-five children) and further categorized as (a) less than five individuals and (b) greater than or equal to five individuals. This classification was based on the average household size in Ethiopia reported by the Ethiopian Demography and health survey of 2016 (10).

Data collection procedures

Survey

All relevant baseline data were collected as part of an ongoing randomized controlled trial study. Face-to-face interviews using structured and pretested questionnaires and observational checklists were conducted by trained first-degree environmental health professionals in the local language (Amharic). The key data were collected on economic status (using the list of assets owned by the households), housing characteristics (floor, wall, roof, number of rooms, windows, and doors), kitchen characteristics (size, presence of windows, and location), fuel types, frequency of cooking, and frequency of Injera baking. Injera is the staple food in Ethiopia which is a flatbread-like pancake prepared from a tiny grain called Teff. Baking Injera is very energy-intensive to cook which uses approximately 50% of the energy consumed in the household (42). We also collected updated information on fuels used and the time activity pattern of the day during the particle measurement phase.

Particulate matter ($PM_{2.5}$) measurements

In this study, kitchen $PM_{2.5}$ concentrations were measured in 86 households using Particle and Temperature Sensor Plus (PATS+) which is a light-scattering particle sensor developed by Berkeley Air Monitoring Group, California. PATS+ is quite popular in this field as it is easy to transport and required less place to install. It had an internal power supply for 80 h of continuous measurement after being completely charged and provided data in a minute interval of time (43, 44). The device had a lower particulate matter detection limit of 10 μg/m^3 and an upper particulate matter detection limit of 50,000 μg/m^3 with a logging particle concentration interval of 1 min. Previous field validation tests have shown that PATS+ relates well to gravimetric $PM_{2.5}$ estimates in laboratory settings ($R^2 = 0.97$) and in rural biomass-using households ($R^2 = 0.74$) (43).

PATS+ was calibrated using gravimetric filters co-located in a previous study conducted in Ethiopia. Based on the regression result, an adjustment factor was estimated to be 0.8065 (14). But, for this particular study, it was not possible to calibrate the instrument specifically for local particulate matter due to the harsh sampling environments. Instead, we conducted side-by-side inter-comparison tests between PATS+ and DylosDC1700 air monitor devices in a real setting in 11 kitchens following standardized experimental procedures. The result confirmed good data comparability across PATS+ devices (Pearson correlation coefficients: 0.75 to 0.86).

A 24-h continuous kitchen air monitoring was carried out covering all Ethiopian main meals of the day (breakfast, lunch, and dinner) during the study period. Then, for each household, average concentrations were calculated as the means of these minute-by-minute average concentrations for each household with data on a sufficient number of hours (more than 20 h). In each household, monitoring for $PM_{2.5}$ started in the morning at around 8:30 am. We used the morning to the morning as starting and ending points of a sampling day. A total of 4 PATS+ were rotated through households during this study.

Instrument placement in the kitchens

The air monitoring devices were placed in the main kitchen at least 1 m away from the edge of the stove (to prevent from damaging as the devices cannot tolerate extreme temperatures and to represent the general cooking area), at a height of 1.5 m above the floor (the approximate breathing height of standing women), 1.5 m away from doors, windows, and other openings horizontally (to minimize ambient air entering the room) (45), and at a safe location to minimize the risk of interrupting normal household activities or being disturbed (Figure 3). The air monitors were attached to a wall or suspended from the ceiling and run for 24 h to consider households' typical daily cooking activities. In addition to measuring mean $PM_{2.5}$ concentrations, the PATS+ monitors also measured humidity and temperature.

Data quality

Field workers were trained in the use of the sampling equipment (PATS+ and Dylos DC1700), and a detailed manual with pictorial aids developed by the Berkeley air monitoring group (46) was used to assist them. They instructed to follow the standard operating procedures for installing indoor air pollution instruments in a home (45) in gathering kitchen air samples. To ensure that each 24-h period was representative (capturing a typical number of cooking events), measurements of $PM_{2.5}$ concentrations were removed from analysis when the total sampling time was shorter than 20 h.

In a previous study, PATS+ has been validated against gravimetric samples in Ethiopian settings, with the resulting strong linear

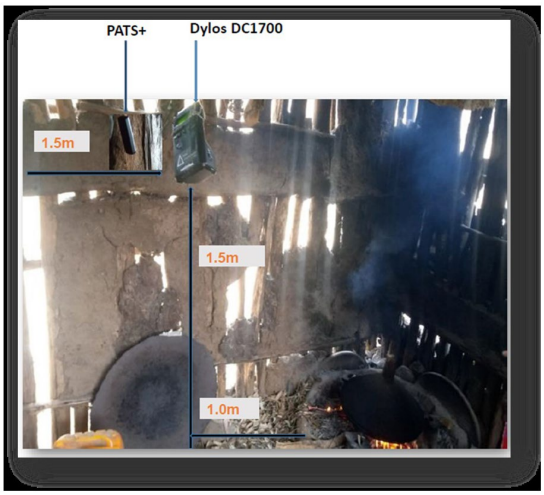

FIGURE 3
Placement position of particulate matter monitoring devices in the kitchen area.

correlation ($r^2 > 0.80$) (14). We have also conducted side-by-side inter-comparison tests between PATS+ and DylosDC1700 air monitor devices in a real setting in 11 kitchens following standardized experimental procedures which yield comparable data across PATS+ devices (Pearson correlation coefficients: 0.75 to 0.86). All PATS+ were zeroed in a plastic bag for 10 min before and after deployment in the kitchens. Though readings of optical air monitors are significantly affected by relative humidity levels usually at >80%, the relative humidity recorded in this study area ranged from 53 to 61% and would be unlikely to affect readings by more than 5% as reported from previous literature (47).

Data analysis

Data from the PATS+ air monitoring devices were downloaded in electronic form using the Platform for Integrated Cook Stove Assessment (PICA) software to the computer with CSV format Excel spreadsheets and text files. Paper-based data on the socioeconomics and demographic characteristics including housing conditions, kitchen types, fuel types, and cooking behavior were entered into SPSS software. Before formal statistical analyzes, simple tabulations and diagrams were constructed to gain a good understanding of the data and to identify gross outliers. Then, descriptive statistics including frequencies and percentages for categorical variables, and mean and standard deviations for continuous variables were calculated and presented using tables and graphs. In addition, we examined the pick hours at which the pollutant concentration in the kitchen measures high.

One-way analysis of variance (ANOVA) within 95% limits of a confidence interval, and value of $p < 0.05$ was used to test differences in $PM_{2.5}$ concentrations among different characteristics with multiple levels. Tukey's Honest Significant Difference (HSD) test was done following ANOVA, to assess the significance of differences between pairs of groups. An independent sample t-test was used to check for differences in $PM_{2.5}$ concentrations between two different characteristics at a significant level of 5%. Data were analyzed using the statistical package for social science (SPSS) version 24.0 software and Microsoft Excel for better graphical visuals.

Ethical approval

This study was approved by the institutional review boards of Jimma University with ethical clearance provided (Ref No: IHRPGD/538/2021) to conduct the study. Information about the purpose of the study and potential study outcomes were provided to all participants. All participants were asked to give consent for participation before the commencing of the data collection. As a significant proportion of this population was illiterate, verbal informed consent was received from all participating households. Official letters of cooperation were given to the south Gondar zone health department and respective district health offices and permission to conduct the study was obtained. The right of the respondent to withdraw from the interview or not to participate was respected. During air pollution monitoring sessions, field staff received permission from participants to place air pollution monitoring devices in their kitchens. Devices chosen for pollution have no risk for participants.

Results

Household characteristics

In this study, a total of 86 households (HHs) with eligible pregnant women were approached for kitchen $PM_{2.5}$ concentration measurement. However, air monitoring data from 3 HHs were discarded due to the following reasons; (a) in one HH, an air monitoring device (PATS+) was taken from the kitchen to the main house to prevent it from theft, (b) in another HH, an air monitoring device was covered with the cloth to prevent it from damaging by children and (c) data from the third HH was discarded due to short sampling period (18 h).

All participants were Amhara by ethnicity, Orthodox Christian, and most of them were married. They were living on an earthen floor, wood/mud wall, and corrugated iron sheet (CIS) roof house which is typical in the study area. The mean age of the respondents was 28.7 (SD ± 5.34) years. In this study, there were an average of 4.5 (SD ±1.4) individuals permanently living in the household.

Kitchen characteristics

All households included in this study had a one-roomed separate kitchen with earthen floors and without windows. Nearly, three-fourths of participants had congregated iron sheet (CIS) roofed kitchens 64 (76.7%) and the rest 19 (23.3%) cooked in thatched roofed kitchens near the main house. When cooking, the kitchen doors of all participants' kitchens opened partially or completely. The thatched roof kitchens have no sufficient opening to vent out cooking smoke, making pregnant women more vulnerable. Whereas the kitchens with CIS roofs, though there were no formal ventilations, there were openings between the wall and the ceiling which provided informal ventilation and reduces smoke exposure.

Cooking practices

All participants lived in households where cooking was regularly practiced. Mixed fuels (mainly wood with dung) were the most common fuels used by 34 (40.7%) of the respondents followed by firewood where 27 (32.6%) of the interviewed pregnant women used to cook their food. Nearly three-fourths of the participants 62 (74.7%) used additional fuel to start the kitchen fire, from whom 22 (35.5%) used dried plant leaves and 19(30.6%) used agricultural straws. All participants were baking Injera at least twice per week and other meals daily (average cooking time = 2.8 (SD 0.92) hours/ day) for an average of 5 (SD 1.4) individuals during the study period (Table 1).

Kitchen $PM_{2.5}$ concentration

The average daily sampling time per household was 22.7 h with a range of 21 to 24 h. Because, some of the participating women faced

TABLE 1 Cooking related characteristics and distribution of kitchen $PM_{2.5}$ concentration in rural households of north-west Ethiopia ($n = 83$).

Characteristics	Number	Mean (SD) of $PM_{2.5}$ (ug/m^3)
Age group, in years		
18–24	19	481 [155]
25–31	35	435 [205]
32–38	28	321 [253]
Kitchen roof material		
Corrugated metal roof	64	336 [182]
Thatched roof	19	639 [181]
Types of fuel used during the study period		
Wood	28	358 [190]
Dung	14	414 [204]
Crop residues	9	231 [167]
Mixed fuels	32	493 [233]
Baking *Ijera* during the measurement period		
Yes	29	523 [209]
No	54	343 [202]
Family size		
≥ 5 individuals	42	427 [229]
<5 individuals	41	384 [212]
Number of meals cooked per day		
Twice	10	377 [160]
Three times	28	392 [211]
Four and more times	45	420[240]
Kitchen size		
< 15m^3	27	485 [255]
≥15 m^3	56	367 [193]
Use another fuel to start the fire		
Yes	62	407 [223]
No	20	402 [222]
Types of fuel used to start the fire ($n = 62$)		
Leaves	22	343 [190]
Straw	19	372 [245]
Paper	13	443 [182]
Kerosene	8	613 [224]
Number of meals cooked per day		
One meal	10	377 [160]
Two meals	28	392 [211]
Three and more meals	45	420 [240]
Opening between the kitchen wall and roof		
Yes	15	316 [226]
No	67	429 [215]

unexpected social issues like funerals, health problems, and other family issues that enforced them to go far away from their residences. In this case, they have to lock their kitchen and the installed air monitors have to be uninstalled. Since we planned to consider measurements undertaken for more than 20 h, we excluded one measurement due to the short sampling period (18 h). The average temperature was 20.4°C, while the average humidity was 57% for the cooking area.

The average 24-h kitchen area $PM_{2.5}$ concentrations were estimated to be 405 μg/m^3 (SD 221 μg/m^3) ranging from 52 to 965 μg/m^3 and the median concentrations were less than the mean at 383 μg/m^3. The continuous $PM_{2.5}$ concentration profile consistently showed slight diurnal peaks reflecting morning and evening cooking periods and was lowest overnight when the stove was likely off (Figure 4).

$PM_{2.5}$ concentrations by kitchen characteristics

The presence of an enclosed kitchen was one of the criteria for the HHs to be included in the kitchen area $PM_{2.5}$ concentration measurement. The average $PM_{2.5}$ concentrations was highest in the kitchen with a thatched roof (639 μg/m^3) with daily average concentration ranging from 309 to 965 μg/m^3 as compared with CIS roofed kitchen at an average concentration of 337 μg/m^3 with a range from 52 to 671 μg/m^3 (Figure 5).

The difference in average $PM_{2.5}$ concentrations is mainly due to a lack of outlet between the wall and the roof in the thatched roof kitchen where cooking smoke is trapped. Because the thatched roof kitchens had low-lying ceilings and very tightly enclosed walls resulting in the accumulation of dense biomass smoke during meal cooking. While the CIS roofed kitchen had many outlets at the highest part of the roof which served as smoke removal.

$PM_{2.5}$ concentrations by fuel types

In this study, the average $PM_{2.5}$ concentrations vary with different biomass fuel types used to cook the meal. Burning of mixed biomass fuel in the kitchen produces the highest average $PM_{2.5}$ concentrations. In the kitchens where mixed fuel was used, the average $PM_{2.5}$ concentrations were estimated to be 493 μg/m^3 with a median of 527 μg/m^3. The corresponding average concentration in kitchens with cow dung fuel was estimated to be 414 μg/m^3. For firewood cooking fuel, the average particle concentration was 358 μg/m^3 with a median of 344 μg/m^3 and the least particle concentration was recorded among agricultural residue users at the $PM_{2.5}$ concentrations of 231 μg/m^3 (Figure 6).

In addition to cooking fuel, the use of additional starter fuel to initiate the wood fire affects the concentration of particles in the kitchen. Accordingly, in the kitchen where kerosene was used to start the fire, the average $PM_{2.5}$ concentrations was 493 μg/m^3 followed by 414 μg/m^3 among straw/grass starter fuel users (Figure 7).

Determinants of daily average kitchen concentrations of $PM_{2.5}$

In addition to graphical visualization of raw relationships between different factors and average particle concentration, the model-based analysis provides a quantitative confirmation of important findings.

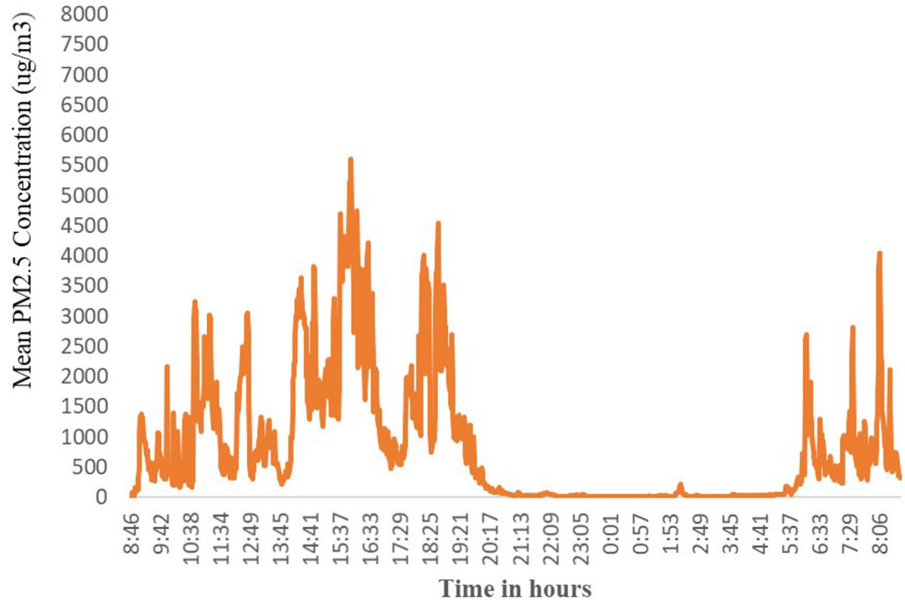

FIGURE 4
The distribution of kitchen area hourly average concentrations of $PM_{2.5}$ (μg/m³) by the time of day.

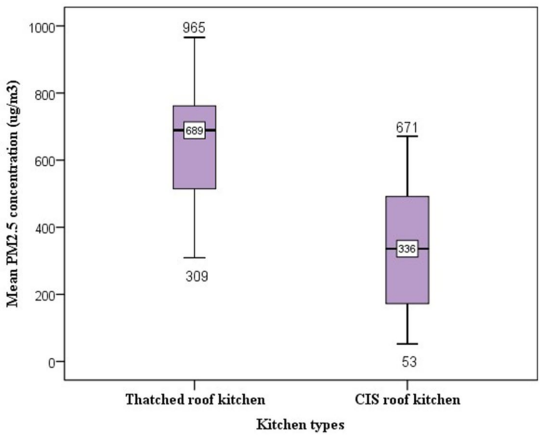

FIGURE 5
Box and whisker plots of 24- h kitchen $PM_{2.5}$ concentrations by kitchen roof type. The ends of the box are at quartiles, so that the length of the box is the interquartile range (IQR). The median is marked by a line within the box. The two whiskers outside the box extend to the smallest and largest observations.

As a result, we used the one-way analysis of variance (ANOVA) test to determine whether there is a significant difference in the mean concentration of $PM_{2.5}$ by each of, the fuel types used to cook, fuel types used to start the fire, number of meals cooked per day and other variables with more than two groups.

An independent sampling t-test was also used to compare the average concentration of two different groups and check for significant differences between these average concentrations. All significance values of Levene's test/statistics based on a comparison of the average concentration were greater than 0.05 indicating the requirement of homogeneity of variance has been met and the ANOVA and independent sample t-tests can be considered to be robust.

Accordingly, a statistically significant difference was observed in average $PM_{2.5}$ concentrations between the thatched roof and CIS roof kitchens. The results indicated that cooking in a thatched roof kitchen emitted on average 639 μg/m³ (SD = 181) $PM_{2.5}$ concentrations, compared with cooking in a CIS roofed kitchen which emitted an average concentration of 336 μg/m³ (SD = 182) $PM_{2.5.}$ This difference was statistically significant at 0.05 level ($t = 6.37$, $p < 0.001$). Using eta-square to examine the effect size, about 33.4% of the variation of $PM_{2.5}$ concentrations could be explained by kitchen roof types.

Similarly, in the kitchen where *Injera* was baked the average concentration of $PM_{2.5}$ was recorded to be 523 μg/m³ (SD = 209), compared with the kitchen where *Injera* was not baked which emitted an average of 343 μg/m³ (SD = 202) $PM_{2.5.}$ This difference was statistically significant at the 0.05 level ($t = 3.81$, $p < 0.001$). Based on the eta-square effect size estimate, only 15.2% of the variation could be explained by Injera baking events.

Regardless of the kitchen type, the result of one-way ANOVA showed a significant difference between fuel types used during the air monitoring period (firewood, cow dung, crop residue, and mixed fuel) and the average concentration of $PM_{2.5}$ ($F = 4.46$, $p = 0.006$). A Tukey *post hoc* test showed that burning of mixed biomass fuel (mean = 493 ug/m³, SD = 233 ug/m³) emitted significantly high average $PM_{2.5}$ concentrations than using both firewood (mean = 347 ug/m³, SD = 189 ug/m³) and agricultural residues (mean = 232 ug/m³, SD = 167 ug/m³). But there is no significant difference in average kitchen $PM_{2.5}$ concentrations among firewood, cow dung, and crop residue users.

Similarly, a statistically significant difference was observed between the types of fuel used to start the fire (dried leaves, straw/grass, and kerosene) and the average concentration of $PM_{2.5}$ ($F = 3.48$, $p = 0.021$). Accordingly, a Tukey *post hoc* pairwise comparison test showed that the use of kerosene to start the fire (mean = 613 ug/m³, SD = 224 ug/m³) has significantly higher average $PM_{2.5}$ concentrations than using dried plant leaves (mean = 343 ug/m³, SD = 190 ug/m³), straw/grass (mean = 372 ug/m³, SD = 245 ug/m³) and papers

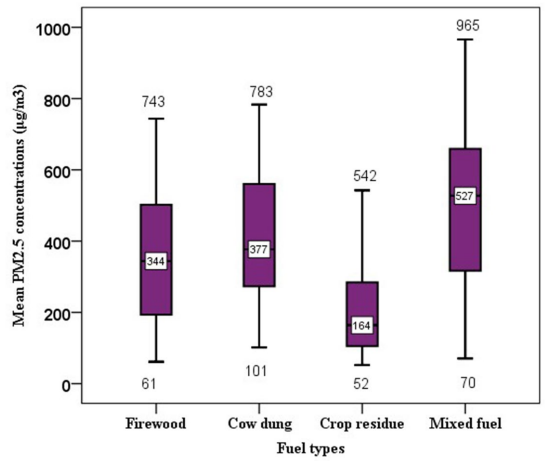

FIGURE 6
Box and whisker plots of 24- h kitchen $PM_{2.5}$ concentrations by types of cooking fuel used during sampling period. The whole boxes represent the interquartile range; numbers on the horizontal line inside the box indicate median. The top and bottom whiskers are minimum and maximum values, respectively.

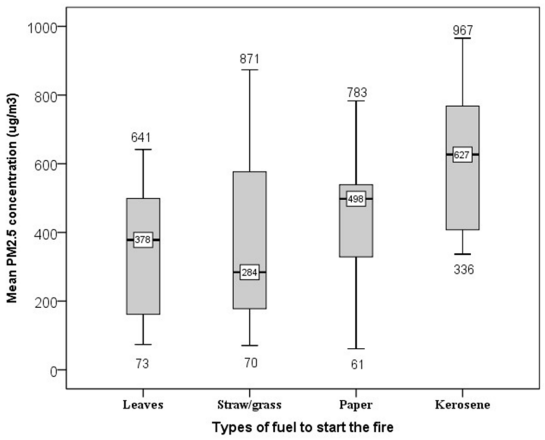

FIGURE 7
Box plot presenting the 24-h Kitchen area $PM_{2.5}$ concentrations using different fuel types to start the fire in the kitchen. The whole boxes represent the interquartile range; numbers on the horizontal line inside the box indicate median. The top and bottom whiskers are minimum and maximum values, respectively.

(mean = 443 ug/m^3, SD = 182 ug/m^3) to initiate the fire in the kitchen. Although 24-h average $PM_{2.5}$ concentrations at different meal cooking frequencies and the presence of openings between the kitchen wall and roof differed, the pairwise comparison indicated that it is not statistically significant ($p > 0.05$; Table 2).

TABLE 2 Cooking practices and kitchen characteristics associated with average $PM_{2.5}$ concentrations in rural households of north-west Ethiopia.

Characteristics	Average $PM_{2.5}$ difference (ug/m^3)	95% CI	*p*-value	Eta square
Kitchen types				
Thatched roof	Reference	–		33.4%
CIS roof	303	[260, 344]	<0.001	
Fuel types used				
Mixed fuel	Reference	–		14.5%
Firewood	146	[4, 288]	0.042	
Cow dung	63	[−107, 233]	0.766	
Crop residues	261	[56, 466]	0.007	
Fuel types used to start the fire				
Kerosene	Reference	–	–	15.3%
Dried leaves	269	[38, 501]	0.016	
Straw/grass	240	[5, 477]	0.044	
Papers	170	[−81, 422]	0.289	
Injera was baked				
Yes	Reference	–		15.2%
No	180	[86, 273]	<0.001	
Number of meals cooked per day				
One meal	Reference	–		
Two meals	−15	[−211, 181]	0.982	
Three and above meals	−43	[−229, 143]	0.846	
Opening between the wall and roof				
Yes	Reference	–		
No	−113	[−237,10]	0.072	

Discussion

In the study area, solid biomass fuels are often used with inefficient and poorly vented cook stoves that result in a high concentration of toxic pollutants (13, 48, 49). In this study, mixed fuels (mainly firewood with cow dung) were the main type of fuel used for cooking. Similar studies reported biomass fuel as the main domestic energy source for rural Ethiopia (11, 50, 51). The study on fuel consumption patterns in India also revealed that the majority of households used solid biomass fuel (predominantly cow dung and wood) for cooking (52). However, this study's findings are different from results reported in Uganda and Kenya where charcoal and firewood only were reported to be the most commonly used cooking fuels, respectively (53, 54). These differences in fuel preference could be due to accessibility, types of a meal cooked, the design of used stoves, local temperature, and other behavioral and environmental factors.

In this study, the 24-h average kitchen area $PM_{2.5}$ concentration was estimated to be 405 µg/m^3 which is 27 times higher than the safety limit of 15 µg/m^3 recommended by the WHO 24-h mean air quality guideline and five times higher than the most flexible interim WHO target (IT-I) of 75 µg/m^3 (7) indicating the severity of kitchen area $PM_{2.5}$ levels in study rural households.

This estimated 24-h average kitchen area concentration of $PM_{2.5}$ was comparable to what is observed from the results of other kitchen

air pollution monitoring studies in Ethiopia. Studies conducted in southern Ethiopia using similar (13) and different (15) air monitor devices in the kitchen have reported comparable results of 410 μg/m^3 and 413 μg/m^3, respectively. Another published review report in Ethiopia also revealed 24-h average $PM_{2.5}$ concentration of 477 μg/m^3 (55). Another measurement of $PM_{2.5}$ during a single Injera baking event in Northwest Ethiopia reported an average $PM_{2.5}$ concentration of 855 μg/m^3 (56).

Nearly similar results were reported from studies conducted in India where a 24-h average concentration of 468 μg/m^3 was reported (57) and in Nepal with a 48-h average concentration of 417 ug/m^3 (58). A relatively higher concentration was reported in Pakistan where the average $PM_{2.5}$ concentration was 531 μg/m^3 (59) and in four states in India, 24-h average kitchen $PM_{2.5}$ concentrations of 600 μg/m^3 were reported (60). The differences in kitchen particle concentration suggest possible differences in local cooking practices, types of a meal cooked, and fuel types used. These high concentrations of $PM_{2.5}$ as reported both from this study and previously conducted research in the kitchens might be due to the inefficient burning of biomass fuels and inefficient dispersion of particles in the kitchen area.

Because of the differences in kitchen design, the kitchen area concentration of $PM_{2.5}$ also varies (61). Based on the independent sampling t-test, we found higher kitchen $PM_{2.5}$ concentrations in households with thatched roof kitchens compared to households with metal sheet roofed kitchens. This result is similar to research reports conducted in Nepal and Peru where having metal sheet roof kitchens showed some association with decreased $PM_{2.5}$ concentrations compared to roofs made of thatched/grass/straw (62, 63). Research results from Punjab in India also revealed that the concentration of $PM_{2.5}$ varies across different kitchen types (52). As was also evidenced by another study, having a thatched roof was positively associated with increased 24-h PM concentrations (64). The possible reason might be due to better and faster dilution and dispersion of the pollutant taking place in different openings (in the case of metal sheet roofed kitchens) as compared to the confined kitchen (most thatched/grass roofed kitchens).

In this study, we also found that kitchen $PM_{2.5}$ concentrations varied with different fuel types used for cooking. Hence, burning of mixed biomass fuels (mainly firewood with cow dung) emitted average higher $PM_{2.5}$ concentrations than using firewood or agricultural residues only. A similar study on the effect of the fuel type used for cooking in the household showed that women who cooked with dung cake had the highest exposures compared with those who cooked with crop residues and firewood, respectively, in Ethiopia (12). Similarly, the maximum $PM_{2.5}$ emissions were reported from the burning of dung cakes followed by agricultural residues and mixed fuel (wood and dung) uses in India (52). Another study in Nepal reported that biomass fuel was the most significant source of $PM_{2.5}$ followed by kerosene (62). But, in Uganda, women who used crop residues had higher exposures to $PM_{2.5}$ compared to those using wood (12). Because, many characteristics, including heating value, moisture content, chemical composition, and the size and density of the fuel, affect the amount of particles released and these characteristics can vary from fuel to fuel (65).

It is also common practice to use additional fuel to start the wood fire in the kitchen. Dried plant leaves, paper, kerosene, and straw/grass were commonly used wood fire starter fuels in the study area. We also found high $PM_{2.5}$ levels variability by starter fuel type. In the kitchen where kerosene was used to start the wood fire, the average $PM_{2.5}$ concentrations were higher followed by straw/grass users. It is also evidenced that rural Indian women commonly used kerosene to start a fire in the kitchen (66). Though the epidemiological evidence is limited in this regard, paper, plastics, or kerosene are used to start the fire because they have low ignition temperatures which help to catch fire immediately and help the wood or the dung to reach its required ignition temperature.

Recognizing the public health impact of HAP from biomass fuel use and considering the use of biomass fuels in developing countries is likely to remain stable in the near future, WHO suggested several practical interventions for a clean cooking transition before widespread affordable access to electricity (67–69). The introduction of locally acceptable improved stoves, improved housing and ventilation design (replacing thatched roof kitchen with CIS roofed kitchen), and education and awareness-raising to support necessary changes in cultural habits related to cooking are some of the strategies for reducing exposure to household air pollution (17, 56, 70). There is an evidence that a chimney-fitted improved stove reduced wood smoke exposures and was associated with reduced low birth weight occurrence (71). But the most effective way to improve indoor air quality is the use of cleaner fuels, such as biogas, ethanol, and liquefied petroleum gas (9, 17, 72) and electric, wind, and solar are the cleanest option for health (1, 67, 73) however, transition to these fuels is not yet feasible for low-income countries.

Conclusion

Rural households in the study area entirely depend on biomass fuel with traditional three-stone stoves for cooking which emits high levels of particulate matter that exceeded WHO guideline values. The reported kitchen $PM_{2.5}$ concentrations in this study are sufficiently high to be a cause for public health concerns. Since the average $PM_{2.5}$ concentrations were found to be highest in the thatched roof kitchens, replacing the kitchen's roof with CIS to ensure that it allows air exchange during cooking times may be of benefit. Types of cooking fuel, types of fuel used for igniting the cooking fuel, and Injera baking events are also significantly associated with higher $PM_{2.5}$ concentrations. Simple cost-effective interventions like the use of chimney-fitted improved stoves could also reduce kitchen PM $_{2.5}$ levels in the future. This study may be used as a starting point for intervention studies employing quantification of $PM_{2.5}$ levels and other parameters that has to be considered in reducing the $PM_{2.5}$ levels. Our findings also highlight the need to create awareness of the effects of HAP exposure and to identify best practices for reducing exposure in the kitchen to reduce pollution levels.

Potential limitations

Though seasonal variations were reported in previous studies with high concentrations recorded during the cold season (19, 62), the presence of this variation was not captured in this study. The PATS+ measures fine particles at concentrations ranging from 10 to 50,000 ug/m^3 and performed well when tested against a gravimetric standard. Due to the harsh sampling environment,

we were unable to validate our continuous monitoring against the gravimetric analysis of samples collected in parallel. Therefore, the absolute values of the $PM_{2.5}$ measurements may not be fully accurate and should be interpreted with caution. Although households were randomly selected for air monitoring from those participating in the stove trail study, the latter were recruited based on inclusion criteria which may exclude relevant households. Finally, we did not measure ambient air pollution and therefore cannot account for the proportion of concentration from ambient $PM_{2.5}$ sources.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the institutional review boards of Jimma University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HE and AH: conceptualization, designing of the methodology, recruitment, training of supervisors, and data collectors. SM and AH: formal data analysis, interpreting the result, writing draft manuscript, and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

Publisher's note

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Environmental pollutants increase the risks of acute exacerbation in patients with chronic airway disease

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Objective: Respiratory infections are a common cause of acute exacerbations in patients with chronic airway disease, however, environmental factors such as air pollution can also contribute to these exacerbations. The study aimed to determine the correlation between pollutant levels and exacerbation risks in areas exposed to environmental pollution sources.

Methods: From 2015 to 2016, a total of 788 patients with chronic airway diseases were enrolled in a study. Their medical records, including hospital visits due to acute exacerbations of varying severity were analyzed. Additionally, data on daily pollutant levels from the Air Quality Monitoring Network from 2014 to 2016 was also collected and analyzed.

Results: Patients with chronic airway disease and poor lung function (FEV1 $<$ 50% or obstructive ventilatory defect) have a higher risk of severe acute exacerbations and are more likely to experience more than two severe acute exacerbations within a year. The study found that in areas exposed to environmental pollution sources, there is a significant correlation between NO_2, O_3, and humidity with the main causes of severe acute exacerbation. When the levels of NO_2 were higher than 16.65 ppb, O_3 higher than 35.65 ppb, or humidity higher than 76.95%, the risk of severe acute exacerbation in patients with chronic airway disease increased.

Conclusion: Acute exacerbations of chronic airway disease can be triggered by both the underlying disease state and the presence of air pollution. Computer simulations and early warning systems should be developed to predict acute exacerbations of chronic airway disease based on dynamic changes in air pollution.

KEYWORDS

air pollution, chronic airway disease, acute exacerbation, nitrogen dioxide, ozone

Introduction

Chronic airway diseases, such as chronic obstructive pulmonary disease (COPD) and asthma, are characterized by chronic inflammation of the airways. Both conditions have common risk factors, such as tobacco smoking, exposure to air pollution, pulmonary infection, genetics, and aging. Smoking is the main cause of COPD (1), leading to increased respiratory symptoms and higher mortality rates due to rapid decline in lung function from long-term tobacco smoke exposure (2).

Exposure to high doses of pesticides, dusts, chemical agents, and fumes in environmental settings also contribute to the burden of COPD and asthma (3). Exposure to particulate matter (PM), such as $PM_{2.5}$, is also a significant risk factor for COPD and asthma. Studies have shown that the concentration of $PM_{2.5}$ in households with smokers is 10 times higher than in households without smokers (4). High concentrations of $PM_{2.5}$ could increase the risk of hospitalization in COPD patients (5). Studies have also demonstrated a correlation between exposure to $PM_{2.5}$ and respiratory infections (6). An increase of 10 $\mu g/m^3$ of $PM_{2.5}$ per cubic meter can increase the mortality rate of cardiopulmonary diseases by 6%. Conversely, a decrease of 10 $\mu g/m^3$ in $PM_{2.5}$ concentration can increase the average life expectancy of residents in an area by 0.61 years (7).

Asthma is a chronic lung disease that affects millions of people worldwide. The causes of asthma are varied and can include genetics, allergies, infections, or a combination of these factors. About 30% of asthmatic patients have an allergic constitution, with dust mites being the most common and important allergen in Taiwan (8). A recent integrated analysis study has shown that exposure to traffic-related air pollution during childhood, such as black carbon, NO_2, $PM_{2.5}$, and PM_{10}, is statistically significantly positively correlated with the subsequent occurrence of asthma (9). Additionally, a large study involving over 600,000 participants across three European generations found that long-term exposure to environmental air pollutants, particularly PM_{10} is positively associated with the prevalence of asthma (10). The study found that a 10 mg/m^3 increase in PM_{10} concentration resulted in a 12.8% increase in asthma prevalence, and the effect was particularly significant in individuals over the age of 50, with a history of smoking and lower educational levels.

Acute exacerbation of chronic airway diseases can lead to a decline in the quality of life of patients, and may result in complications such as sepsis or cardiopulmonary failure. In severe cases, it may even increase the risk of death and cause a heavy social and economic burden and medical expenditure. Current clinical treatments for chronic airway diseases mainly consist of inhaled bronchodilators and inhaled steroids, which can improve symptoms and reduce the risk of acute exacerbation (1). However, even with regular drug use, external environmental factors such as exposure to allergens, air pollutants, mold, haze, and cigarettes can still cause acute exacerbation. Respiratory tract infections are the most common cause of acute exacerbation, but about two-thirds of patients with acute exacerbation have no clear pathogenic bacteria.

Air pollution, particularly in urban areas, can have negative effects on individuals with pre-existing heart or lung conditions. Studies have shown a correlation between high levels of particulate matter in the air and increased incidence of COPD and asthma (11). However, more research is needed to fully understand the relationship between air pollution and respiratory health, including the effects of both short-term, high-peak exposures and long-term, low-level exposures (12). Numerous studies have linked air pollution to the development and exacerbation of airway diseases. However, identifying the specific pollutants or combinations that have the greatest impact on chronic airway diseases is crucial for targeted interventions. Investigating the susceptibility of certain populations, including those with pre-existing respiratory conditions, is also necessary. Further evaluation of mitigation strategies is required to effectively reduce air pollution and improve respiratory health. Therefore, a comprehensive research is required to gain a deeper understanding of how specific components of air pollution interact with other contributing factors in the development and exacerbation of airway diseases. The goal of this study is to investigate the relationship between intrinsic clinical conditions and extrinsic environmental factors (air pollution) and its impact on severe exacerbation of chronic respiratory diseases. The study will determine the correlation between air pollutant changes and acute exacerbations and use statistics to analyze the influence of intrinsic and extrinsic factors on exacerbation.

Materials and methods

The study participants of this research are patients diagnosed with chronic airway diseases in a medical center in Yunlin County, Taiwan, from 2015 to 2016, to explore the intrinsic clinical factors (age, gender, diagnosis classification, smoking history, comorbidities, laboratory examination values, lung function, blood data) and extrinsic environmental factors (air pollution indicators, carbon monoxide, nitrogen dioxide, ozone, PM_{10}, $PM_{2.5}$, sulfur dioxide, humidity, daily maximum temperature, daily minimum temperature) of these patients and, respectively, with whether there is severe acute exacerbation, and the frequency of exacerbation in these 2 years.

Research participation

The main purpose of this study is to investigate the impact of environmental factors on the long-term control of severe chronic airway disease patients. The study used the International Statistical Classification of Diseases and Related Health Problems 9th Revision (ICD−9) codes CM490−493, 496 and ICD−10 codes J42—J46, which are codes for COPD, Asthma and Asthma/COPD overlapping (ACO), to select patients with chronic airway diseases who were diagnosed during their visits to National Taiwan University Hospital Yunlin Branch in Douliou City, Yunlin County, Taiwan. Participants under 18 years old and those who did not continue to receive treatment after diagnosis would be excluded from the study.

Data collection

This is a retrospective study, and it was approved by the Research Ethics Committee with approval number 201411019RINB. Data collection from medical records included basic information such as sex, age, smoking history, medical history (cardiovascular disease, chronic kidney disease, diabetes, tuberculosis, viral hepatitis, lung cancer, other malignant tumors, etc.), diagnosis of chronic respiratory disease (COPD, asthma, ACO), time of diagnosis, laboratory values [such as white blood cell count (WBC) and its differentiation, IgE, allergen screening], and date and events of acute exacerbation to emergency department (ED) or hospital admission.

The diagnosis of COPD is based on symptoms such as dyspnea, chronic cough, sputum production, a history of recurrent lower respiratory tract infections, and exposure to risk factors. Confirming the diagnosis requires spirometry with a forced vital capacity maneuver, which shows a post-bronchodilator FEV1/FVC ratio below 0.7. (1). In contrast, asthma diagnosis relies on characteristic symptom patterns and evidence of variable expiratory airflow limitation, which is confirmed through bronchodilator reversibility testing (13). Asthma-COPD Overlap Syndrome (ACOS) is characterized by persistent airflow limitation and combines features of both asthma and COPD. It is identified by the presence of shared characteristics from both conditions (14).

The lung function test uses the Master Screen Body (JAEGER, GERMANY) instrument and the bronchodilator test, with the medication used being Berotec N (Fenoterol) Metered Aerosol 100 mcg/puff, 200 puffs/btl, and the data collected mainly includes post-forced expiratory volume in one second (FEV1) and post-FEV1/forced vital capacity (FVC) values.

The environmental factor registration data archives historical information from the Executive Yuan's Air Quality Monitoring Network, specifically from the Douliou Station. This data encompasses a range of critical metrics, including the air pollution index (PSI), carbon monoxide (CO), nitrogen dioxide (NO_2), ozone (O_3), PM_{10}, $PM_{2.5}$, sulfur dioxide (SO_2), humidity, daily high and low temperature.

Severe acute exacerbation of chronic airway disease is defined as a sudden and severe worsening of symptoms (e.g., coughing, wheezing, shortness of breath), which lead to visit emergency department or hospitalization.

Data processing and statistical analysis

This study used SPSS 22 software to perform various statistical analyses. Participant number, percentage, mean, and standard deviation were used to describe the distribution of participants with chronic airway diseases during acute exacerbation.

Pearson's chi-square test was utilized to assess the impact of intrinsic factors, which are categorical variables encompassing age ($\geq$70 years or below), gender (female or male), diagnosis (asthma, COPD, or ACO), smoking history (ex- and current or non-smokers), lung function (FEV1 $\geq$ 80%, 50% $\leq$ FEV1 $<$ 80%, 30% $\leq$ FEV1 $<$ 50%, FEV1 $<$ 30%), comorbidities (presence or absence of diabetes mellitus, cardiovascular disease, and lung cancer), and blood data (blood eosinophil $>$ 2 or $\leq$ 2%, neutrophil $>$ 65 or $\leq$ 65%), with respect to their influence on the frequency and presence of severe exacerbations in chronic airway disease. Univariate analysis was initially employed to identify intrinsic factors that significantly affect acute exacerbations, followed by multivariate logistic regression analysis to identify the most significant independent factors.

The *T*-test was employed to assess continuous variables and ascertain whether extrinsic environmental factors, specifically daily pollution values comprising CO, NO_2, O_3, SO_2, PM_{10}, and humidity, exerted a significant influence on the occurrence of exacerbations. Subsequently, a multivariate logistic regression analysis was conducted to identify the primary extrinsic factors contributing to acute exacerbations in patients with chronic airway disease.

ANOVA was employed to investigate the average monthly concentrations of NO_2, O_3, and humidity. Pearson's chi-square analysis was performed to inspect the occurrences of events in the months when patients with chronic airway diseases necessitated emergency care or hospitalization due to acute exacerbation. Furthermore, a multivariate linear regression analysis was conducted to evaluate the impact of NO_2, O_3, and humidity on the occurrence of severe acute exacerbations in individuals with chronic airway diseases.

Receiver operating characteristic (ROC) curves were employed to pinpoint pollution thresholds most likely to trigger acute exacerbations in patients with chronic airway diseases. Statistical significance was determined using a threshold of *p*-values below 0.05.

Results

Basic characteristics of patients with chronic airway disease

This study collected a total of 4,678 participants of patients diagnosed with chronic airway diseases and excluded 3,890 participants of patients who were under 18 years old or who did not continue to seek medical treatment after diagnosis, resulting in a total of 788 participants.

There were a total of 558 patients (70.8%) with COPD, 175 patients (22.2%) with Asthma, and 55 patients (7.0%) with ACO. The average age was 68.4 years old, with 417 patients (52.9%) being over 70 years old and there were 580 male patients (73.6%). Of the chronic airway disease patients collected in this study, 211 (26.8%) had never smoked, 162 (20.6%) were currently smoking, 311 (39.5%) had quit smoking, 7 (0.9%) were exposed to passive smoke. In terms of lung function, 259 patients (32.9%) had a Post-FEV1% $>$80%, 261 patients (33.1%) had a Post-FEV1% between 50 and 80, 108 patients (13.7%) had a Post-FEV1% between 30 and 50%, and 13 patients (1.6%) had a post-FEV1% $<$ 30%.

The most common comorbidities among chronic airway disease patients in this study were cardiovascular disease (CVD) (34.3%, $n = 270$), followed by chronic kidney disease (CKD) (17.6%, $n = 139$), diabetes mellitus (DM) (16.5%, $n = 130$), and lung cancer (3.6%, $n = 28$) (Table 1).

Blood biomarkers of patients with chronic airway diseases

In this study, several blood markers were collected from patients with chronic airway diseases. The mean value of white blood cells (WBC) was 10,140/mm^3, the mean value of neutrophils was 6,031.63/μl, the mean percentage of neutrophils was 67.41%, the mean value of eosinophils was 228.55/μl, the mean percentage of eosinophils was 2.48%, and the mean value of IgE was 267.79 U/L. Additionally, 158 patients underwent allergy screening, with dust mite allergy being the most common at 36.1%, followed by German cockroach allergy at 19.0%, fungus allergy at 8.2%, animal

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TABLE 1 The basic characteristics of patients with chronic respiratory diseases.

Clinical data	*N* (%)
Age (mean ± standard deviation) (years old)	68.4 ± 14.2
≧70	417 (52.9)
<70	371 (47.1)
Gender	
Male	580 (73.6)
Female	208 (26.4)
Cigarrete smoking	
None	211 (26.8)
Current	162 (20.6)
Quitted	311 (39.5)
Passive	7 (0.9)
Unreported	97 (12.3)
Diagnosis	
COPD	558 (70.8)
Asthma	175 (22.2)
ACO	55 (7.0)
Lung function Post-FEV1%	
FEV1 ≧ 80%	259 (32.9)
50% ≦ FEV1 < 80%	261 (33.1)
30% ≦ FEV1 < 50%	108 (13.7)
FEV1 < 30%	13 (1.6)
No report	147 (18.7)
Comorbidities	
Cardiovascular disease	270 (34.3)
Chronic kidney disease	139 (17.6)
Diabetes mellitus	130 (16.5)
Pulmonary tuberculosis	45 (5.7)
Virus hepatitis	37 (4.7)
Lung cancer	28 (3.6)
Other malignancy	43 (5.5)
Other disease	44 (5.6)
Blood biomarkers	**Mean ± standard deviation**
WBC (mm^3)	10.14 ± 43.70
Neutrophil counts (μl)	6,031.63 ± 31,630.94
Neutrophil (%)	67.41 ± 13.60
Eosinophil counts (μl)	228.55 ± 1,025.11
Eosinophil (%)	2.48 ± 2.95
IgE (U/L)	267.79 ± 525.09
Phadiotop	(*n* = 158, %)
Positive	79 (50.0)
Allergen	
Dust mite	57 (36.1)
Cockroach, German	30 (19.0)
Fungus	13 (8.2)
Animal (mixes)	11 (7.0)
Food	9 (5.7)
Grass (mixes)	5 (3.2)

COPD, chronic obstructive pulmonary disease; ACO, asthma/COPD overlapping; FEV1, forced expiratory volume in one second.

fur allergy at 7.0%, food allergy at 5.7%, and grass pollen allergy at 3.2% (Table 1).

Analysis of the intrinsic clinical factors that impact severe acute exacerbations in patients with chronic airway disease

The elderly group (70 years or older) had a higher likelihood of severe acute exacerbations of their chronic airway disease, with 39.09% experiencing such exacerbations ($p < 0.001$). Additionally, this group was found to be more likely to experience more than two exacerbations per year (21.10%, $p = 0.004$).

Male patients had a higher chance of experiencing severe acute exacerbations of their chronic airway disease, with 35.34% experiencing such exacerbations ($p = 0.05$). Furthermore, men were found to be more likely to have more than two severe acute exacerbations per year than women (19.14%, $p = 0.03$).

Patients with ACO had a higher likelihood of experiencing severe acute exacerbations (41.82%, $p < 0.001$) compared to other airway disease groups. Both COPD and ACO patients were more likely to experience two or more severe acute exacerbations per year (20.79 and 7.43%, respectively) compared to Asthma patients ($p < 0.001$).

Patients who have ever smoked or currently smoke had a correlation with severe acute exacerbation. The proportion of patients who have ever smoked or currently smoke and have severe acute exacerbation is higher at 36.58% ($p = 0.02$). The proportion of patients who have ever smoked or currently smoke and have two or more severe acute exacerbations per year is significantly higher at 19.87% ($p = 0.024$) than that of patients who have never smoked.

Patients with worse lung function (FEV1 between 30 and 50%) had a higher proportion of severe acute exacerbation (51.85%, $p < 0.001$). The proportion of patients with FEV1 < 30% and have two or more severe acute exacerbations per year is significantly higher at 30.77% ($p < 0.001$) than those with better lung function.

Patients with a history of diabetes have a higher likelihood of experiencing severe acute exacerbations (43.85%, $p = 0.006$). Patients with diabetes were found to be more likely to have two or more severe acute exacerbations per year (22.59%, $p = 0.03$). Similarly, patients with a history of cardiovascular disease were

more likely to experience severe acute exacerbations (41.11%, $p = 0.001$) and have a correlation with the number of severe exacerbations per year, with those more likely to have two or more severe acute exacerbations per year (22.59%, $p = 0.005$). Additionally, patients with a history of lung cancer had a higher probability of severe acute exacerbation (57.14%, $p = 0.007$) and were also found to have a correlation with the number of severe exacerbations per year, with those more likely to have two or more severe acute exacerbations per year (39.29%, $p = 0.002$) (Table 2).

Patients with Eosinophil (EOS) levels <2% had a higher likelihood of experiencing a severe acute exacerbation (53.79%, $p < 0.05$) and, when compared to the number of severe acute exacerbations per year, it was found that these patients were also more likely to experience two or more severe exacerbations per year (28.28%, $p < 0.05$). Similarly, patients with Neutrophil levels > 65% had a higher likelihood of experiencing a severe acute exacerbation (53.26%, $p < 0.05$) and, when compared to the number of severe acute exacerbations per year, it was found that these patients were also more likely to experience two or more severe exacerbations per year (29.21%, $p < 0.05$). These findings suggest that during acute exacerbation or infection, there is a tendency for an increase in Neutrophil levels and a decrease in Eosinophil levels (Table 2).

Multivariate logistic analysis was conducted to investigate the relationship between intrinsic factors (such as age, gender, diagnosis of lung disease, smoking history, comorbidities, blood data, and lung function) and the presence of severe acute exacerbation. It was found that patients with chronic airway disease and poor lung function (FEV1 < 50%), diabetes and blood data EOS < 2% were significantly related to severe acute exacerbation (Figure 1A). Patients with obstructive lung disease (COPD and ACO), have a significant correlation with experiencing two or more acute exacerbations annually (Figure 1B).

The relationship between acute exacerbation and air pollutant

A comparison analysis of acute exacerbation days of chronic airway disease patients with recorded daily pollution values (CO, NO_2, O_3, SO_2, PM_{10}, and humidity) (Figure 2A) shows that the presence of acute exacerbation days has reached a significant level ($p < 0.05$) in the values of these pollutants, indicating that on the day of patients with acute exacerbation, there are higher levels of CO, NO_2, O_3, SO_2, PM_{10}, and humidity (Figures 2B–G). After performing a multivariate logistic regression combining daily pollution values, it was found that the main extrinsic factors that may cause acute exacerbation in patients with chronic airway disease are likely to be NO_2, O_3, and humidity (Figure 2H). Environmental factors monthly and annual trend graphs showed that the concentration of NO_2 and O_3 is higher in spring and winter, while the relative humidity is higher in May of each year (Supplementary Figure 1).

The analysis of the possible main causes of acute exacerbations of chronic airway disease (NO_2, O_3, humidity) in relation to the average monthly concentrations of 2014–2016, revealed that the concentration of NO_2 (Supplementary Table 1) was significantly higher between November and January than in other months; the concentration of O_3 (Supplementary Table 2) was significantly higher between September and November than in other months. This indicates that the concentrations of NO_2 and O_3 are significantly higher in the spring and winter seasons, which is consistent with the fact that patients with chronic airway diseases often experience severe acute exacerbations during these seasons. Humidity (Supplementary Table 3) was significantly higher between April and June, which is consistent with the fact that it is the rainy season and humidity is heavier during this period.

Cross-analysis of patients with chronic airway disease during severe acute exacerbation

This study analyzes the dates on which patients with chronic airway diseases visited emergency or hospitalized due to acute deterioration, and examines whether certain months are more likely to cause severe acute exacerbation in patients. Although the test results are not significant, it can be seen that the proportion of patients experiencing severe acute exacerbation in spring and winter is higher than in other months (Supplementary Table 4).

This study compares the monthly averages of NO_2, O_3, and humidity levels from 2014 to 2016 with the months in which patients with chronic airway diseases visited the emergency department or were hospitalized. The comparison is shown in Figures 3A, B. It is found that the levels of NO_2 and O_3 are higher in spring and winter, and there are also more people visiting the hospital. In terms of humidity, the previous statistical analysis stated that humidity is significantly higher in April-June than in other months, but this figure shows that May, when humidity is high, is not the month when the most people visit the hospital.

Monthly acute exacerbation and air pollutant regression analysis

Multivariate linear regression analysis was used to examine the effects of NO_2, O_3, and humidity on the occurrence of severe acute exacerbations of chronic airway diseases. It was found that humidity had the greatest effect on the occurrence of severe acute exacerbations, followed by NO_2, while O_3 had no significant effect (Table 3). The combined explanatory power of the three variables was 71.8%. The results of the multiple regression analysis showed that for every 1 ppb increase in NO_2, the number of severe acute exacerbations increased by 46.4%, and for every 1% increase in humidity, the number of severe acute exacerbations increased by 52.6%. Both were statistically significant, as shown in Table 3.

The study aimed to examine the relationship between daily pollution values of NO2, O3, and humidity, and the incidence of acute exacerbation days in patients with chronic airway disease using ROC curve analysis (Figure 4). Concentrations of NO2 in the air greater than 16.65 ppb were found to be associated with an increased risk of severe acute exacerbation [area under curve (AUC): 0.597, 95% CI: 0.560–0.633]. Similarly, O3 concentrations exceeding 35.65 ppb were linked to a higher risk of severe acute exacerbation (AUC: 0.557, 95% CI: 0.519–0.595). Additionally,

TABLE 2 The relationship between intrinsic clinical factors and severe acute exacerbation (AE) in chronic airway diseases.

	Severe AE				X^2	Events of severe AE in 1 year**				X^2
	No		Yes			≦1		≧2		
	n = 525		*n* = 263			*n* = 651		*n* = 137		
Age (*n*, %)										
<70 y/o	271	73.05%	100	26.95%	13.00***	322	86.79%	49	13.21%	8.521**
≧70 y/o	254	60.91%	163	39.09%		329	78.90%	88	21.10%	
Gender (*n*, %)										
Male	375	64.66%	205	35.34%	3.83*	469	80.86%	111	19.14%	4.697*
Female	150	72.12%	58	27.88%		182	87.50%	26	12.50%	
Diagnosis (*n*, %)										
COPD	355	63.62%	203	36.38%	15.81***	442	79.21%	116	20.79%	16.89***
Asthma	138	78.86%	37	21.14%		162	92.57%	13	7.43%	
ACO	32	58.18%	23	41.82%		47	85.45%	8	14.55%	
Smoking (*n*, %)										
Never	225	71.43%	90	28.57%	5.45*	272	86.35%	43	13.65%	5.10*
Yes	300	63.42%	173	36.58%		379	80.13%	94	19.87%	
Lung function (*n*, %)										
No report	80	54.42%	67	45.58%	42.98***	114	77.55%	33	22.45%	20.84***
FEV1 ≧ 80%	200	77.22%	59	22.78%		235	90.73%	24	9.27%	
50% ≦ FEV1 < 80%	186	71.26%	75	28.74%		212	81.23%	49	18.77%	
30% ≦ FEV1 < 50%	52	48.15%	56	51.85%		81	75.00%	27	25.00%	
FEV1 < 30%	7	53.85%	6	46.15%		9	69.23%	4	30.77%	
DM (*n*, %)										
No	452	68.69%	206	31.31%	7.68*	552	83.89%	106	16.11%	4.524*
Yes	73	56.15%	57	43.85%		99	76.15%	31	23.85%	
CVD (*n*, %)										
No	366	70.66%	152	29.34%	11.05*	442	85.33%	76	14.67%	7.753*
Yes	159	58.89%	111	41.11%		209	77.41%	61	22.59%	
Lung cancer (*n*, %)										
No	513	67.50%	247	32.50%	7.38*	634	83.42%	126	16.58%	9.694*
Yes	12	42.86%	16	57.14%		17	60.71%	11	39.29%	
Eosinophil										
Eosinophil < 2%	134	46.21%	156	53.79%	12.310*	208	71.72%	82	28.28%	4.060*
Eosinophil > 2%	151	61.38%	95	38.62%		195	79.27%	51	20.73%	
Neutrophil										
Neutrophil < 65%	149	60.82%	96	39.18%	10.592*	197	80.41%	48	19.59%	6.595*
Neutrophil > 65%	136	46.74%	155	53.26%		206	70.79%	85	29.21%	

AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; ACO, Asthma/COPD overlapping; DM, diabetes mellitus; CVD, cardiovascular disease.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

humidity levels above 76.95% were associated with an elevated risk of severe acute exacerbation (AUC: 0.575, 95% CI: 0.536–0.614). The results demonstrated that exceeding specific concentration thresholds of NO_2, O_3, and humidity plays a crucial role in the occurrence of severe acute exacerbation in patients with chronic airway disease.

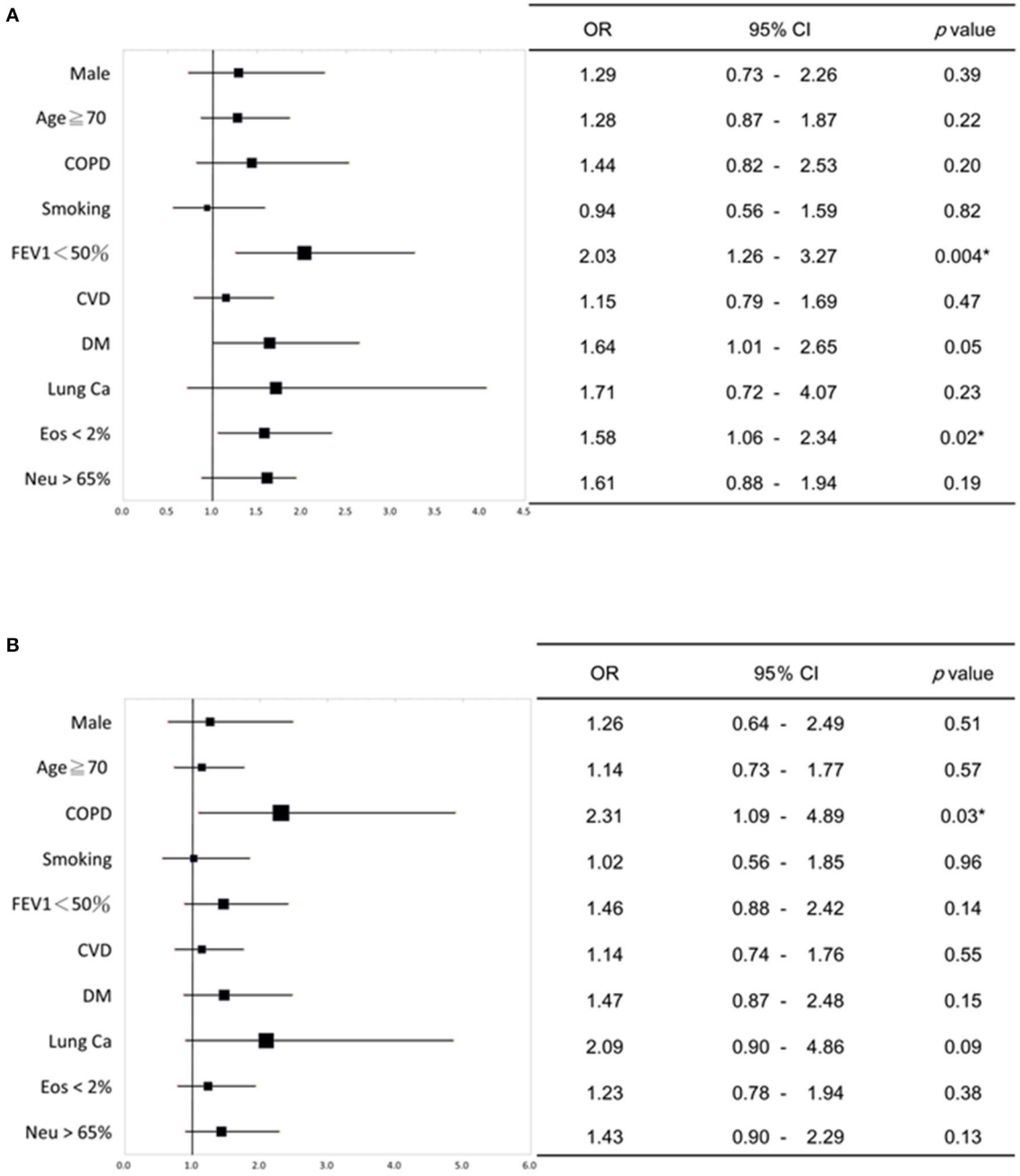


FIGURE 1
Multivariate logistic regression analysis of the relationship between intrinsic factors and severe acute exacerbation of chronic airway disease. **(A)** Patients with chronic airway disease, impaired lung function (FEV1 < 50%), diabetes, and low eosinophil levels in blood (<2%) showed a significant link to severe acute exacerbation. **(B)** Patients with obstructive lung diseases (COPD and ACO) showed a significant relationship with having two or more acute exacerbations per year. The forest plots in **(A, B)** depict the odds ratio (OR) values, while the upper and lower lines indicate the 95% confidence interval (CI). *P*-values below 0.05 were considered statistically significant. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; CVD, cardiovascular disease; DM, diabetes mellitus; Ca, Cancer; Eos, Eosinophil; Neu, neutrophil. *$P < 0.05$.

Discussion

The findings of our study demonstrate a significant association between severe acute exacerbation and specific clinical factors in patients with chronic airway diseases. Specifically, impaired lung function (FEV1 < 50%), diabetes, and low eosinophil levels in the blood (<2%) were strongly linked to the occurrence of severe acute exacerbations. Moreover, patients diagnosed with obstructive lung diseases, such as COPD and ACO, exhibited a significant relationship with experiencing two or more acute exacerbations per

A

Pollutants	AE days	Mean	SD	*t*
PSI	Yes	62.62	18.83	1.48
	No	60.79	18.56	
CO (ppm)	Yes	0.47	0.16	4.01*
	No	0.43	0.15	
NO_2 (ppb)	Yes	17.64	6.94	5.05*
	No	15.4	6.59	
O_3 (ppb)	Yes	37.93	20.7	3.26*
	No	33.82	18.45	
SO_2 (ppb)	Yes	3.85	1.63	2.66*
	No	3.59	1.38	
$PM_{2.5}$ ($\mu g/m^3$)	Yes	35.9	21.56	1.92
	No	33.33	19.73	
PM_{10} ($\mu g/m^3$)	Yes	62.48	29.21	2.39*
	No	58.18	26.53	
Humidity (%)	Yes	76.46	8.45	3.61*
	No	74.73	6.74	
Temperature difference	Yes	7.84	2.72	0.12
	No	7.83	2.47	

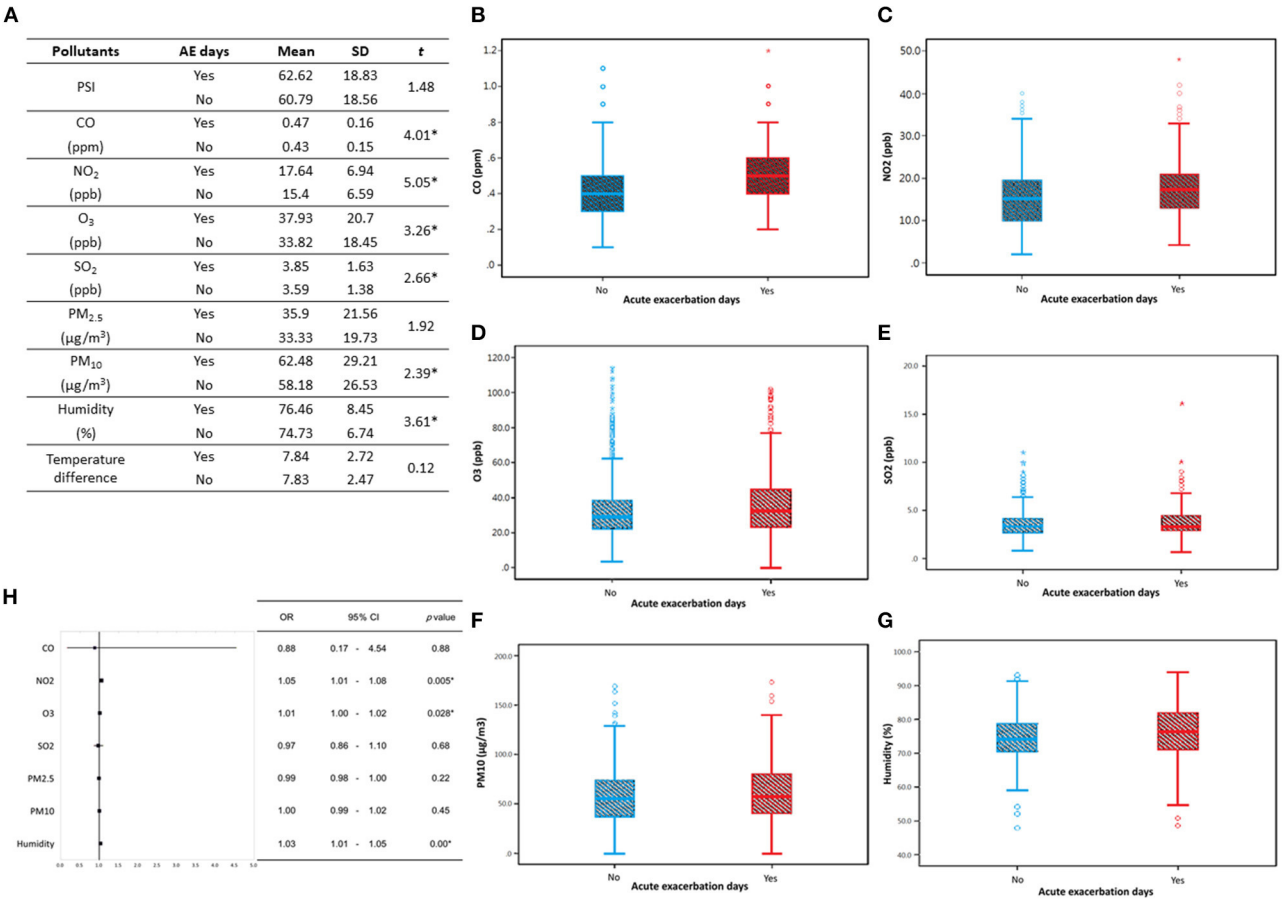


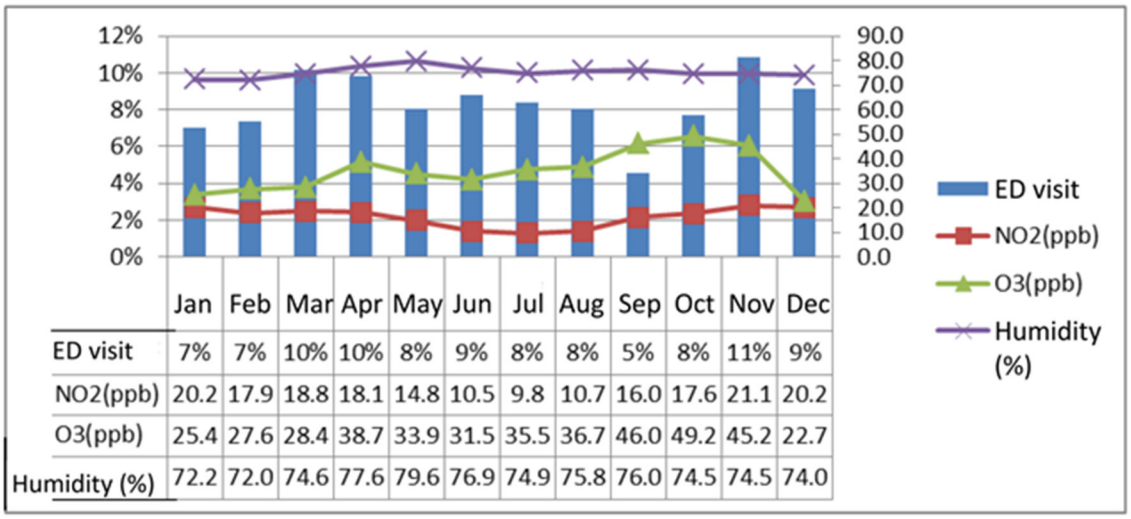
FIGURE 2
Compare the acute exacerbation days of chronic respiratory disease patients with the recorded daily pollution values. **(A)** There is a significant difference in the daily pollution values (CO, NO_2, O_3, SO_2, PM_{10}, humidity) on the days of acute exacerbation analyzed by independence *T*-test. Analyze the daily pollution values **(B)** CO; **(C)** NO_2; **(D)** O_3; **(E)** SO_2; **(F)** PM_{10}; **(G)** humidity, with or without acute exacerbation. The bar graphs indicated mean value with one standard deviation, and the box indicated the 25–75 percentile of each pollution values. These pollutants show higher levels at the days of acute exacerbation. **(H)** A multivariate logistic regression analysis combining daily pollution values revealed that the potential causes of acute exacerbation in patients with chronic respiratory disease could be NO_2, O_3, and humidity. The forest plots illustrate the odds ratio (OR) values, with the upper and lower lines representing the 95% confidence interval (CI). Statistical significance was determined using a threshold of *p*-values below 0.05. AE, Acute exacerbation; SD, standard deviation; PSI, pollutant standards index; OR, odds ratio; CI, confidence interval. *$P < 0.05$.

year. The study also found that there are higher levels of CO, NO_2, O_3, SO_2, PM_{10}, and humidity on the day of acute exacerbation, and that the main causes of acute exacerbation in patients with chronic airway disease are significantly related to NO_2, O_3, and humidity. When the air NO_2 > 16.65 ppb, O_3 > 4.75 ppb, or humidity > 76.95%, there is a risk of acute exacerbation in patients with chronic airway disease.

This study found that patients over the age of 70, men, those who have previously smoked and those who currently smoke, as well as those with worse lung function (FEV1 < 50%), had a higher proportion of acute exacerbations of chronic airway disease. Therefore, quitting smoking early, elderly patients should receive regular flu and pneumonia vaccinations, and lung rehabilitation exercises and breathing exercises can effectively reduce the risk of acute exacerbation of chronic airway disease by slowing the deterioration of lung function (1).

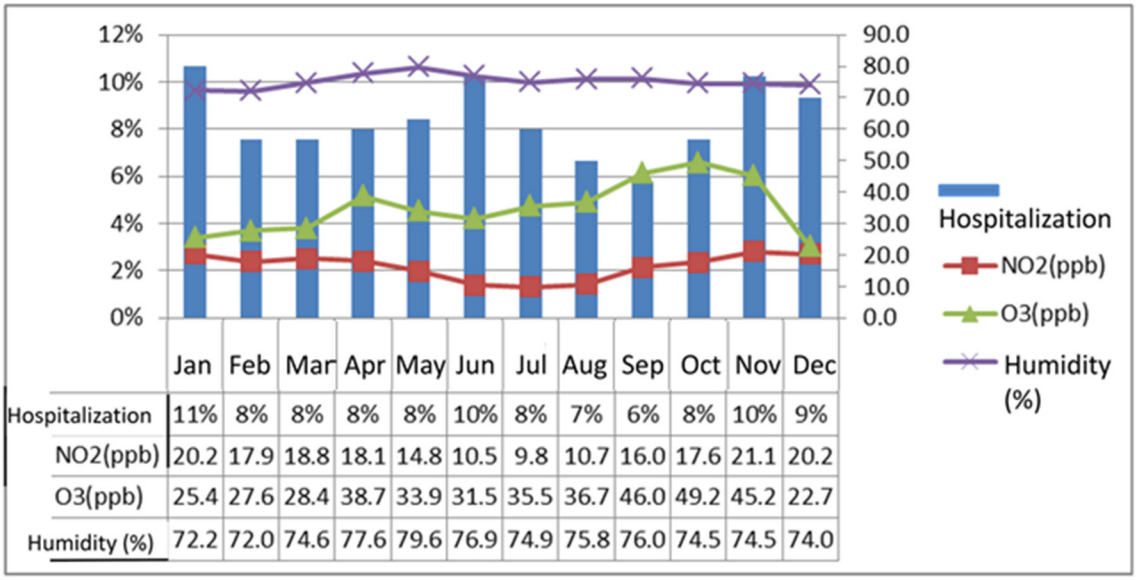
The interest in utilizing biomarkers to identify COPD and asthma patients at risk of exacerbations is rapidly growing. An association has been observed between increased blood and sputum eosinophils and more frequent exacerbations (15). Currently, blood eosinophil counts (≥300 cells/μL) serve as a guideline for identifying COPD and asthma patients at higher risk of exacerbations, as well as those more likely to benefit from treatment with inhaled corticosteroids or biologic agents (13, 16). Patients with higher blood eosinophil counts in COPD and asthma also exhibit elevated lung eosinophil numbers and higher levels of markers indicating type-2 inflammation in the airways (17, 18). Furthermore, there is an increase in neutrophil extracellular trap formation among patients with severe COPD, which is associated with more frequent exacerbations and a loss of microbiota (19). This neutrophil extracellular trap formation is also linked to an increased exacerbation risk in patients with COPD and asthma. Our study revealed that patients with EOS levels below 2% and those with neutrophil levels above 65% are more likely to experience severe and more frequent acute exacerbations. These findings suggest that during acute exacerbation or infection, there

A



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
ED visit	7%	7%	10%	10%	8%	9%	8%	8%	5%	8%	11%	9%
NO2(ppb)	20.2	17.9	18.8	18.1	14.8	10.5	9.8	10.7	16.0	17.6	21.1	20.2
O3(ppb)	25.4	27.6	28.4	38.7	33.9	31.5	35.5	36.7	46.0	49.2	45.2	22.7
Humidity (%)	72.2	72.0	74.6	77.6	79.6	76.9	74.9	75.8	76.0	74.5	74.5	74.0

B



	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Hospitalization	11%	8%	8%	8%	8%	10%	8%	7%	6%	8%	10%	9%
NO2(ppb)	20.2	17.9	18.8	18.1	14.8	10.5	9.8	10.7	16.0	17.6	21.1	20.2
O3(ppb)	25.4	27.6	28.4	38.7	33.9	31.5	35.5	36.7	46.0	49.2	45.2	22.7
Humidity (%)	72.2	72.0	74.6	77.6	79.6	76.9	74.9	75.8	76.0	74.5	74.5	74.0

FIGURE 3
This study compares the monthly average concentrations of NO_2, O_3, and humidity from 2014 to 2016 with the months in which patients with chronic airway disease experienced acute exacerbation and sought treatment at the emergency department (ED) or were hospitalized. The analysis, as depicted in **(A, B)**, reveals that NO_2 and O_3 concentrations are higher in spring and winter, and correspondingly, a higher number of patients seek medical treatment. While statistical analysis shows that humidity is highest from April to June, the number of patients visiting the hospital during these months is not necessarily the highest, particularly in May when humidity is at its peak.

is a tendency for an increase in neutrophil levels and a decrease in eosinophil levels. Despite the clinical heterogeneity of chronic airway disease, identifying distinct inflammatory endotypes has proven challenging, although rare genetic endotypes of COPD and asthma have been recognized. Further research is necessary to establish connections between inflammatory endotypes and clinical manifestations and outcomes in chronic airway disease, particularly in predicting the response to precision medicines.

The development of lung cancer may be related to smoking mainly. However, air pollution has been linked to the development of lung cancer. Long-term exposure to air pollution, particularly fine particulate matter ($PM_{2.5}$) and nitrogen oxides (NOx), has been associated with an increased risk of lung cancer as found in studies (20, 21). Studies have also revealed a positive association between exposure to ambient air pollution and lung cancer incidence and mortality (22, 23). The World Health Organization's International Agency for Research on Cancer (IARC) has classified outdoor air pollution as a carcinogen to humans (24). In Taiwan, more than 50% of patients with lung cancer had never smoked. $PM_{2.5}$ level changes can affect lung cancer incidence and patient

TABLE 3 Linear regression analysis of monthly acute exacerbation events and air pollutants NO_2, O_3, and humidity.

Model		Non-standardized coefficient		Standardized coefficient	*t*	*p*
		B	Standard error	Beta		
1	(Constant)	−0.428	3.019		−0.142	0.888
	NO_2	0.591	0.177	0.496	3.334	0.002
2	(Constant)	−1.177	3.171		−0.371	0.713
	NO_2	0.51	0.204	0.429	2.504	0.017
	O_3	0.058	0.072	0.139	0.811	0.423
3	(Constant)	−60.81	14.776		−4.115	<0.001
	NO_2	0.553	0.168	0.464	3.292	0.002
	O_3	−0.011	0.061	−0.025	−0.172	0.864
	Humidity	0.815	0.199	0.526	4.1	<0.001

Independent variable: events of severe acute exacerbations.

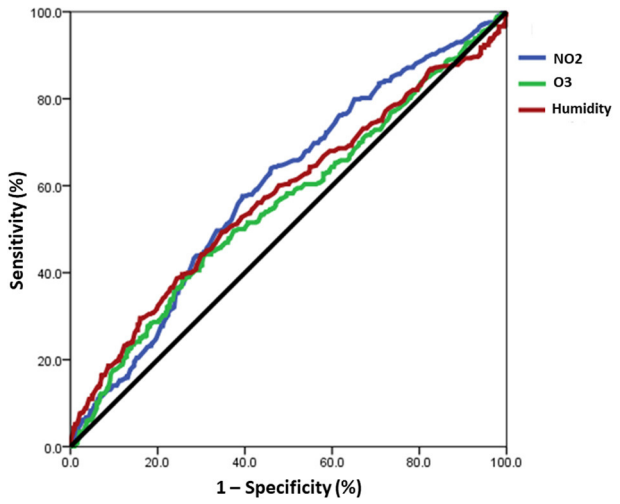


FIGURE 4
The ROC curve analysis revealed a correlation between the daily values of NO_2, O_3, and humidity and the occurrence of acute exacerbation days in patients with chronic airway disease. A risk of severe acute exacerbation of chronic airway disease in patients with chronic airway disease was found when the concentration of NO_2 in the air exceeds 16.65 ppb (AUC: 0.597), O_3 exceeds 35.65 ppb (AUC: 0.557), and humidity is above 76.95% (AUC: 0.575).

survival (25). Therefore, high-risk patients need to regularly follow up with low-dose computed tomography screening for lung cancer. This study found a relationship between comorbidities and acute exacerbations, with lung cancer being the most common comorbidity of chronic airway disease. Meanwhile, cardiovascular disease and diabetes should be controlled through medication and lifestyle improvements, which can also effectively control chronic airway diseases.

Air pollution is a major cause of airway and allergic diseases such as asthma and COPD. Traffic and domestic fires using biomass fuels are significant sources of air pollution. Despite the challenge of measuring personal exposure to pollutants, new methods are revealing links between air pollution and airway diseases (26). COPD patients, who are often former or current smokers, are particularly sensitive to air pollution and should be protected from high levels of particulate matter (27). Studies have shown particulate matter air pollution to be a key factor in the development and exacerbation of COPD and asthma (28, 29). In addition, increased levels of NO_2, CO, O_3, and PM_{10} and fluctuating temperature were linked to acute COPD exacerbation in older patients (30). $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, O_3, average temperature, and diurnal temperature range were found to impact COPD exacerbations among various air pollutants and meteorological factors (31).

Exacerbations are primarily instigated by respiratory viral infections; however, bacterial infections and environmental factors, including ambient air pollution and elevated temperatures, can also contribute to initiating and amplifying these events (32, 33). Short-term exposure to fine particulate matter ($PM_{2.5}$) and coarse particulate matter (PM_{10}) is linked to escalated rates of hospitalizations, ED visits, outpatient consultations (33), and heightened mortality in cases of COPD exacerbations (32, 34, 35). A growing body of research indicates the association between air pollution and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (36–38). Our study results revealed that the highest number of hospitalizations occurred during the first month when both NO2 and O3 levels were at their lowest. Similar patterns were observed in March and April for ED visits. Exposure to high levels of $PM_{2.5}$, PM_{10}, and SO_2, as well as low levels of NO_2 and high levels of CO, were found to increase the risk of AECOPD. The cumulative exposure-response curves showed different trends: approximately linear for $PM_{2.5}$, "V"-shaped for PM_{10}, "U"-shaped for NO_2, and inverted-"V" for SO_2, CO, and O_3. Specifically, high levels of SO_2, NO_2, and extreme concentrations of $PM_{2.5}$ had the most pronounced impact on the day of exposure, and these effects persisted for a certain duration. This suggests that the immediate effects of these air pollutants were stronger than the delayed effects. Furthermore, low levels of SO_2 and CO exhibited a protective effect on AECOPD, which gradually increased over time until a lag of 27 days (39). The nonlinear effects of different air pollutants on AECOPD varied based on factors such as gender, age, and seasons (40).

According to the study results, it was found that there is a relationship between NO_2, O_3, humidity, and acute exacerbation of chronic airway diseases, but no obvious connection with suspended particulate matter $PM_{2.5}$ and PM_{10}. Therefore, the exacerbation of chronic airway diseases may be caused by pollutants carried by suspended particulate matter. However, current air pollution prevention laws do not have regulations on the concentration limits of these pollutants. In the future, it is hoped that further research will confirm the harmful effects of certain concentrations of NO_2 and O_3 on human health, leading to legislation that monitors pollution sources and reduces emissions. Taiwan has an island climate with high humidity. However, it remains unknown if the proportion of acute exacerbation of chronic airway diseases in Taiwan is higher than in countries with a continental climate. The study results showed that humidity is linked to acute exacerbation of chronic airway diseases and a humid environment can promote the growth of dust mites, mosquitoes, or fungi. Therefore, it is recommended that patients with chronic airway diseases use dehumidifiers and other equipment to reduce the humidity in their homes.

The study has some limitations. It only sampled patients with chronic airway diseases from a single medical center in Taiwan between 2015 and 2016, with insufficient sample size and reference time, and may not reflect patient behavior or regional differences. The study didn't consider patients who sought treatment elsewhere during acute episodes and didn't examine physician medication choices or patient medication adherence. In the future, the study aims to obtain more data via the National Health Insurance database.

Conclusions

This study found that patients over the age of 70, who are male, smokers, and have worse lung function, had a higher proportion of acute exacerbations of chronic airway disease. Additionally, the study found that patients with certain blood cell counts and those exposed to certain air pollutants had a higher likelihood of experiencing severe acute exacerbations. The study suggests that reducing exposure to these pollutants and encouraging quitting smoking could help lower the risk of acute exacerbations. The findings of this study may be useful in identifying patients at high risk for severe acute exacerbations and in developing targeted interventions to prevent exacerbations. Reduced air pollution from industrial upgrades, vehicle and fuel renovations, better public transportation and healthy city development can prevent respiratory diseases. A comprehensive national environmental policy is needed to address this pressing issue (24). A warning system, such as a mobile app, should be created to help patients with chronic respiratory diseases prepare and take preventive measures in advance.

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 humans were approved by the Research Ethics Committee of National Taiwan University Hospital and National Taiwan University Hospital Yunlin Branch (201411019RINB). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this is a retrospective study.

Author contributions

C-HC and Y-FC wrote the main manuscript text. H-CP prepared figures. C-YC revised the manuscript. B-WC supervised the study. All authors reviewed the manuscript. 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.2023.1215224/full#supplementary-material

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Systemic inflammation mediates environmental polycyclic aromatic hydrocarbons to increase chronic obstructive pulmonary disease risk in United States adults: a cross-sectional NHANES study

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Introduction: This study explored the relationship between environmental polycyclic aromatic hydrocarbons (PAHs) and Chronic obstructive pulmonary disease (COPD), and identified systemic inflammation as a mediator of the increased risk of COPD from PAHs.

Methods: Data were obtained from 60,936 middle-aged and older Americans recruited in the National Health and Nutrition Examination Survey 2005–2016. Environmental PAHs were measured in terms of urinary concentrations of PAHs metabolites (NAP: 1-hydroxynaphthalene, FLU: 2-hydroxyfluorene, PA: 1-hydroxyphenanthrene, and PYR: 1-hydroxypyrene). We used multifactor logical analysis to figure out the link between PAHs and COPD, and the non-linear relationship was examined using Restricted cubic spline. Spearman correlation analysis was utilized to analyze the connection between PAHs and systemic immune-inflammation index (SII).

Results: The results showed that the COPD population had higher NAP (3.550 vs. 3.282, $p < 0.001$), FLU (2.501 vs. 2.307, $p < 0.001$), PA (2.155 vs. 2.082, $p = 0.005$), and PYR (2.013 vs. 1.959, $p = 0.008$) levels than non-COPD population. In unadjusted logistics analysis, the risk of COPD with log NAP was higher [OR = 1.461, 95% CI (1.258–1.698), $p < 0.001$]. Upon taking into account, confounders like sex, age, race, and log NAP still increased a possible COPD risk [OR = 1.429, 95% CI (1.224–1.669), $p < 0.001$]. Similarly, FLU, PA, and PYR significantly increased the risk of COPD (all OR > 1, $p < 0.05$), both unadjusted and adjusted. Furthermore, Restricted cubic spline demonstrated a strong link between PAHs levels and COPD risk ($p < 0.05$). Additionally, a Spearman correlation analysis revealed a favorable association between log FLU and log SII ($R = 0.43$, $p = 0.006$), while NAP, PA, and PYR levels were not associated with log SII (all $p > 0.05$). Ultimately, the mediating effect analysis revealed a mediating effect capacity of 5.34% for the SII-mediated association between FLU and COPD.

Conclusion: The findings suggest that the risk of COPD is significantly increased when environmental PAHs exposure is at high levels, and that systemic inflammation may be involved in the process.

KEYWORDS

polycyclic aromatic hydrocarbons, chronic obstructive pulmonary disease, systemic immune-inflammation index, mediation analyses, NHANES

1 Introduction

Chronic obstructive pulmonary disease (COPD), a prevalent chronic airway disease, is distinguished by persistent respiratory symptoms and irreversible airflow limitation (1). As a heterogeneous disease, COPD develops frequently in adults over 40 and is intimately linked to environmental pollution, especially with exposure to toxic gases (2, 3). Currently, as environmental pollution aggravates and the population ages, a growing number of people are suffering from COPD. Meanwhile, high morbidity and mortality rates are associated with COPD, which imposes a significant disease burden on the international community (4).

Polycyclic aromatic hydrocarbons (PAHs) are a collection of compounds that are produced through the incomplete combustion of oil, coal and natural waste, gas, and other organic materials. PAHs have been linked to a variety of health risks (5, 6). PAHs can be derived from a broad variety of sources, including but not limited to vehicle exhaust, asphalt, coal tar, wildfires, agricultural burning, food that has been grilled, and tobacco smoke (7, 8). After entering the human body, PAHs are metabolized by means of the peroxidase pathways, and produce carcinogens such as reactive diol epoxides, o-quinones, and free radical cations (9). Although PAHs are known to be a health hazard, the association between PAHs and COPD has not been fully elucidated so far, and the specific pathways by which PAHs affect COPD are not yet known.

A recently developed inflammatory indicator is known as the systemic immune-inflammation index (SII) that simply combines the functions of neutrophil, platelet, and lymphocyte counts; due to its high stability, it can effectively reflect systemic inflammation (10, 11). SII is strongly associated with prognosis and survival of cancer (11), endocrine disease (12), and kidney disease (10). SII and COPD are closely related, and previous studies have confirmed that blood SII is associated with COPD exacerbations (13). Higher SII levels in COPD patients also significantly increase the risk of death (14). Besides, SII mediates the development of many related disorders. For instance, You et al. (15) found that SII mediated the association between sedentary behavior and sleep disorders. Yin et al. (16) also demonstrated that elevated SII levels slightly mediated the association between sleep disturbance and depression. Furthermore, additionally, SII might act as a mediator between fetal famine exposure on the development of cardiovascular disease in adulthood (17).

Apparently, there is a paucity of direct robust evidence supporting the link between PAHs and the risk of COPD, and there is little known about whether PAHs progress by increasing systemic inflammation and thereby influence the development of COPD. Therefore, we desire to investigate the link between PAHs and COPD in middle-aged and older adults among participants recruited by the National Health and Nutrition Examination Survey (NHANES). In addition, we included SII as a mediator to assess whether SII was involved in the connection between COPD and PAHs in adults over 40 years old.

2 Materials and methods

2.1 Source of subjects

The NHANES is a survey that is carried out by the National Center for Health Statistics in conjunction with the Centers for Disease Control and Prevention. Since it stores data from the civilian population of the United States, it is nationally representative. The Ethics Review Committee gave their stamp of approval to the protocol for collecting the data, and before they were questioned or evaluated, each participant in the study gave their informed consent. Hence, the study did not require additional informed consent as well as ethical endorsement. The NHANES public data file from 2005 to 2016 was used to construct the dataset in this study, and this research was carried out with the assistance of a total of 60,936 people.

2.2 PAHs metabolites measurement

The main exposure variable in this study was PAH with reference to the former studies (8), we used urine PAHs to measure the level of PAHs in individuals. The NHANES database participants' urine PAHs were first extracted in (ng/L), including 1-hydroxynaphthalene (NAP), 2-hydroxyfluorene (FLU), 1-hydroxyphenanthrene (PA), and 1-hydroxypyrene (PYR). The measurement of PAHs was accomplished principally through the enzymatic digestion of urine, followed by extraction, derivatization, and examination by means of capillary gas chromatography coupled with high-resolution mass spectrometry. In brief, we used isotopic dilutions of carbon-13-labeled internal standards. The ions of each analyte and each carbon-13 labeled by internal standard were monitored and the abundance of each ion was measured. In this way, the levels of PAHs were measured by the analysis of certain urine analytes. Since urine PAH concentrations are skewed distribution data, the log10 log transformation was taken (18). The specific measurement method is described in detail in the NHANES at https://www.cdc.gov/nchs/nhanes/index.htm.

2.3 COPD definition

Referring to previous studies (19), if the following conditions are met, it can be diagnosed as COPD: (1) FEV1/FVC < 0.7 after inhaling bronchodilators; (2) concerning questions from the MCQ questionnaire "mcq160g" or "mcq160p": "ever told you had emphysema," answering "yes" was considered COPD; and (3) Over 40 years of age, long-term use of selective phosphodiesterase-4 inhibitor, mast cell stabilizer, leukotriene modulator and inhaled corticosteroids, and a history of smoking or chronic bronchitis.

2.4 Mediating variable

The mediating variable in this study was systemic inflammation, which was assessed based on SII. SII = P × N/L (P: peripheral platelet, N: neutrophil, L: lymphocyte, in $\times 10^9$/L) (10). A higher SII represents a higher level of systemic inflammation in the study population. Since SII is also skewed distribution data, $\log_{10}$ log transformation was also taken.

2.5 Other covariates

Patient baseline information variables were selected primarily in terms of demographics, social factors, lifestyle habits, and comorbidities. As well as demographics such as gender, age, and race, social factors such as education level and marriage were also considered. Behavioral data were collected on smoking and alcohol consumption as part of the study. Also, variables associated with

medical comorbidities, such as BMI, hypertension, diabetes, and hyperlipidemia, were collected. In this study, smoking was not considered as a covariate in the subsequent logistic regression because of the high correlation between smoking and the level of exposure to PAHs (20). Missing data were filled by interpolation.

2.6 Statistical analysis

Quantitative data were verified using the *t*-test or rank sum test, and the categorical variable data were verified using the χ^2 test to examine variations in cohort characteristics between outcome variable groups. Determine the covariates that need to be adjusted, including age, race, sex, and BMI. Preliminary analysis included multifactorial logistic regression to investigate the relationship between PAHs and CPOD. Restricted cubic spline was used to examine the nonlinear relationship between the COPDs variables and PAHs. An analysis of Spearman correlations was performed to assess the relationship between PAHs and SII. Finally, In order to identify the potential mediating effects of mediating variables on the association between PAHs and COPD, we used a mediation effect model (21). R.3.5.2[1] was used for all data analysis. A sample size calculation was not performed ex ante, just based on available data. $p < 0.05$ was set as the level of statistical significance.

3 Results

3.1 Characteristics of NHANES participants

Initially, a total of 60,936 participants participated in the survey. Among them, 4,241 people were included in the final analysis. Ultimately, excluding data without outcomes or exposures, 4,241 middle-aged and older United States participants (COPD: 291, and non-COPD: 3950) were included (Figure 1).

Table 1 shows the basic characteristics for study participants. Participants with COPD numbered 291 and those non-COPD numbered 3,950 (Table 1). With increasing age, COPD prevalence increased, specifically in participants of 40–49 years (14.8%), 50–59 years (19.9%), and ≥ 60 years (65.3%) (Table 1). Also, there was a significant difference between the COPD and non-COPD groups in terms of the proportion of age ≥ 60 years [(65.3%) vs. (47.7%), $p < 0.001$] and the proportion of men [(57.7%) vs. (49.6%), $p = 0.007$] were significantly higher in the COPD group than in the non-COPD group (Table 1). Divorced, separated, and widowed [(35.7%) vs. (29.1%), $p = 0.040$] individuals were more common in the COPD group in comparison to non-COPD patients, while in terms of higher education [(70.4%) vs. (71.4%), $p = 0.040$], the two groups were not significantly different (Table 1). Furthermore, there was a significant increase in "Former" smoking [(47.8%) vs. (29.3%), $p < 0.001$] and "Now" smoking [(34.7%) vs. (18.1%), $p < 0.001$] behavior in the COPD population compared with the non-COPD population. Similarly, COPD patients consumed more alcohol than non-COPD patients [(88.3%) vs. (79.1%), $p < 0.001$; Table 1]. In terms of phlebotomy, there was no significant difference in Alanine aminotransferase (AST) and Aspartate aminotransferase (ALT) between the two groups (all $p > 0.005$, Table 1). In contrast, estimated glomerular filtration rate (eGFR) levels were lower in the COPD population compared to those without COPD population [(78.0) vs. (86.9), $p < 0.001$; Table 1]. Furthermore, for medical comorbidities, there was a greater prevalence of hypertension [(68.7%) vs. (54.6%), $p < 0.001$] and diabetes [(29.6%) vs. (23.8%), $p = 0.026$] among people with COPD than among people without COPD (Table 1). BMI and hyperlipidemia did not differ significantly between these two groups (all $p > 0.005$, Table 1).

1 http://www.R-project.org

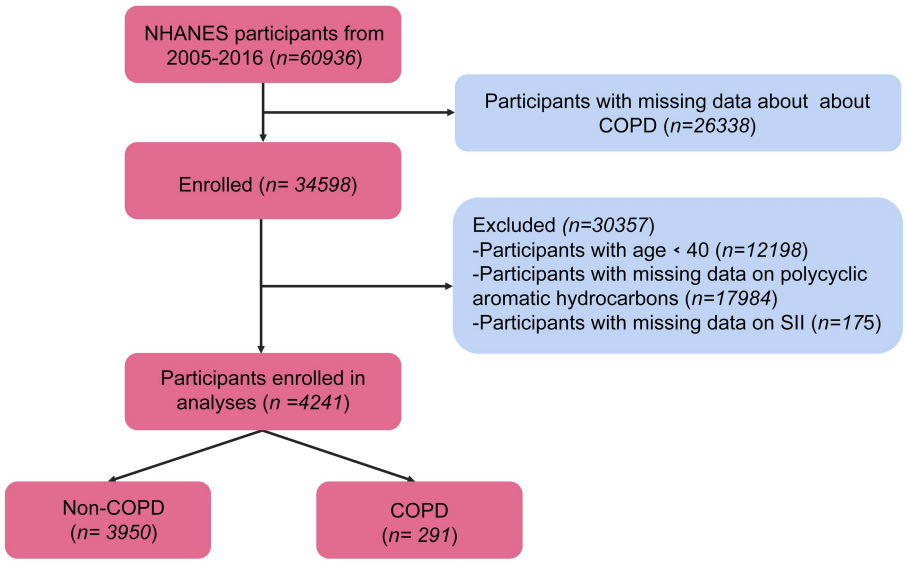

FIGURE 1
Flow diagram of the screening and selection process.

TABLE 1 Characteristics of participants enrolled in study.

Characteristic	Non-COPD (*n* = 3,950)	COPD (*n* = 291)	*p* value
Age (years)			<0.001
40–49	1,085 (27.5%)	43 (14.8%)	
50–59	981 (24.8%)	58 (19.9%)	
≥60	1,884 (47.7%)	190 (65.3%)	
Male sex	1,958 (49.6%)	168 (57.7%)	0.007
Race			<0.001
Hispanic	977 (24.7%)	32 (11.0%)	
Non-Hispanic white	1,967 (49.8%)	204 (70.1%)	
Non-Hispanic black	765 (19.4%)	43 (14.8%)	
Other	241 (6.1%)	12 (4.1%)	
Education beyond high school	2,819 (71.4%)	205 (70.4%)	0.738
Marital status			0.040
Never married	332 (8.405%)	18 (6.2%)	
Married or living with partner	2,467 (62.5%)	169 (58.1%)	
Divorced, separated, or widowed	1,151 (29.1%)	104 (35.7%)	
BMI (kg/m^2)			0.176
<25	1,003 (25.4%)	88 (30.2)%	
25–29	1,382 (35.0%)	98 (33.7%)	
≥30	1,565 (39.6%)	105 (36.1%)	
ALT (U/L)	22.0 (17.0–28.0)	21.0 (16.0,28.0)	0.257
AST (U/L)	24.0 (20.0–28.0)	23.0 (21.0,29.0)	0.67
eGFR (mL/min per 1.73 m^2)	86.9 (71.6–99.7)	78.0 (63.8,94.5)	<0.001
Alcohol user	3,126 (79.1%)	257 (88.3%)	<0.001
Smoker			<0.001
Never	2,079 (52.6%)	51 (17.5%)	
Former	1,157 (29.3%)	139 (47.8%)	
Now	714 (18.1%)	101 (34.7%)	
Diabetes	939 (23.8%)	86 (29.6%)	0.026
Hypertension	2,156 (54.6%)	200 (68.7%)	<0.001
Hyperlipidemia	3,097 (78.4%)	242 (83.2%)	0.056
PAHs			
Log NAP	3.282 (2.898–3.834)	3.550 (3.087–4.051)	<0.001
Log FLU	2.307 (2.009–2.702)	2.501 (2.138–2.961)	<0.001
Log PA	2.082 (1.806–2.354)	2.155 (1.880–2.433)	0.005
Log PYR	1.959 (1.695–2.267)	2.013 (1.747–2.362)	0.008

Categorical data are displayed as *n* %. Non-normal distribution data are displayed as median (Q1–Q3). χ^2 analysis is used to test significance between groups for categorical data. Kruskal Wallis rank sum test is used to test significance between groups for non-normal distribution data. BMI, Body mass index; eGFR, Estimated glomerular filtration rate; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; NAP, 1-hydroxynaphthalene; FLU, 2-hydroxyfluoren; PA, 1-hydroxyphenanthrene; and PYR, 1-hydroxypyrene.

3.2 Association between PAHs levels and COPD risk

According to Table 1, COPD patients had higher NAP [(3.550) vs. (3.282), $p < 0.001$], FLU [(2.501) vs. (2.307), $p < 0.001$], PA [(2.155) vs. (2.082), $p = 0.005$], and PYR [(2.013) vs. (1.959), $p = 0.008$] levels compared with non-COPD patients.

Also, in unadjusted logistics analysis (Table 2), the risk of developing COPD was higher with the growth of log NAP. Each 1 unit increase in log NAP meant a 1.461-fold increase in COPD risk [OR = 1.461, 95% CI (1.258–1.698), $p < 0.001$]. Taking into account sex, age, race, and BMI as covariates, with the increase of log NAP, the risk of developing COPD remained high [OR = 1.429, 95% CI (1.224–1.669), $p < 0.001$; Table 2]. Similarly, an increased risk of COPD was associated with FLU, PA, and PYR

TABLE 2 Odds ratios for associations between PAHs and COPD.

OR (95% CI)	Un-adjusted	*p* value	Adjusted	*p* value
Log NAP	1.461 (1.258–1.698)	<0.001	1.429 (1.224–1.669)	<0.001
Log FLU	1.804 (1.461–2.227)	<0.001	2.072 (1.654–2.597)	<0.001
Log PA	1.403 (1.055–1.864)	0.020	1.417 (1.056–1.901)	0.027
Log PYR	1.357 (1.054–1.747)	0.018	1.677 (1.290–2.180)	<0.001

Adjusted for age, race, sex, and BMI.

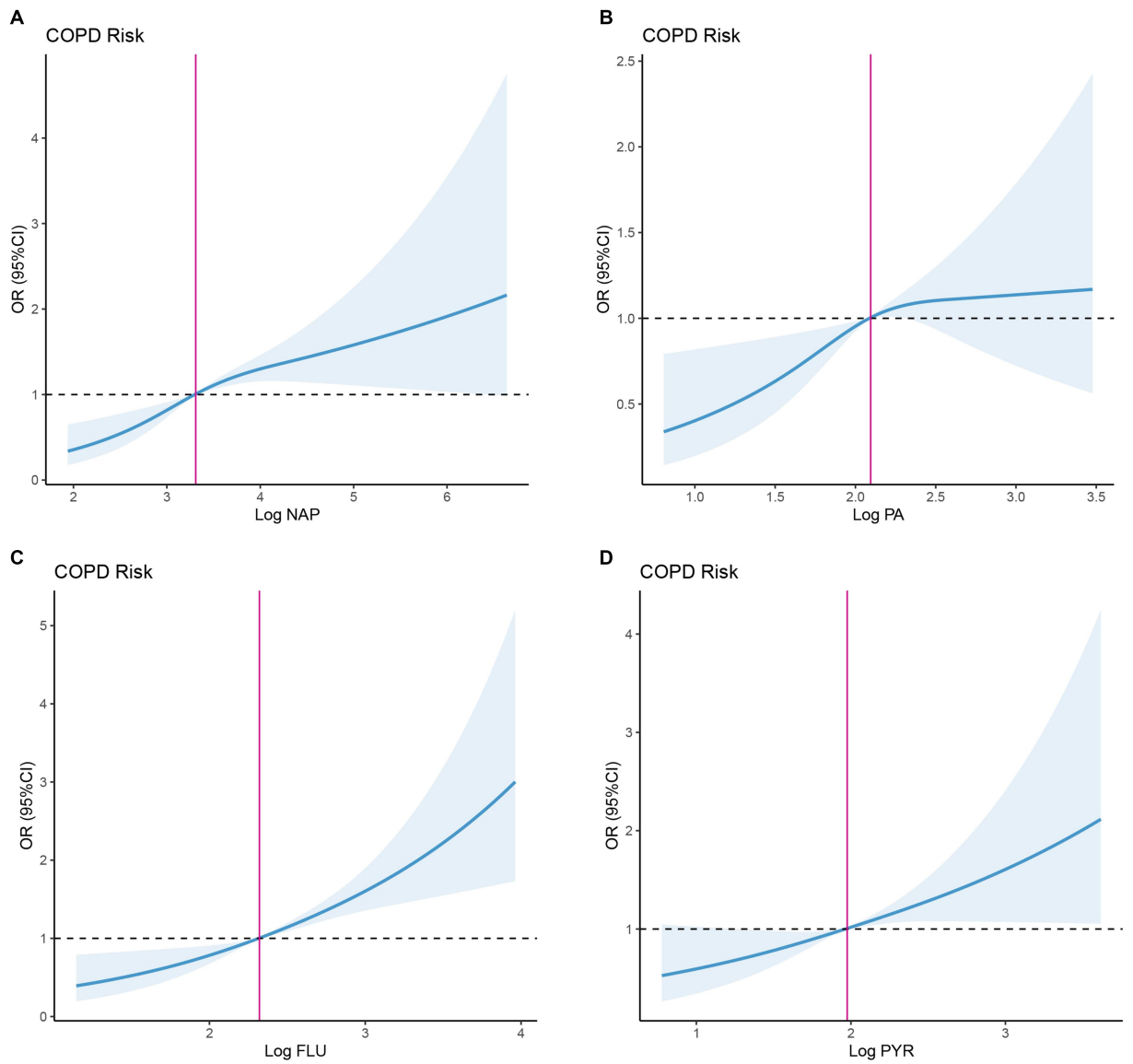

FIGURE 2
Dose–response association between PAHs and OR of COPD. **(A)** Dose–response association between NAP and OR of COPD. **(B)** Dose–response association between FLU and OR of COPD. **(C)** Dose–response association between PA and OR of COPD. **(D)** Dose–response association between PYR and OR of COPD. NAP, 1-hydroxynaphthalene; FLU, 2-hydroxyfluorene; PA, 1-hydroxyphenanthrene; and PYR, 1-hydroxypyrene.

(all OR > 1, $p < 0.05$; Table 2), both unadjusted and adjusted.

Moreover, we analyzed the non-linear relationship between PAHs and COPD prevalence risk based on RCS. Overall, risks of COPD were positively correlated with PAH levels (Figure 2). Specifically, COPD risk tended to increase with the rise of log NAP, with the inflection point (OR = 1) occurring at log NAP = 3.309 (Figure 2A; Table 3), and this trend was not significant in the period before and after the inflection point ($p > 0.05$). Similarly, there was a similar intra-segmental variation around the inflection point for log PA (Figure 2B;

Table 3). However, there was no significant trend in COPD risk with the increase of log FLU in the pre-inflection point segment, but a significant trend in COPD risk with the increase of log FLU in the post-inflection point segment ($p < 0.05$; Figure 2C; Table 3). Log PYR, conversely, was significantly correlated with COPD risk in both pre-and post-inflection point segments ($p < 0.05$; Figure 2D; Table 3).

3.3 Association between PAHs levels and systemic inflammation

Besides, we explored the association between PAHs levels and SII. Spearman analysis revealed a positive correlation between log FLU and log SII in the overall study population ($R = 0.43$, $p = 0.006$, Supplementary Table S1; Figure 3A), while other types of PAHs exposure levels were not significantly correlated with log SII (all $p > 0.05$, Figure 3A). Furthermore, based on the log FLU median, participants were divided into two groups: high-log FLU and low-log FLU. As compared with the low-log FLU group, the high-log FLU group had significantly higher SII ($p = 0.016$; Figure 3B), suggesting that as log FLU levels increased, systemic inflammation levels also tended to increase.

TABLE 3 Threshold effect analysis of PAHs on odds ratios for COPD using the restricted cubic spline model.

ITEM	Inflection point (OR = 1)	Adjusted β (95%CI)	*p* value
Log NAP	3.309		
< Inflection point		1.745 (0.866–3.518)	0.119
≥Inflection point		1.211 (0.942–1.555)	0.135
Log FLU	2.321		
< Inflection point		1.555 (0.681–3.550)	0.295
≥Inflection point		1.915 (1.303–2.816)	<0.001
Log PA	2.095		
< Inflection point		1.660 (0.749–3.678)	0.212
≥Inflection point		1.314 (0.623–2.063)	0.681
Log PYR	1.976		
< Inflection point		2.226 (1.064–4.662)	0.034
≥Inflection point		1.722 (1.062–2.792)	0.027

β represented increased value of odds ratios for COPD when log PAHs increased by 1 unit. All was adjusted for age, race, sex, and BMI.

3.4 Mediating effect analysis

Finally, we analyzed the mediating effects of log FLU, log SII, and COPD risk after covariate adjustment. As shown in Figure 4, an increase in log FLU increased the risk of COPD, with a total effect value was 0.046 (95% CI: 0.031–0.060, $p < 0.001$), including a direct effect value was 0.044 (95% CI: 0.028–0.060, $p < 0.001$). In addition, the indirect effect value for log FLU leading to COPD prevalence risk via log SII was 0.002 [(95% CI (0.001–0.003), $p < 0.001$); Figure 4].

To conclude, the mediating effect of systemic inflammation mediating the association between FLU and COPD prevalence risk produced a mediating effect capacity of 5.34% (Figure 4).

4 Discussion

In general, PAHs are mainly exposed to people through breathing indoor and outdoor polluted air and smoking (22). PAHs exposure is not a single effect, but often has multiple pathways, depending on the level of exposure (duration of time), the concentration of exposure to PAHs, toxicity, and routes of exposure, such as inhalation, ingestion, or dermal contact, as well as factors influencing human age, habits of living, and health status (23).

During large cross-sectional study of middle-aged and older adult people in the United States, higher concentrations of

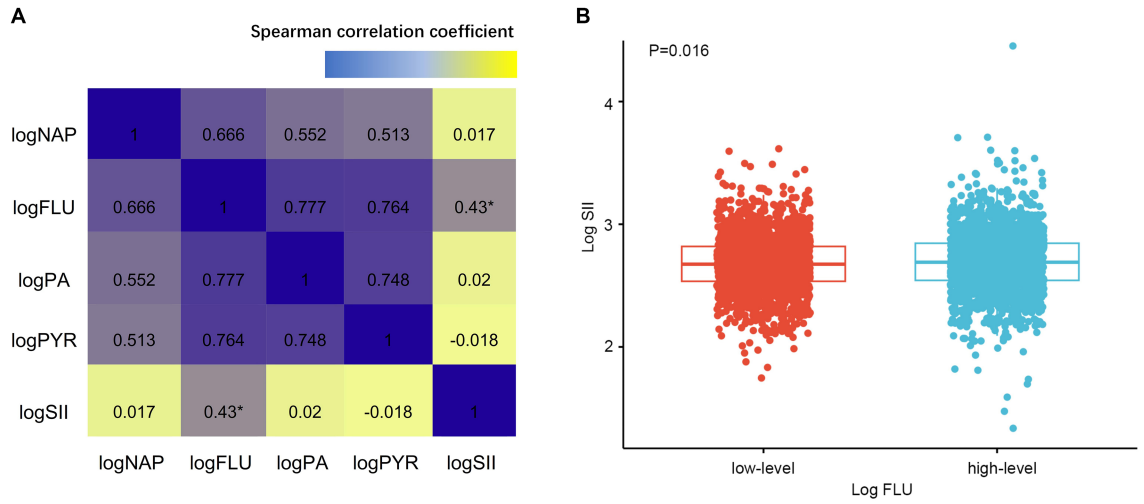

FIGURE 3
(A) Associations between PAHs and SII by Spearman correlation analysis. **(B)** Different SII levels of FLU. SII, Systemic immune-inflammation index. *$p < 0.005$.

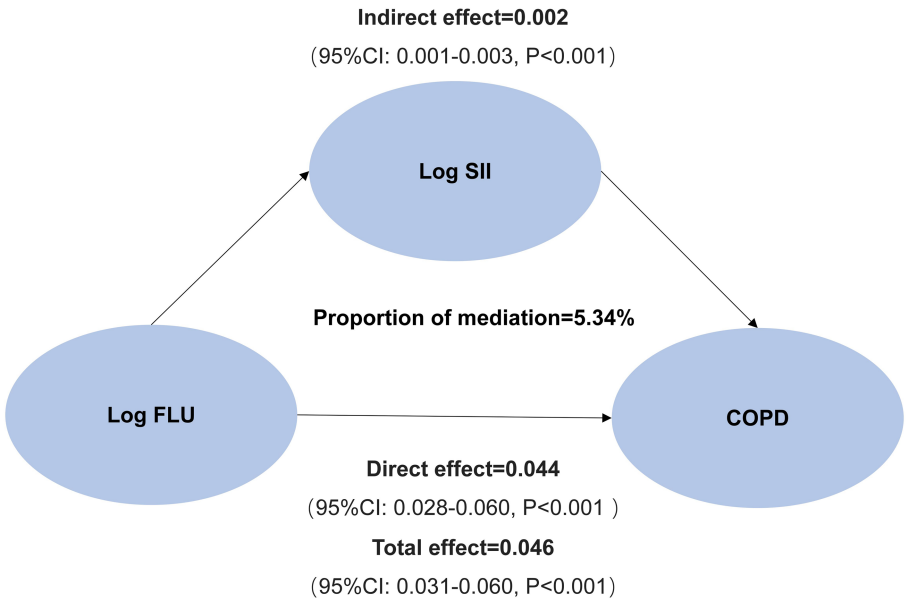

FIGURE 4
Mediation analysis of SII on the interaction between FLU and prevalence of COPD.

environmental PAHs were positively correlated with the risk of COPD. Previous studies have also shown similar results. For instance, Peng et al. (18) found that PAHs, both present and continuous exposure, contributed significantly to COPD risk, particularly NAP (OR: 1.83, $p < 0.005$) and FLU (OR: 2.29, $p < 0.005$). Furthermore, we verified that COPD patients are generally older male, and have a higher prevalence of smoking as well as alcohol consumption in accordance with previous research (18). Previous studies (18) have found that there was an independent association between lower BMI and COPD risk in nonsmokers. In contrast, the BMI of the two groups did not differ significantly, which might be attributed to errors caused by the period of data collection (NHANES 2007–2016), sample size (COPD: 500) of Peng et al. (18) not being exactly the same as ours, as well as our inclusion of a population restricted to >40 years. The main cause of chronic obstructive pulmonary disease is chronic airway inflammation and oxidative stress (24). PAHs can contribute to the activation of airway inflammation through Wnt5a-YAP/TAZ signaling, leading to acute lung dysfunction (25). Our study also found that FLU was positively associated with SII, and the mediating effect showed that SII mediated the association between FLU and COPD prevalence risk, but other types of PAHs exposure levels were not significantly associated with SII. As a result of its association with chronic bronchitis, FLU has been linked to various lung diseases (26), emphysema, asthma (27), lung infection, and COPD, which in line with our study's findings (28).

Currently, research on the human hazards caused by PAHs primarily focuses on deformities, carcinogenicity, and neurotoxicity, while studies on the chronic lung inflammation caused by direct exposure to PAHs are relatively limited (29). Through mediating effects analysis, we found that FLU may significantly increase the risk of COPD in the population by increasing systemic inflammation. It has been shown that PAHs can increase oxidative stress and thus increase the risk of asthma in children (30). Therefore, it can be inferred that the oxidative stress caused by PAHs, represented by FLU, causes an elevated level of systemic inflammation and increases the risk of slow COPD disease in exposed populations.

Polycyclic aromatic hydrocarbons are primarily generated during the incomplete combustion of organic materials (31). PAHs are also present in certain manufactured goods such as dyes, plastics, and pesticides. Due to their widespread presence, human exposure to PAHs is almost inevitable, with inhalation and ingestion being the primary routes of exposure (31).

The impact of PAHs on human health is significant, particularly in relation to lung health. Inhalation of PAHs can lead to both acute and chronic respiratory conditions (32). Preventing or minimizing exposure to PAHs is crucial for lung health. This can be achieved through a multi-pronged approach. At an individual level, lifestyle changes such as quitting smoking, reducing consumption of charred foods, and avoiding exposure to vehicle exhausts can significantly reduce PAH exposure (33). From an occupational perspective, workers in high-risk industries should be provided with appropriate personal protective equipment and safety training (33). At a broader societal level, stricter regulation and enforcement of industrial emissions, promotion of cleaner sources of energy, and regular monitoring of air quality can help control the levels of PAHs in the environment (34).

2-hydroxyfluorene, as a type of PAH, has been associated with various health effects largely related to its ability to induce oxidative stress and inflammation. In our study, after adjusting for covariates such as age, sex, race, and BMI, log FLU had a positive effect on the risk of COPD prevalence, and the indirect effect of log FLU leading to the risk of COPD prevalence through log SII accounted for 5.34% of the risk of COPD prevalence, suggesting that SII is an important pathway for FLU to increase the risk of COPD prevalence, and that the overall effect of 5.34% of the risk of COPD prevalence due to FLU may be realized through the systemic inflammatory response realized.

Although this mediating effect may appear relatively small, it is statistically significant and represents an important contribution to the overall effect of the disease in a complex disease pathology. According to Ferguson et al. (35) urinary PAH metabolites, which are biomarkers of internal PAH exposure, are associated with biomarkers of inflammation, angiogenesis, and oxidative stress in pregnant women. Although their study focuses on pregnant women, it demonstrates the potential of PAHs, including FLU, to induce systemic inflammation. Moreover, Cheng et al. (36) found that IL-22, a cytokine involved in immune response and inflammation, might be a potential mediator of associations between urinary PAH metabolites and health outcomes including fasting plasma glucose and type 2 diabetes. This study provides further evidence of the mechanism through which PAH exposure, including FLU, can lead to systemic inflammation. In a similar vein, Zhang et al. (37) showed that exposure to PAHs in outdoor air was associated with respiratory health, inflammation, and oxidative stress biomarkers in healthy young adults. Indeed, it remains unclear as to how FLU specifically affects systemic inflammation, but this finding also re-enforces the link between PAH exposure and inflammation and extends these findings to respiratory health, which is relevant to our research on COPD.

In light of these findings, we hypothesize that exposure to FLU may lead to systemic inflammation, as measured by SII, through the induction of oxidative stress and the production of pro-inflammatory cytokines. This increased systemic inflammation then may contribute to the development or exacerbation of COPD. However, the specific mechanisms through which FLU influences SII and COPD risk warrant further study.

Nonetheless, there are still some limitations to our study. At first, the present study is a cross-sectional study and cannot analyze the association between PAHs and COPD over time, which needs to be complemented by a longitudinal study. Besides, PAHs or SII can only be used as a qualitative diagnostic tool for COPD and cannot assess the extent of COPD as well as lung function. Therefore, the correlation between the dose of PAHs exposure and the severity of COPD needs to be elucidated by further experiments. Also, the present study is an association study and cannot explain causes and effects of COPD caused by PAHs. Furthermore, how PAHs affect COPD is very complex, and more basic validation of the relationship is needed, and future studies need to fully elucidate the specific molecular biological mechanisms of NAP and FLU-induced COPD.

5 Conclusion

In the study, we found a strong association between exposure to PAHs and COPD risk among a representative sample across the middle-aged and older adult people in United States and that there is a mediation effect, a process mediated through systemic inflammation. In particular, FLU has the potential to elevate SII and thereby increase the risk of COPD.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Centers for Disease Control and Prevention in United States. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

YX carried out the acquisition and interpretation of data and was the major contributor to drafting the manuscript. YX and LZ carried out the clinical partial data collection and analysis. WH and YX participated in drawing tables and diagrams. HL was responsible for correcting the language and grammar. WH was responsible for reviewing and revising some drawings and tables. HL and WH contributed to the ideas of the article and reviewed the manuscript. 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.2023.1248812/full#supplementary-material

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Cigarette smoking and $PM_{2.5}$ might jointly exacerbate the risk of metabolic syndrome

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Background: Cigarette smoking and particulate matter (PM) with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) are major preventable cardiovascular mortality and morbidity promoters. Their joint role in metabolic syndrome (MS) pathogenesis is unknown. We determined the risk of MS based on $PM_{2.5}$ and cigarette smoking in Taiwanese adults.

Methods: The study included 126,366 Taiwanese between 30 and 70 years old with no personal history of cancer. The Taiwan Biobank (TWB) contained information on MS, cigarette smoking, and covariates, while the Environmental Protection Administration (EPA), Taiwan, contained the $PM_{2.5}$ information. Individuals were categorized as current, former, and nonsmokers. $PM_{2.5}$ levels were categorized into quartiles: $PM_{2.5} \leq Q1$, $Q1 < PM_{2.5} \leq Q2$, $Q2 < PM_{2.5} \leq Q3$, and $PM_{2.5} > Q3$, corresponding to $PM_{2.5} \leq 27.137$, $27.137 < PM_{2.5} \leq 32.589$, $32.589 < PM_{2.5} \leq 38.205$, and $PM_{2.5} > 38.205$ μg/m^3.

Results: The prevalence of MS was significantly different according to $PM_{2.5}$ exposure (p-value = 0.0280) and cigarette smoking (p-value < 0.0001). Higher $PM_{2.5}$ levels were significantly associated with a higher risk of MS: odds ratio (OR); 95% confidence interval (CI) = 1.058; 1.014–1.104, 1.185; 1.134–1.238, and 1.149; 1.101–1.200 for $27.137 < PM_{2.5} \leq 32.589$, $32.589 < PM_{2.5} \leq 38.205$, and $PM_{2.5} > 38.205$ μg/m^3, respectively. The risk of MS was significantly higher among former and current smokers with OR; 95% CI = 1.062; 1.008–1.118 and 1.531; 1.450–1.616, respectively, and a dose-dependent p-value < 0.0001. The interaction between both exposures regarding MS was significant (p-value = 0.0157). Stratification by cigarette smoking revealed a significant risk of MS due to $PM_{2.5}$ exposure among nonsmokers: OR (95% CI) = 1.074 (1.022–1.128), 1.226 (1.166–1.290), and 1.187 (1.129–1.247) for $27.137 < PM_{2.5} \leq 32.589$, $32.589 < PM_{2.5} \leq 38.205$, and $PM_{2.5} > 38.205$ μg/m^3, respectively. According to $PM_{2.5}$ quartiles, current smokers had a higher risk of MS, regardless of $PM_{2.5}$ levels (OR); 95% CI = 1.605; 1.444–1.785, 1.561; 1.409–1.728, 1.359; 1.211–1.524, and 1.585; 1.418–1.772 for $PM_{2.5} \leq 27.137$, $27.137 < PM_{2.5} \leq 32.589$, $32.589 < PM_{2.5} \leq 38.205$, and $PM_{2.5} > 38.205$ μg/m^3, respectively. After combining both exposures, the group, current smokers; $PM_{2.5} > 38.205$ μg/m^3 had the highest odds (1.801; 95% CI =1.625–1.995).

Conclusion: $PM_{2.5}$ and cigarette smoking were independently and jointly associated with a higher risk of MS. Stratified analyses revealed that cigarette

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smoking might have a much higher effect on MS than $PM_{2.5}$. Nonetheless, exposure to both $PM_{2.5}$ and cigarette smoking could compound the risk of MS.

KEYWORDS

cigarette smoking, $PM_{2.5}$, interaction, adults, Taiwan

Background

Metabolic syndrome (MS) is a condition characterized by the coexistence of at least three metabolic risk markers, including impaired fasting blood glucose (sugar), dyslipidemia (low high-density cholesterol and high triglyceride), abdominal obesity (high waist circumference), and elevated blood pressure (1–4). MS is a public health challenge with a huge global burden: it enhances morbidity and mortality related to chronic diseases such as cancer, stroke, diabetes, asthma, and atherosclerotic and nonatherosclerotic cardiovascular disease (5–7). Metabolic risk factors such as blood pressure, fasting plasma glucose, and high total cholesterol were among the ten largest contributors to global disability-adjusted life years (DALYs) in 2015 (8). MS has multiple promoting factors including, age (9), unhealthy diet (10, 11), obesity (11), alcohol consumption (12, 13), physical inactivity (11, 13), cigarette smoking (13–23), and $PM_{2.5}$ (24–27).

Cigarette smoking is a major preventable promoter of global cardiovascular mortality and morbidity (16, 28, 29). In 2015, it was among the five top risk factors attributable to global DALYs in 109 countries (8). The influence of cigarette smoking on MS and its components is contentious (14, 30). For instance, cigarette smoking was a significant cause of MS among Chinese (14), Koreans (31–33), and Japanese (18, 23). Nonetheless, it was not significantly associated with MS among Japanese (34) and Chinese (35). Furthermore, heavy cigarette smoking among Turkish women was suggested as being protective against future MS (36).

Air pollution, especially $PM_{2.5}$ (fine PM) is an urgent global public health concern, with continuously increasing implications (4, 9, 37–46). It significantly enhances neurological and cardiovascular morbidity and mortality (47, 48). Several studies reported contrasting findings regarding the relationship between MS and $PM_{2.5}$ (14–23, 31–33, 49–51). A recent systematic review and meta-analysis found that $PM_{2.5}$ could contribute to as much as 12.28% of MS (52). In several original studies, $PM_{2.5}$ exposure significantly elevated the risk of MS among Chinese (25–27, 53, 54), Saudi (55), and Korean adults (56). On the contrary, $PM_{2.5}$ did not significantly affect the risk of MS among Germans (57) and Chinese (50).

The positive association between $PM_{2.5}$ and MS was more prominent in cigarette smokers, alcohol drinkers, and obese people (25, 26, 53). This suggests that smoking and other unhealthy habits could exacerbate the adverse effects of air pollution (25, 26, 53). Smoking could also confound the effect of air pollution on cardiovascular health (58). Hence, pinpointing the combined effect of cigarette smoking and $PM_{2.5}$ could narrow the data gap for the burden of disease attributable to both exposures (59). Moreover, determining the interaction between $PM_{2.5}$ and smoking could provide insightful knowledge regarding the susceptibility to $PM_{2.5}$-related adverse health conditions in smokers and nonsmokers (59). High exposure to $PM_{2.5}$ among Chinese was recently associated with a higher risk of hypertension caused by smoking (60). However, robust studies have not been conducted to determine the combined effect of $PM_{2.5}$ and cigarette smoking on MS. In the current study, we determined the independent association of ambient $PM_{2.5}$ and smoking with MS in Taiwanese adults. Moreover, we determined the interaction between $PM_{2.5}$ and smoking regarding MS.

Methods

Study participants and data acquisition

We acquired information relating to MS, cigarette smoking, sex, age, weight, height, alcohol drinking, exercise, marital status, educational level, secondhand smoke exposure, and duration of residence from the TWB (2008–2020). The TWB database is one of the human biological databases currently supplying data for biomedical research in Taiwan (61). The TWB project is a community-based prospective study whose participants are exclusively Taiwanese adults with no personal history of cancer (62, 63). At the start of the project, only Taiwanese aged 30–70 were eligible for enrolment (63). Currently, individuals between 20 and 70 years old without a diagnosis of cancer can enroll in the project (62). The TWB biobank currently contains over 30 recruitment sites all over Taiwan (62). All volunteers sign informed consent forms before enrolment. At enrolment, each volunteer fills out the TWB questionnaire, undergoes anthropometric examinations, and provides blood/urine samples for biochemical testing. The questionnaire contains information on cigarette smoking, sex, age, alcohol drinking, exercise, etc. The anthropometry examination determines weight, height, waist circumference, and blood pressure. The biochemical tests determine fasting blood glucose (FBG), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C), among others.

Currently, the TWB database lacks $PM_{2.5}$ data. Notwithstanding, the Taiwan Environmental Protection Administration (EPA) contains about 71 automated stations that record daily average $PM_{2.5}$ concentrations. We used the EPA daily average data from 2000 to 2016 and computed the annual average $PM_{2.5}$ concentrations ($\mu g/m^3$). The spatial–temporal variability of $PM_{2.5}$ in 349 areas in Taiwan was assessed using machine learning-coupled land-use regression (LUR) as previously described (64). The $PM_{2.5}$ data for each area was considered the exposure data for the participants' current residing there. The initial study sample was 131,498. However, we excluded 5,132 individuals with missing information for at least one variable. The final analysis included 126,366 people with complete data. The Institutional Review Board (IRB) of the Chung Shan Medical University Hospital granted ethical approval for this study (IRB: CS1-20009).

Definition of variables

MS was defined as the presence of at least three of the following metabolic markers: (1) waist circumference ≥ 90 cm in men or ≥ 80 cm in women; (2) systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg; (3) FBG ≥ 100 mg/dL; (4) HDL-C < 40 mg/dL for men and < 50 mg/dL for women; (5) triglyceride (TG) ≥ 150 mg/dL. This definition was based on the guidelines of the Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Mean annual $PM_{2.5}$ concentrations between 2000 and 2016 were grouped into quartiles: $PM_{2.5} \leq Q1$ ($PM_{2.5} \leq 27.137$ μg/m^3), $Q1 < PM_{2.5} \leq Q2$ ($27.137 < PM_{2.5} \leq 32.589$ μg/m^3), $Q2 < PM_{2.5} \leq Q3$ ($32.589 < PM_{2.5} \leq 38.205$ μg/m^3), and $PM_{2.5} > Q3$ ($PM_{2.5} > 38.205$ μg/m^3). Smoking habits were self-reported, and individuals were categorized as current, former, or nonsmokers. Current smokers included those who smoked cigarettes for at least six months and were still smoking during the data collection period. Former smokers were those who smoked cigarettes for at least six months in the past but had quit the habit for over six months. Nonsmokers were those with no personal history of cigarette smoking.

The body mass index (BMI) was computed as weight/height squared (kg/m^2). The cutoff values for BMI categories were BMI < 18.5, 18.5 ≤ BMI < 24, 24 ≤ BMI < 27, and BMI ≥ 27 kg/m^2, corresponding to normal weight, underweight, overweight, and obesity. Current drinkers were individuals who confirmed having a regular habit of consuming at least 150 mL of alcohol per week continuously for half a year or more. Former drinkers included those who drank 150 mL of alcohol per week continuously for at least half a year in the past but had quit the habit for over six months. Nondrinkers included those who drank <150 mL of alcohol per week. Physically active individuals included those who had a habit of regularly engaging in physical activities (lasting over half an hour) at least three times weekly. Exposure to secondhand smoke referred to habitual exposure to secondhand smoke for 5 min or more in an hour. For marital status, participants were regarded as being married (still married), single, divorced/separated (not yet married/divorced or separated from their spouses), or widowed (lost a partner). Educational level categories included, elementary and below, junior and senior high school, or university and above. The quartiles for the duration of residence were < 7.58, 7.58–17.58, 17.58–29.58, and ≥ 29.58 years.

Statistical analyses

The differences in age (a continuous variable) between participants with and without MS were determined with the Student t-test. The differences in the percentage distribution of categorical variables (e.g., sex, cigarette smoking) between those with and without MS were determined using the Chi-square test. Age was presented in mean ± standard error (SE) while the categorical variables were presented as *n* (%). The risk of MS based on $PM_{2.5}$, cigarette smoking, and the interaction between both exposures was determined by multivariate logistic regression. In the logistic regression model assessing the interaction between cigarette smoking and $PM_{2.5}$ on MS, the *p*-value was obtained by putting the interaction term (cigarette smoking*$PM_{2.5}$) as the main exposure (independent variable) and MS as the outcome variable. In all the regression analyses, adjustments were made for sex, age, weight, height, alcohol drinking, exercise, marital status, educational level, secondhand smoke exposure, and duration of residence. A *p*-value < 0.05 was set as the threshold for statistical significance. Data were managed and analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

Table 1 shows the demographic characteristics of the 126,366 study participants comprising 26,767 MS cases and 99,599 individuals without MS. The $PM_{2.5}$ quartiles were $PM_{2.5} \leq Q1$ ($PM_{2.5} \leq 27.137$), $Q1 < PM_{2.5} \leq Q2$ ($27.137 < PM_{2.5} \leq 32.589$ μg/m^3), $Q2 < PM_{2.5} \leq Q3$ ($32.589 < PM_{2.5} \leq 38.205$ μg/m^3), and $PM_{2.5} > Q3$ ($PM_{2.5} > 38.205$ μg/m^3). Individuals with and without MS significantly differed in terms of $PM_{2.5}$ concentration (*p*-value = 0.0280), cigarette smoking, and other variables, including sex, age, BMI, alcohol intake, marital status, educational level, secondhand smoke exposure, and duration of residence (*p*-value < 0.0001). Among the 99,599 individuals without MS, 24,378 (24.48%), 27,157 (27.27%), 23,147 (23.24%), 24,917 (25.02%) were within the $PM_{2.5}$ quartiles, $PM_{2.5} \leq Q1$, $Q1 < PM_{2.5} \leq Q2$, $Q2 < PM_{2.5} \leq Q3$, and $PM_{2.5} > Q3$, respectively. Among the 26,767 MS cases, 6,370 (23.80%), 7,250 (27.09%), 6,414 (23.96%), and 6,733 (25.15%) were within the $PM_{2.5}$ quartiles, $PM_{2.5} \leq Q1$, $Q1 < PM_{2.5} \leq Q2$, $Q2 < PM_{2.5} \leq Q3$, and $PM_{2.5} > Q3$, respectively. The group without MS comprised 81,706 (82.03%) nonsmokers, 9,687 (9.73%) former smokers, and 8,206 (8.24%) current smokers. The MS group comprised 19,541 (73.00%) nonsmokers, 3,628 (13.55%) former smokers, and 3,598 (13.44%) nonsmokers.

Table 2 and Supplementary Figures S1, S2 present the association of MS with $PM_{2.5}$ and cigarette smoking. Higher compared to lower $PM_{2.5}$ levels ($27.137 < PM_{2.5} \leq 32.589$, $32.589 < PM_{2.5} \leq 38.205$, and $PM_{2.5} > 38.205$ vs. $PM_{2.5} \leq 27.137$ μg/m^3) were significantly associated with a higher risk of MS (OR; 95% CI = 1.058; 1.014–1.104 for $27.137 < PM_{2.5} \leq 32.589$ μg/m^3, 1.185; 1.134–1.238 for $32.589 < PM_{2.5} \leq 38.205$ μg/m^3, and 1.149; 1.101–1.200 for $PM_{2.5} > 38.205$ μg/m^3). Compared to nonsmokers, former and current smokers had a higher risk of MS (OR = 1.062, 95% CI = 1.008–1.118 for former smokers and 1.531; 1.450–1.616 for current smokers). The dose–response relationship between smoking and MS was significant (p-trend <0.0001). According to the quantity of cigarettes smoked, a weekly consumption of ≥140 cigarettes per week was significantly associated with a higher risk of MS in both former and current smokers (Supplementary Table S1). The interaction between $PM_{2.5}$ and cigarette smoking was significant: *p*-value = 0.0157 (Table 2). The risk of MS was also significantly higher among people who were ≥ 50 years (OR = 2.277, 95% CI = 2.190–2.367), overweight (OR; 95% CI = 4.219; 4.056–4.388), obese (OR; 95% CI = 13.232; 12.707–13.778), current alcohol drinkers (OR = 1.162, 95% CI = 1.092–1.236), divorced/separated (OR; 95% CI = 1.097; 1.039–1.159), and widowed (OR; 95% CI = 1.178;1.098–1.264). However, the risk was lower among underweight individuals (OR = 0.084, 95% CI = 0.057–0.124), those who exercised regularly (OR = 0.866, 95% CI = 0.839–0.895), single people (OR; 95% CI = 0.928; 0.882–0.976), those who attained a junior and senior high school level (OR; 95% CI = 0.821; 0.769–0.876), and university education and above (OR = 0.692, 95% CI = 0.648–0.740).

Table 3 shows the association between $PM_{2.5}$ and MS in current, former, and nonsmokers. $PM_{2.5}$ was significantly associated with a higher risk of MS among nonsmokers: OR = 1.074, 95% CI = 1.022–1.128, 1.226; 1.166–1.290, and 1.187; 1.129–1.247 for $27.137 < PM_{2.5} \leq 32.589$, $32.589 < PM_{2.5} \leq 38.205$, and $PM_{2.5} > 38.205$ μg/m^3, respectively.

Table 4 illustrates the association between cigarette smoking and MS stratified by $PM_{2.5}$ quartiles. Compared to nonsmokers, the

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TABLE 1 Demographic characteristics of the study participants stratified by metabolic syndrome.

Variables	No metabolic syndrome (n = 99,599)	Metabolic syndrome (n = 26,767)	p-value
$PM_{2.5}$ quartile, n (%)			0.0280
$PM_{2.5} \leq Q1$ ($PM_{2.5} \leq 27.137\,\mu g/m^3$)	24,378 (24.48)	63,70 (23.80)	
$Q1 < PM_{2.5} \leq Q2$ ($27.137 < PM_{2.5} \leq 32.589\,\mu g/m^3$)	27,157 (27.27)	7,250 (27.09)	
$Q2 < PM_{2.5} \leq Q3$ ($32.589 < PM_{2.5} \leq 38.205\,\mu g/m^3$)	23,147 (23.24)	64,14 (23.96)	
$PM_{2.5} > Q3$ ($PM_{2.5} > 38.205\,\mu g/m^3$)	24,917 (25.02)	6,733 (25.15)	
Cigarette smoking status, n (%)			<0.0001
Nonsmokers	81,706 (82.03)	19,541 (73.00)	
Former smokers	9,687 (9.73)	3,628 (13.55)	
Current smokers	8,206 (8.24)	3,598 (13.44)	
Sex, n (%)			<0.0001
Women	6,5,749 (66.01)	14,973 (55.94)	
Men	33,850 (33.99)	11,794 (44.06)	
Age, n (%)			<0.0001
Age < 50 years	50,614 (50.82)	8,935 (33.38)	
Age ≥ 50 years	48,985 (49.18)	17,832 (66.62)	
BMI, n (%)			<0.0001
Underweight ($BMI < 18.5\,kg/m^2$)	4,192 (4.21)	26 (0.10)	
Normal weight ($18.5 \leq BMI < 24\,kg/m^2$)	57,268 (57.50)	4,682 (17.49)	
Overweight ($24 \leq BMI < 27\,kg/m^2$)	25,174 (25.28)	9,037 (33.76)	
Obesity ($BMI \geq 27\,kg/m^2$)	12,965 (13.02)	13,022 (48.65)	
Alcohol intake status, n (%)			<0.0001
Nondrinkers	9,1946 (93.32)	23,573 (88.07)	
Former drinkers	2,323 (2.33)	1,012 (3.78)	
Current drinkers	5,330 (5.35)	2,182 (8.15)	
Exercise, n (%)			0.1665
No	59,543 (59.78)	16,127 (60.25)	
Yes	40,056 (40.22)	10,640 (39.75)	
Marital status, n (%)			<0.0001
Married	72,256 (72.55)	19,849 (74.15)	
Single	15,113 (15.17)	2,804 (10.48)	
Divorced or separated	8,251 (8.28)	2,501 (9.34)	
Widowed	3,979 (4.00)	1,613 (6.03)	
Educational level, n (%)			<0.0001
Elementary school and below	3,924 (3.94)	2,189 (8.18)	
Junior and senior high school	34,053 (34.19)	11,330 (42.33)	
University and above	61,622 (61.87)	13,248 (49.49)	
Secondhand smoke exposure, n (%)			<0.0001
No	89,566 (89.93)	23,529 (87.90)	
Yes	10,033 (10.07)	3,238 (12.10)	
Duration of residence, n (%)			<0.0001
<7.58 years	26,129 (26.23)	5,448 (20.35)	
7.58–17.58 years	25,695 (25.80)	5,847 (21.84)	
17.58–29.58 years	24,310 (24.41)	7,143 (26.69)	
≥29.58 years	23,465 (23.56)	8,329 (31.12)	

n, sample size; %, percent; BMI, body mass index; kg, kilogram; m^2, meter squared.

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TABLE 2 Association of $PM_{2.5}$ and cigarette smoking with metabolic syndrome.

Variables	OR	95% CI	*p*-value
$PM_{2.5}$ quartile			
$PM_{2.5} \leq 27.137$ (ref.)	1		
$27.137 < PM_{2.5} \leq 32.589$	1.058	1.014–1.104	0.0096
$32.589 < PM_{2.5} \leq 38.205$	1.185	1.134–1.238	<0.0001
$PM_{2.5} > 38.205$	1.149	1.101–1.200	<0.0001
P-trend	NA		
Cigarette smoking status			
Nonsmokers (ref.)	1		
Former smokers	1.062	1.008–1.118	0.0232
Current smokers	1.531	1.450–1.616	<0.0001
P-trend	<0.0001		
Sex			
Women (ref.)	1		
Men	0.966	0.930–1.003	0.0705
Age			
Age < 50 (ref.)	1		
Age ≥ 50	2.277	2.190–2.367	<0.0001
BMI			
Normal weight (ref.)	1		
Underweight	0.084	0.057–0.124	<0.0001
Overweight	4.219	4.056–4.388	<0.0001
Obesity	13.232	12.707–13.778	<0.0001
Alcohol intake status			
Nondrinkers (ref.)	1		
Former drinkers	1.056	0.968–1.152	0.2198
Current drinkers	1.162	1.092–1.236	<0.0001
Exercise			
No (ref.)	1		
Yes	0.866	0.839–0.895	<0.0001
Marital status			
Married (ref.)	1		
Single	0.928	0.882–0.976	0.0036
Divorced or separated	1.097	1.039–1.159	0.0009
Widowed	1.178	1.098–1.264	<0.0001
Educational level			
Elementary school and below (ref.)	1		
Junior and senior high school	0.821	0.769–0.876	<0.0001
University and above	0.692	0.648–0.740	<0.0001
Secondhand smoke exposure			
No (ref.)	1		
Yes	1.048	0.998–1.100	0.0614
Duration of residence			
<7.58 (ref.)	1		
7.58–17.58	1.065	1.017–1.114	0.0070
17.58–29.58	1.128	1.078–1.182	<0.0001
≥29.58	1.146	1.092–1.203	<0.0001
$PM_{2.5}$*cigarette smoking	*p*-value = 0.0157		

OR, odds ratio; CI, confidence interval; ref., reference; BMI, body mass index; NA, not applicable (the trend is nonlinear).

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TABLE 3 Association between $PM_{2.5}$ and metabolic syndrome in current, former, nonsmokers.

Variables	Nonsmokers			Former smokers			Current smokers		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
$PM_{2.5}$ quartile									
$PM_{2.5} \leq 27.137$ (ref.)	1								
$27.137 < PM_{2.5} \leq 32.589$	1.074	1.022–1.128	0.0047	1.042	0.927–1.172	0.4856	0.983	0.871–1.110	0.7860
$32.589 < PM_{2.5} \leq 38.205$	1.226	1.166–1.290	<0.0001	1.075	0.951–1.215	0.2485	1.044	0.917–1.188	0.5187
$PM_{2.5} > 38.205$	1.187	1.129–1.247	<0.0001	0.975	0.862–1.103	0.6864	1.094	0.962–1.244	0.1714
P-trend	NA			NA			0.1193		
Sex									
Women (ref.)	1								
Men	0.941	0.903–0.981	0.0042	1.179	1.023–1.359	0.0227	1.341	1.171–1.534	<0.0001
Age									
Age < 50 (ref.)	1								
Age ≥ 50	2.403	2.296–2.514	<0.0001	1.913	1.716–2.133	<0.0001	1.915	1.718–2.135	<0.0001
BMI									
Normal weight (ref.)	1								
Underweight	0.074	0.048–0.115	<0.0001	<0.001	<0.001- > 999.999	0.9431	0.226	0.100–0.511	0.0004
Overweight	4.193	4.013–4.381	<0.0001	4.458	3.916–5.074	<0.0001	4.523	3.971–5.153	<0.0001
Obesity	12.508	11.950–13.091	<0.0001	15.036	13.202–17.125	<0.0001	17.416	15.290–19.839	<0.0001
Alcohol intake status									
Nondrinkers (ref.)	1								
Former drinkers	1.181	1.012–1.377	0.0344	1.021	0.888–1.174	0.7728	1.070	0.905–1.265	0.4313
Current drinkers	1.007	0.908–1.117	0.8941	1.287	1.144–1.447	<0.0001	1.238	1.111–1.380	0.0001
Exercise									
No (ref.)	1								
Yes	0.866	0.834–0.898	<0.0001	0.842	0.770–0.920	0.0002	0.853	0.769–0.947	0.0027
Marital status									
Married (ref.)	1								
Single	0.947	0.894–1.003	0.0646	0.989	0.830–1.179	0.9032	0.863	0.755–0.986	0.0308
Divorced or separated	1.059	0.992–1.130	0.0853	1.321	1.128–1.547	0.0006	1.213	1.056–1.394	0.0063
Widowed	1.161	1.078–1.249	<0.0001	1.192	0.879–1.616	0.2574	1.167	0.828–1.646	0.3773
Educational level									
Elementary school and below (ref.)	1								
Junior and senior high school	0.808	0.753–0.868	<0.0001	1.016	0.823–1.254	0.8845	0.776	0.597–1.009	0.0585
University and above	0.678	0.630–0.729	<0.0001	0.891	0.721–1.102	0.2866	0.673	0.516–0.878	0.0035
Secondhand smoke exposure									
No (ref.)	1								
Yes	1.048	0.986–1.115	0.1303	0.962	0.843–1.097	0.5583	1.102	0.993–1.224	0.0677
Duration of residence									
<7.58 (ref.)	1								
7.58–17.58	1.071	1.016–1.130	0.0112	1.044	0.917–1.189	0.5154	1.045	0.927–1.179	0.4729
17.58–29.58	1.115	1.056–1.177	<0.0001	1.105	0.975–1.252	0.1194	1.196	1.054–1.357	0.0057
≥29.58	1.150	1.087–1.216	<0.0001	1.098	0.959–1.258	0.1765	1.092	0.938–1.273	0.2572

OR, odds ratio; CI, confidence interval; ref., reference; BMI, body mass index; NA, not applicable (the trend is nonlinear).

TABLE 4 Association between cigarette smoking and metabolic syndrome stratified by $PM_{2.5}$ quartiles.

Variables	$PM_{2.5} \leq 27.137\ \mu g/m^3$			$27.137 < PM_{2.5} \leq 32.589 \mu g/m^3$			$32.589 < PM_{2.5} \leq 38.205 \mu g/m^3$			$PM_{2.5} > 38.205\ \mu g/m^3$		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Cigarette smoking status												
Nonsmokers (ref.)	1											
Former smokers	1.139	1.027–1.263	0.0139	1.138	1.032–1.254	0.0094	0.960	0.863–1.068	0.4513	1.003	0.901–1.116	0.9590
Current smokers	1.605	1.444–1.785	<0.0001	1.561	1.409–1.728	<0.0001	1.359	1.211–1.524	<0.0001	1.585	1.418–1.772	<0.0001
P-trend	<0.0001			<0.0001			<0.0001			<0.0001		
Sex												
Women (ref.)	1											
Men	0.976	0.904–1.054	0.5371	0.935	0.870–1.005	0.0689	1.056	0.978–1.140	0.1624	0.912	0.846–0.984	0.0177
Age												
Age < 50 (ref.)	1											
Age ≥ 50	2.349	2.169–2.543	<0.0001	2.159	2.002–2.329	<0.0001	2.315	2.139–2.505	<0.0001	2.295	2.126–2.477	<0.0001
BMI												
Normal weight (ref.)	1											
Underweight	0.113	0.054–0.239	<0.0001	0.048	0.018–0.128	<0.0001	0.127	0.066–0.246	<0.0001	0.064	0.029–0.143	<0.0001
Overweight	4.381	4.030–4.762	<0.0001	4.272	3.960–4.609	<0.0001	4.228	3.901–4.583	<0.0001	4.060	3.762–4.381	<0.0001
Obesity	14.795	13.600–16.095	<0.0001	13.166	12.182–14.231	<0.0001	13.506	12.424–14.683	<0.0001	11.850	10.944–12.831	<0.0001
Alcohol intake status												
Nondrinkers (ref.)	1											
Former drinkers	1.052	0.874–1.266	0.5931	1.059	0.890–1.260	0.5167	1.112	0.932–1.327	0.2372	1.033	0.876–1.218	0.7031
Current drinkers	1.165	1.028–1.319	0.0163	1.113	0.993–1.247	0.0654	1.222	1.075–1.389	0.0021	1.171	1.025–1.339	0.0204
Exercise												
No (ref.)	1											
Yes	0.834	0.780–0.891	<0.0001	0.883	0.829–0.939	<0.0001	0.853	0.797–0.912	<0.0001	0.892	0.836–0.951	0.0005
Marital status												
Married (ref.)	1											
Single	0.943	0.847–1.049	0.2788	0.880	0.798–0.970	0.0100	0.898	0.809–0.995	0.0405	0.995	0.902–1.098	0.9218
Divorced or separated	1.118	1.002–1.248	0.0460	1.027	0.923–1.142	0.6282	1.205	1.072–1.355	0.0018	1.065	0.958–1.184	0.2417
Widowed	1.152	0.999–1.329	0.0515	1.172	1.026–1.340	0.0196	1.332	1.150–1.543	0.0001	1.088	0.946–1.252	0.2364

(Continued)

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TABLE 4 (Continued)

Variables	$PM_{2.5} \leq 27.137$ μg/m^3			27.137<$PM_{2.5} \leq$32.589μg/m^3			32.589<$PM_{2.5} \leq$38.205μg/m^3			$PM_{2.5} > 38.205$ μg/m^3		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Educational level												
Elementary school and below (ref.)	1											
Junior and senior high school	0.808	0.705–0.925	0.0020	0.814	0.719–0.921	0.0011	0.819	0.720–0.930	0.0021	0.836	0.729–0.958	0.0100
University and above	0.692	0.601–0.795	<0.0001	0.683	0.602–0.776	<0.0001	0.722	0.633–0.824	<0.0001	0.674	0.586–0.776	<0.0001
Secondhand smoke exposure												
No (ref.)	1											
Yes	1.088	0.984–1.203	0.0985	1.065	0.971–1.168	0.1787	1.032	0.940–1.133	0.5140	1.002	0.901–1.114	0.9760
Duration of residence												
<7.58 (ref.)	1											
7.58–17.58	1.038	0.945–1.139	0.4379	1.120	1.022–1.226	0.0149	1.149	0.958–1.149	0.2990	1.053	0.963–1.151	0.2576
17.58–29.58	1.079	0.983–1.185	0.1097	1.166	1.064–1.278	0.0010	1.175	1.071–1.290	0.0007	1.096	1.001–1.200	0.0476
≥29.58	1.080	0.980–1.191	0.1198	1.215	1.106–1.335	<0.0001	1.160	1.046–1.286	0.0048	1.129	1.027–1.242	0.0119

OR, odds ratio; CI, confidence interval; ref., reference; BMI, body mass index.

risk of MS was significantly higher in former smokers when the $PM_{2.5}$ concentration was ≤32.589 μg/m^3: OR (95% CI) = 1.139 (1.027–1.263) for $PM_{2.5} \leq 27.137$ μg/m^3 and 1.138 (1.032–1.254) for $27.137 < PM_{2.5} \leq 32.589$ μg/m^3. The risk of MS was significantly higher among current smokers, regardless of the $PM_{2.5}$ concentration. The ORs; 95% CIs were 1.605; 1.444–1.785, 1.561; 1.409–1.728, 1.359; 1.211–1.524; and 1.585; 1.418–1.772 for $PM_{2.5} \leq 27.137$, $27.137 < PM_{2.5} \leq 32.589$, $32.589 < PM_{2.5} \leq 38.205$, and $PM_{2.5} > 38.205$ μg/m^3, respectively.

Table 5 and Supplementary Figure S3 show the risk of MS according to cigarette smoking and $PM_{2.5}$ exposure. Compared to nonsmokers with low $PM_{2.5}$ exposure ($PM_{2.5} \leq 27.137$ μg/m^3), the risk of MS was significantly higher in all the categories. Of note, the category comprising current smokers and $PM_{2.5} > 38.205$ μg/m^3 had the highest risk of MS (OR = 1.801, 95% CI = 1.625–1.995).

Discussion

Cigarette smoking and $PM_{2.5}$ have significant adverse effects on individual and public health. A systematic analysis of the global burden of disease ranked $PM_{2.5}$ and cigarette smoking among the ten leading causes of death and disability in 2015 (8). We evaluated the independent and joint association of both factors with MS in Taiwan Biobank volunteers. Smoking and $PM_{2.5}$ were independently associated with higher odds of MS. Moreover, both exposures were interactively associated with MS in a significant manner.

Cigarette smoking has been associated with CVD risk factors such as elevated heart rate, dyslipidemia, hyperinsulinemia, and glucose intolerance (15–17). In line with our study, several original studies and meta-analyses reported cigarette smoking as a metabolic syndrome-promoting factor (14–23, 31–33, 51). For instance, in a meta-analysis including 13 prospective studies, active smoking was positively associated with MS (51). In an original study, life-course cigarette smoking was associated with a higher risk of MS among Chinese, particularly those under 70 years (14). Moreover, a cross-sectional study among Koreans below 40 years found a higher likelihood of MS in smokers than nonsmokers (33). Furthermore, a community-based study involving Taiwanese aged 40 years and above revealed a dose-dependent positive relationship of current smoking with MS and some of its components, including high TG and low HDL (22). In addition, a study among Japanese aged 35–65 also showed a higher incidence of MS among both current and former smokers (23). Another study among Japanese between 20 and 93 years found that the risk of MS in individuals who smoked over 40 cigarettes per day persisted even after 20 years of quitting (18). A cross-sectional study among male Korean former smokers aged at least 19 years showed a higher risk of MS, hypertriglyceridemia, and hyperglycemia among those who had smoked for over 20 years (32). Another cross-sectional among male Koreans aged over 20 years also showed a higher risk of MS among

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TABLE 5 Risk of metabolic syndrome based on a combination of cigarette smoking and $PM_{2.5}$ exposure.

Variables	OR	95% CI	*p*-value
Cigarette smoking status and $PM_{2.5}$ exposure			
Nonsmokers; $PM_{2.5} \leq 27.137$ (ref.)	1		
Nonsmokers; $27.137 < PM_{2.5} \leq 32.589$	1.075	1.023–1.129	0.0043
Nonsmokers; $32.589 < PM_{2.5} \leq 38.205$	1.224	1.164–1.288	<0.0001
Nonsmokers; $PM_{2.5} > 38.205$	1.190	1.132–1.250	<0.0001
Former smokers; $PM_{2.5} \leq 27.1374$	1.155	1.051–1.270	0.0029
Former smokers; $27.137 < PM_{2.5} \leq 32.589$	1.194	1.091–1.307	0.0001
Former smokers; $32.589 < PM_{2.5} \leq 38.205$	1.248	1.132–1.376	<0.0001
Former smokers; $PM_{2.5} > 38.205$	1.136	1.029–1.254	0.0114
Current smokers; $PM_{2.5} \leq 27.137$	1.648	1.498–1.813	<0.0001
Current smokers; $27.137 < PM_{2.5} \leq 32.589$	1.630	1.484–1.791	<0.0001
Current smokers; $32.589 < PM_{2.5} \leq 38.205$	1.758	1.583–1.953	<0.0001
Current smokers; $PM_{2.5} > 38.205$	1.801	1.625–1.995	<0.0001
Sex			
Women (ref.)	1		
Men	0.966	0.931–1.004	0.0755
Age			
Age < 50 (ref.)	1		
Age ≥ 50	2.277	2.191–2.367	<0.0001
BMI			
Normal weight (ref.)	1		
Underweight	0.084	0.057–0.124	<0.0001
Overweight	4.219	4.057–4.389	<0.0001
Obesity	13.239	12.714–13.786	<0.0001
Alcohol intake			
Nondrinkers (ref)	1		
Former drinkers	1.060	0.971–1.156	0.1929
Current drinkers	1.163	1.093–1.238	<0.0001
Exercise			
No (ref.)	1		
Yes	0.867	0.839–0.895	<0.0001
Marital status			
Married (ref.)	1		
Single	0.927	0.881–0.975	0.0033
Divorced or separated	1.097	1.038–1.158	0.0010
Widowed	1.178	1.098–1.264	<0.0001
Educational level			
Elementary school and below (ref.)	1		
Junior and senior high school	0.821	0.769–0.876	<0.0001
University and above	0.692	0.647–0.740	<0.0001
Secondhand smoke exposure			
No (ref)	1		
Yes	1.047	0.997–1.099	0.0638
Duration of residence			
<7.58 (ref.)	1		
7.58–17.58	1.064	1.017–1.114	0.0072
17.58–29.58	1.128	1.077–1.182	<0.0001
≥29.58	1.146	1.092–1.203	<0.0001

OR, odds ratio; CI, confidence interval; ref., reference; BMI, body mass index.

former and current smokers who smoked more than ten packs of cigarettes annually (31). In a cross-sectional study involving individuals of Western European ancestry, cigarette smoking was significantly linked to a higher prevalence of MS, regardless of BMI and sex (65). In the DESIR (Données Epidémiologiques sur le Syndrome d'Insulino-Résistance) study (a longitudinal study involving French), male smokers had a significantly higher risk of MS (66). In another longitudinal study in Norway, heavy smoking increased the incidence of MS in both men and women (13). Using the Third National Health and Nutrition Examination Survey (NHANES) data, a study in the US found a lower risk of MS among normal weight and overweight men and women with no history of smoking (67).

The positive association of $PM_{2.5}$ and MS in the current study is comparable to findings from previous studies (14–23, 31–33, 51). For example, exposure to $PM_{2.5}$ exacerbated the risk of MS among Saudi adults (55) and Korean adults without CVDs (56). Moreover, several original studies found a positive relationship between long-term exposure to $PM_{2.5}$ and MS in adult Chinese (25–27, 53, 54). A meta-analysis of observational studies revealed a borderline positive association between $PM_{2.5}$ and MS (49). Exposure to $PM_{2.5}$ has also been associated with an elevated risk of MS components, including high abdominal obesity (56), FBG (54–56, 68–70), high BP (55, 56, 71), and dyslipidemia (54, 56, 70). Analyses of data from the Heinz Nixdorf Recall (HNR) cohort study in Germany revealed a borderline positive association between $PM_{2.5}$ and MS (57). A study in the US using data from the Normative Aging study found a significantly increased risk of MS due to increasing $PM_{2.5}$ concentrations (70). Nonetheless, data from the Adolescent to Adult Health (Add Health) study (a longitudinal study in the US) showed no significant association between long-term $PM_{2.5}$ exposure and MS (72).

In our study, the interaction of $PM_{2.5}$ and cigarette smoking on MS was significant. It is worth noting that the joint role of both exposures in MS pathogenesis has not received considerable attention. However, some studies investigated the joint role of PM and cigarette smoking on cardiovascular and pulmonary morbidity and mortality (59, 73–75). For instance, Turner and colleagues (59) reported an increased risk of cardiovascular mortality (i.e., about 32 extra deaths per 100,000 person-years) due to smoking-$PM_{2.5}$ interaction. Even though a study on cardiovascular mortality found no interaction between $PM_{2.5}$ and smoking, current smokers with higher exposure to $PM_{2.5}$ had a high relative risk for mortality (76). Exposure to both smoking and $PM_{2.5}$ was associated with a relative excess risk of lung cancer mortality (74). Exposure to particulate matter, especially $PM_{2.5}$, was also significantly associated with a higher risk of cardio-cerebrovascular disease among nonsmokers (73).

The potential mechanisms underpinning the role of smoking and $PM_{2.5}$ on MS are unclear. Nonetheless, the available evidence points toward insulin resistance, induced oxidative stress, inflammation, and endothelial dysfunction. That is, smoking is believed to promote MS by inducing insulin resistance, reducing insulin sensitivity, and causing hyperglycemia, high blood pressure, hyperinsulinemia, oxidative stress, endothelial dysfunction, and systemic inflammation (15, 16, 77, 78). Air pollution, especially $PM_{2.5}$, enhances MS susceptibility by disrupting insulin signaling, inducing inflammation and oxidative stress (73, 79–82). Sung Kyun Park and colleagues (83) found that in MS patients, PM could particularly affect CVDs by causing cardiac autonomic dysfunction.

The current study has some limitations. First, we included only Taiwanese adults aged 30 and 70 who were enrolled in the TWB project. The restriction of enrolment to only Taiwanese within a specific age cohort is a possible source of selection bias. As such, our conclusions may not be generalizable to non-Taiwanese and Taiwanese outside the 30–70 age group. Second, we could not ascertain $PM_{2.5}$ exposure at individual levels since data were obtained from fixed monitoring stations. The non-definitive ascertainment of smoking and $PM_{2.5}$ exposures could have resulted in measurement error or information bias and consequently, wrong classification. Nonetheless, we believe that the misclassification could be nondifferential as it involved both cases and controls from a community-based cohort. The nondifferential misclassification could have resulted in the underestimation of MS risk. We recommend that the findings from this study should be replicated in other populations. Moreover, studies in Taiwan should consider including adults outside the 30–70 years age group. Furthermore, to get the actual effect of cigarette smoking on MS, future studies should consider the number of cigarettes smoked and determine the levels of cotinine (a biomarker of tobacco consumption).

Conclusion

Summarily, $PM_{2.5}$ and smoking were independently and interactively associated with a higher risk of MS. Stratified analyses revealed that cigarette smoking might have a much higher effect on MS than $PM_{2.5}$. After integrating smoking and $PM_{2.5}$ exposure in the same model, the risk of MS was highest among current cigarette smokers exposed to the highest level of $PM_{2.5}$. Quitting smoking could reduce the incidence of MS in individuals exposed to $PM_{2.5}$. As $PM_{2.5}$ could affect nonsmokers, targeting it could also be very beneficial in reducing the risk of MS in these individuals. To curb smoking, $PM_{2.5}$, and their adverse effects, the government could enforce stronger and more sustainable policies such as funding mass media campaigns on the dangers of environmental factors. The government could also provide incentives for smoking cessation treatments.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data that support the findings of this study are available from Taiwan Biobank but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however available from the corresponding author, Y-PL upon reasonable request and with permission of Taiwan Biobank. Requests to access these datasets should be directed to Y-PL, Liawyp@csmu.edu.tw.

Ethics statement

The studies involving humans were approved by the Institutional Review Board (IRB) of the Chung Shan Medical University Hospital granted ethical approval for this study (IRB: CS1-20009). The studies were conducted in accordance with the local legislation and

institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

H-HT, DT, WL, C-YC, and Y-PL did the literature search, conceived, and designed the study. WL and Y-PL analyzed the data. H-HT, DT, and C-YC drafted the manuscript. DT edited the paper. 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.2023.1234799/full#supplementary-material

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The causal effect of air pollution on the risk of essential hypertension: a Mendelian randomization study

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Background: Air pollution poses a major threat to human health by causing various illnesses, such as cardiovascular diseases. While plenty of research indicates a correlation between air pollution and hypertension, a definitive answer has yet to be found.

Methods: Our analyses were performed using the Genome-wide association study (GWAS) of exposure to air pollutants from UKB (PM2.5, PM10, NO_2, and NO_X; n = 423,796 to 456,380), essential hypertension from FinnGen (42,857 cases and 162,837 controls) and from UKB (54,358 cases and 408,652 controls) as a validated cohort. Univariable and multivariable Mendelian randomization (MR) were conducted to investigate the causal relationship between air pollutants and essential hypertension. Body mass index (BMI), alcohol intake frequency, and the number of cigarettes previously smoked daily were included in multivariable MRs (MVMRs) as potential mediators/confounders.

Results: Our findings suggested that higher levels of both PM2.5 (OR [95%CI] per 1 SD increase in predicted exposure = 1.24 [1.02–1.53], p = 3.46E-02 from Finn; OR [95%CI] = 1.04 [1.02–1.06], p = 7.58E-05 from UKB) and PM10 (OR [95%CI] = 1.24 [1.02–1.53], p = 3.46E-02 from Finn; OR [95%CI] = 1.04 [1.02–1.06], p = 7.58E-05 from UKB) were linked to an increased risk for essential hypertension. Even though we used MVMR to adjust for the impacts of smoking and drinking on the relationship between PM2.5 exposure and essential hypertension risks, our findings suggested that although there was a direct positive connection between them, it is not present after adjusting BMI (OR [95%CI] = 1.05 [0.87–1.27], p = 6.17E-01). Based on the study, higher exposure to PM2.5 and PM10 increases the chances of developing essential hypertension, and this influence could occur through mediation by BMI.

Conclusion: Exposure to both PM2.5 and PM10 is thought to have a causal relationship with essential hypertension. Those impacted by substantial levels of air pollution require more significant consideration for their cardiovascular health.

KEYWORDS

PM2.5, PM10, hypertension, Mendelian randomization (MR), air pollution

Introduction

As industrialization advances daily since its inception, air pollution has become an alarming environmental issue that severely endangers modern living standards and public health (1, 2). Approximately 7 million fatalities can be attributed solely to air pollution, according to estimates made by the Global Burden of Disease Study (3). The major constituents of air pollution are particles along with various types of gases (4), while the classification for these tiny solid elements is determined by their size <10 microns [PM10] and <25 microns [PM2.5], (5). The most significant sources of atmospheric pollution from gas components include NO_X and NO_2, which arise from burning fossil fuels at high temperatures (6).

Essential hypertension, a predominant contributor to global morbidity and mortality (7), has witnessed an incremental prevalence in adults, surpassing 30 % post-2010 (8). Effective interventions are urgently needed in low-income countries due to their anticipated heavy burden of hypertension on healthcare systems (9), and essential hypertension is responsible for more than 90% of all reported cases of high blood pressure (10). Recognized established risk factors for hypertension include a diet that is high in sodium but low in potassium (11), lack of physical activity (12), and obesity (13).

The relationship between hypertension and air pollution has been extensively researched over the past decade, with multiple cross-sectional and cohort studies being conducted. Still, the final results are not entirely consistent (14). Various studies have varied in assessing the effects of different air pollutants on hypertension, and some have even been widely divergent (15–17). This may be due to the limitations of most epidemiological evidence, such as the inability to determine the causal relationship between PM2.5 pollution and hypertension, which may lead to confusion in causality; the data used in the studies mostly comes from regions or communities, rather than individuals; and potential confounding factors such as participants' diet, physical activity, and lifestyle cannot be excluded.

The introduction of genetic polymorphisms opens a new frontier in investigating air pollution's impact on health. Genetic variations among individuals can significantly modulate the body's response to pollutants, potentially influencing the onset and progression of conditions like hypertension. This variability underscores the need for a more nuanced understanding of the interplay between genetic factors and environmental exposures (18).

This study carves a novel path by leveraging Mendelian randomization (MR)—a technique that circumvents traditional observational study pitfalls using genetic polymorphisms as instrumental variables to infer causality. MR parallels randomized controlled trials in design, nullifying biases from reverse causality since genotypes are not modifiable by disease states (19). In principle, the MR analyses rely on three basic assumptions: First, the genetic variants should present a robust association with the exposure. Second, the genetic association between the exposure and outcome should be independent of confounders. Third, the genetic variants affect the outcome exclusively via the exposures (20, 21). To deepen our analysis, we employ multivariable Mendelian randomization (MVMR) (22), a method not yet widely applied in this context, to examine the direct effect of air pollution on hypertension after adjusting for common risk factors, including obesity, smoking, and alcohol consumption.

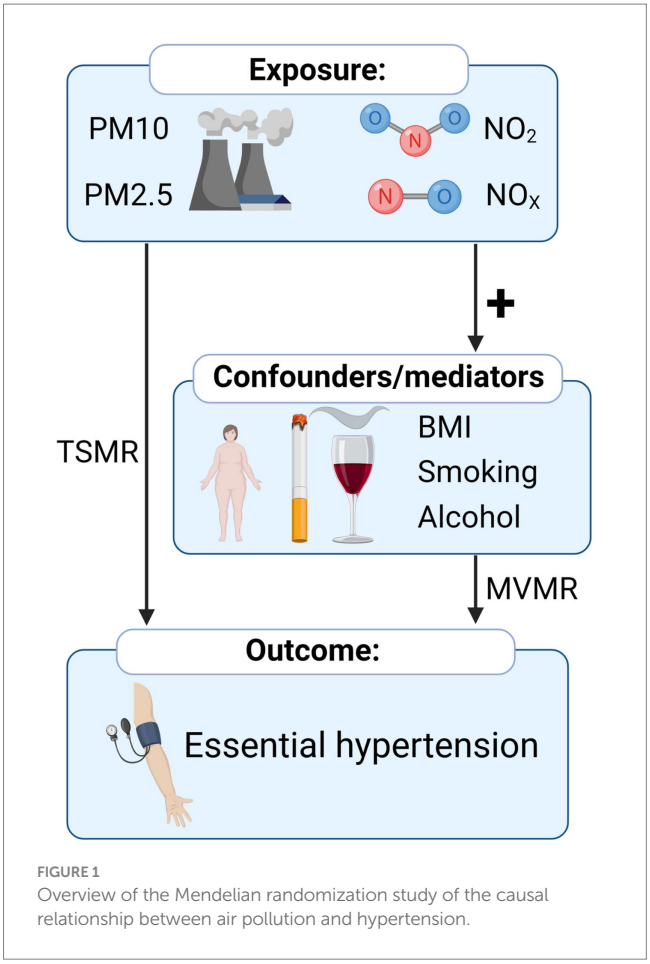

FIGURE 1
Overview of the Mendelian randomization study of the causal relationship between air pollution and hypertension.

In this study, we performed two-sample MR analyses to investigate the causal relationship between four air pollutants (PM2.5, PM10, NO_X, NO_2) and essential hypertension. Although one-sample MR is likely to be biased by the overlapping population between the datasets of exposures and outcomes, recent researches suggest that this potential overlap may not bias the results as previously thought (20, 23). Thus, we performed one-sample MRs to replicate the analysis for two-sample MRs to confirm the validation. To take some confounders and mediators into consideration, we conducted MVMR analyses to explore the more direct causality.

Methods

Study design and GWAS summary data

The flow chart of the study design is shown in Figure 1. All summarized Genome-wide association study (GWAS) summary data for each respective phenotype were obtained from the publicly available datasets (MRC IEU OpenGWAS) (24).[1] The corresponding GWAS ID and basic information about the included GWAS are shown in Supplementary Table 1. The procedure for extracting IVs from

1 https://gwas.mrcieu.ac.uk/

summarized GWAS was followed by the "TwoSampleMR" R package[2] through GWAS ID (24). No restriction of gender, age, income, or education level was set for these GWAS.

The summarized GWAS data of participants living in different air pollution areas were derived from UK Biobank (25–27). The extent of residential air pollution was estimated in different sites in Great London by a land use regression for the annual average 2010. The mean PM10 was 16.24 ± 1.90micro-g/m3, ranging from 11.78 to 31.39 micro-g/m3. The mean PM2.5 was 9.99 ± 1.06 micro-g/m3, ranging from 8.17 to 21.31 micro-g/m3. The summary-level GWAS of PM10 and PM2.5 included 423,796 individuals and 9,851,867 single-nucleotide polymorphisms (SNPs). The mean NO2 was 26.71 ± 7.58 micro-g/m3, ranging from 12.93 to 108.49 micro-g/m3. The mean NOx was 44.11 ± 15.53 micro-g/m3, ranging from 19.74 to 265.94 micro-g/m3. The summary-level GWAS of NO2 and NOx both included 456,380 individuals and a total of 9,851,867 SNPs.

The GWAS data for the potential confounders or mediators, including body mass index (BMI), alcohol intake frequency, and the number of cigarettes previously smoked daily, were also obtained from the UK biobank (24, 25, 28), which included 336,109 participants with 10,894,596 SNPs, 336,965 participants with 10,894,596 SNPs and 78,291 participants with 10,894,596 SNPs, respectively.

For the outcome, the summarized GWAS of essential hypertension in the FinnGen study (release 5) was selected to avoid sample overlapping, generated from longitudinal phenotype and digital health records produced by national health registries (29). This GWAS included 42,857 patients with essential (primary) hypertension, diagnosed according to the International Classification of Diseases (ICD) diagnosis codes (version 10), and 162,837 controls with 16,380,466 SNPs. For the GWAS used for validation, the GWAS of essential hypertension in the UK Biobank (UKB), a prospective cohort recruited from the UK general population between 2006 and 2010, was selected. This GWAS included 54,358 patients with self-reported physician-diagnosed essential (primary) hypertension (PheCode 401.1) and 408,652 controls with 9,851,867 SNPs (24, 25). The large sample size of UKB could further validate the results and enhance the statistical power. As the outcome variable was binary (whether they have hypertension), the effect size of each SNP in the summarized GWAS was represented as beta [log (OR)].

Selection for instrumental variables

To maintain sufficient instrumental variables (IVs) in MR, we set the value of p threshold for genome-wide correlations as 5e-6 to select solid instrumental variables (IVs) (30). Then, linkage disequilibrium analysis ($r^2 < 0.001$, distance <10 MB) based on the 1,000 Genomes Project of the European samples was performed to select independent IVs. IVs strongly associated with the outcome were excluded to meet the MR assumption. F statistics, as an indicator of weak IVs, were calculated by (R2/K)/[(1-R2)(N-K-1)] for each IVs, where K is the number of SNP, N is the sample size, R2 is the variance explained by SNPs calculated by 2*EAF*(1-EAF)*(Beta/SE)^2 (31). IVs with $F < 10$ were excluded to maintain the robustness. Harmonization of IVs was performed by the function of "harmonise_data" in "TwoSampleMR" R package to ensure that the association estimates of genetic variants aligned with the effect of the same allele between exposure and outcome GWAS (24).

Univariable Mendelian randomization

We used three methods (random-effects inverse variance weighting (IVW), weighted median, and MR egger) for TSMR analysis, with IVW as the primary approach and the other two as supplements. IVW provided a weighted regression of IVs outcome effects on exposure effects under the assumption of constrained intercept to zero, which owned the optimal statistical power. However, if horizontal pleiotropy existed in IVs, causal pathways other than exposure would interfere with the outcome. Thus, we supplemented the other two methods, which were relatively robust to horizontal pleiotropy, although the statistical power was partially sacrificed (32). The approach of weighted median selected median MR estimates for causal estimation (33). For MR Egger regression, the intercept was allowed to be estimated freely as a measure of average pleiotropy (34).

To estimate the robustness of the results, we performed analyses for horizontal pleiotropy, including leave-one-out tests and MR egger intercept test of deviation from null (35). The tests differed in their underlying presumptions but fundamentally gaged the degree to which the impact of one or more instrument SNP is overblown in magnitude, operating through the hypothesized pathway and other unaccounted-for-for causal pathways.

Multivariable Mendelian randomization

Multivariable Mendelian randomization (MVMR) allowed for estimating the effects of multiple exposures on an outcome, which depended on the covariance between the effect of the IV on each included exposure (36, 37). In this study, we performed MVMR to investigate the potential mediating role of common risk factors (BMI, alcohol intake frequency, and the number of cigarettes previously smoked daily) in the pathway from air pollution to hypertension. As the number of variables included in MVMR increases, the power of the MVMR would decrease (37). Thus, our MVMR model only included one type of air pollution and one additional risk factor for each analysis. The extraction of IVs, clump process, and harmonization followed the same procedure as univariable MR, as described before. IVs significantly associated with the outcome were excluded.

The MVMR estimates the direct causal effect of the exposure on the outcome adjusting for the mediator, while the univariable MR estimates the total causal effect. The difference between the total causal effect of air pollution on hypertension (from univariable MR) and the direct causal effect (from MVMR) would indicate a mediating role of the common factor. The indirect effect was not calculated because the linear relation between the exposure and outcome, which is required for the estimation of indirect effect, was not secured due to the binary variable of the outcome (38, 39).

All the statistical analyses were conducted in R software (40) by R package "TwoSampleMR" (24) and visualized by R package "ggplot2" (41).

2 https://github.com/MRCIEU/TwoSampleMR

Results

Genetic instruments

After a series of filter processes, we extracted 64, 34, 96, and 83 IVs proxing PM2.5, PM10, NO2, and NOx, respectively (Supplementary Tables 2–5). All the F statistics of the IVs were above 10, suggesting the absence of weak instrument bias.

Univariable MR analysis and sensitivity analyses

We conducted univariable MR analyses for PM2.5, PM10, NO_2, and NO_X on essential hypertension separately by inverse variance weighted, MR Egger, and Weighted median to investigate the causal effects of air pollution on essential hypertension (Supplementary Table 6). Results (Table 1; Figure 2) by IVW showed that there was a positive correlation between the increase of PM2.5 and the occurrence of essential hypertension (OR [95%CI] per 1 SD increase in predicted exposure = 1.24 [1.02–1.53], $p = 3.46E-02$ from Finn; OR [95%CI] = 1.04 [1.02–1.06], $p = 7.58E-05$ from UKB). The effect of PM10 on essential hypertension was also significant (OR [95%CI] = 1.45, [1.02–2.07], $p = 3.92E-02$ from Finn; OR [95%CI] = 1.03 [1.01–1.06], $p = 1.70E-02$ from UKB). However, the effects between NO_2 (OR [95%CI] = 1.03 [0.86–1.24], $p = 7.70E-01$ from Finn; OR [95%CI] = 1.01 [0.99–1.03], $p = 5.30E-01$ from UKB), NO_X (OR [95%CI] = 0.94 [0.79–1.13], $p = 5.30E-01$ from Finn, OR [95%CI] = 1.02 [1.00–1.03], $p = 1.17E-01$ from UKB) and essential hypertension were weak or nonexistent.

We also performed extensive sensitivity analyses to validate the causal association between air pollutants and the occurrence of essential hypertension (Table 2). The Cochran's Q test in the IVW and MR Egger suggested no significant heterogeneity among these air pollution IVs in the Finn group. However, there was substantial evidence of heterogeneity in most IVs in the UKB group, which may be caused by a population overlap between hypertension and air pollution in the UKB. The primary method we used, random-effect IVW, could be fitted to the presence of heterogeneity. No apparent horizontal pleiotropy was observed using MR-Egger, as the intercept did not significantly deviate from zero, which suggested balanced pleiotropy in the univariable MR analysis.

MVMR analyses

When considering their connection to developing essential hypertension, it is crucial to understand how various factors can influence the link between exposure to pollutant particles in the atmosphere, like PM2.5 and PM10. Leveraging MVMR Analysis while incorporating confounders or mediators such as BMI, smoking, and alcohol will help us better understand these complex relations. Our results indicated that there was still a positive relationship between PM2.5 exposure and essential hypertension after adjusting for alcohol and smoking but no direct effect after adjusting for BMI (OR [95%CI] = 1.05 [0.87–1.27], $p = 6.17E-01$; Supplementary Table 7). And for PM10, no significant direct effects were detected after adjusting for alcohol, BMI, and smoking (Table 3; Figure 3; Supplementary Table 7).

Discussion

Our research showed a causal relationship between increased exposure to both PM 2.5 and PM10 levels and an increase in the incidence of essential hypertension. It remained uncertain whether there was a link between essential hypertension risk and exposure to NO_2 or NO_X. Moreover, the increased risk of essential hypertension by PM2.5 was mediated by BMI. At the same time, BMI had the more significant mediating effect in contrast to smoking and alcohol regarding the effects of PM10 on essential hypertension.

Studies have consistently shown a positive relationship between short-term exposure to air pollution and the incidence of essential hypertension (42, 43). It was discovered through a systematic evaluation and meta-analysis report released in 2021 that there is a likelihood for individuals residing in areas where air pollution levels containing PM2.5 and PM10 for extended periods to develop hypertension, while this effect was not significant for NO_2 and NO_X (15). We found similar conclusions based on our research. Moreover, we applied MVMR to correct the impacts of air pollution on hypertension by adjusting for BMI, smoking, and alcohol. BMI has the potential to mediate the relationship between hypertension and exposure to particles such as PM2.5 or PM10. Smoking and alcohol might have a mediating or synergistic effect on the relationship between PM10 and hypertension. These results suggested the complexity of the effects of air pollution and other confounding factors on hypertension.

The impact of air pollution on the risk of hypertension is a complex issue that is affected by various factors. Many previous

TABLE 1 MR results for causal effects of air pollution on essential hypertension by IVW.

Exposure	Outcome	Source	nSNP	OR	LCI	UCI	pval
PM2.5	Essential hypertension	Finn	59	1.24	1.02	1.53	3.46E-02
		UKB	61	1.04	1.02	1.06	7.58E-05
PM10		Finn	33	1.45	1.02	2.07	3.92E-02
		UKB	33	1.03	1.01	1.06	1.70E-02
NO_2		Finn	90	1.03	0.86	1.24	7.70E-01
		UKB	88	1.01	0.99	1.03	1.88E-01
NO_X		Finn	80	0.94	0.79	1.13	5.30E-01
		UKB	78	1.02	1.00	1.03	1.17E-01

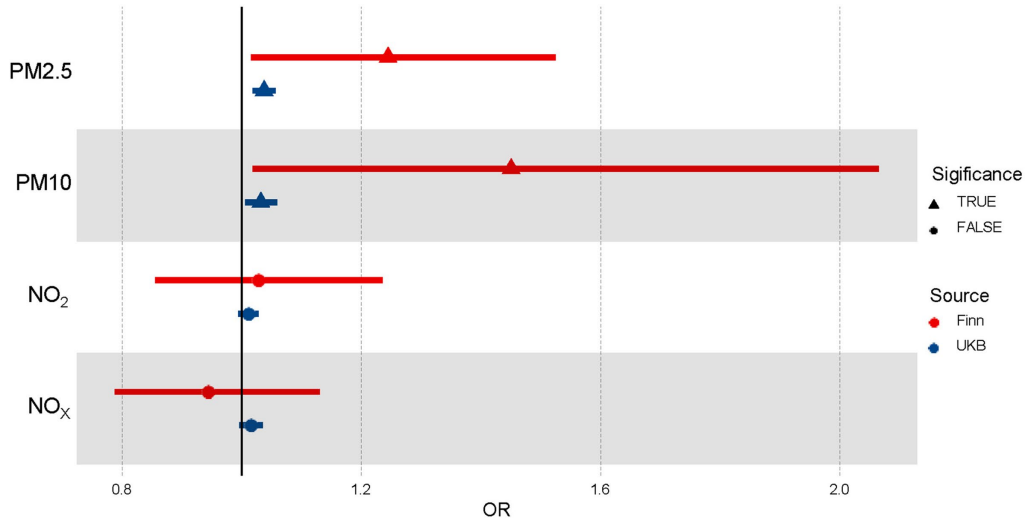

FIGURE 2
Forest plot of the association between air pollutants and hypertension using Univariable Mendelian randomization. OR means odds ratio. TRUE represents the causal association between the air pollutant and hypertension. FALSE represents no significant causal association between the air pollutant and hypertension.

TABLE 2 Sensitivity analyses.

Exposure	Outcome	Source	Pleiotropy			Heterogeneity			
			Egger_ intercept	SE	pval	Method	Q	Q_df	Q_pval
PM2.5	Essential hypertension	Finn	1.80E-03	3.21E-03	5.77E-01	MR Egger	66.64	57	1.79E-01
						Inverse variance weighted	67.01	58	1.95E-01
PM10			7.80E-03	6.51E-03	2.40E-01	MR Egger	35.43	31	2.67E-01
						Inverse variance weighted	37.08	32	2.46E-01
NO_2			1.35E-03	2.77E-03	6.28E-01	MR Egger	101.49	88	1.54E-01
						Inverse variance weighted	101.77	89	1.68E-01
NO_X			-1.67E-03	2.75E-03	5.46E-01	MR Egger	68.71	78	7.65E-01
						Inverse variance weighted	69.08	79	7.80E-01
PM2.5		UKB	4.23E-04	3.79E-04	2.68E-01	MR Egger	78.30	59	4.72E-02
						Inverse variance weighted	79.96	60	4.35E-02
PM10			9.30E-04	4.70E-04	5.66E-02	MR Egger	39.41	31	1.43E-01
						Inverse variance weighted	44.40	32	7.13E-02
NO_2			4.18E-04	3.27E-04	2.05E-01	MR Egger	121.60	86	6.96E-03
						Inverse variance weighted	123.90	87	5.75E-03
NO_X			5.20E-04	4.09E-04	2.08E-01	MR Egger	132.11	76	7.09E-05
						Inverse variance weighted	134.91	77	5.03E-05

studies have shown that BMI, smoking, and alcohol were significant risk factors for developing hypertension (28, 44). These common factors might play crucial mediating roles in air pollution and hypertension. For example, people exposed to heavy air pollution are associated with a higher risk of obesity (45). Obesity is also widely recognized as a long-established risk factor for hypertension (46), suggesting that it may likely be a significant mediating factor between air pollution and the increased risk of hypertension. Besides, obesity could also amplify the negative cardiovascular effects of PM2.5 pollution, especially concerning blood pressure and hypertension rates (47). People with obesity have increased susceptibility to the cardiovascular damage effects of air pollutants (48). For other factors, the association between smoking behavior and hypertension differed based on different levels of air pollution (49). In areas with high PM2.5, smoking was associated with a higher risk of hypertension. While in areas with low PM2.5, this was not observed, indicating that smoking might also act synergistically with air pollutants on hypertension (49).

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TABLE 3 MVMR results for causal effects of air pollution on essential hypertension after adjusting for alcohol, BMI and smoking.

Exposure	Outcome	Adjustment	nSNP	OR	LCI	UCI	pval
PM2.5	Essential hypertension	None	59	1.24	1.02	1.53	3.46E-02
PM2.5		Alcohol	52	1.28	1.01	1.62	3.73E-02
PM2.5		BMI	40	1.05	0.87	1.27	6.17E-01
PM2.5		Smoking	58	1.25	1.02	1.54	2.99E-02
PM10		None	53	1.45	1.02	2.07	3.92E-02
PM10		Alcohol	33	1.40	0.99	1.99	5.71E-02
PM10		BMI	26	0.96	0.75	1.24	7.70E-01
PM10		Smoking	33	1.41	0.99	2.01	5.94E-02

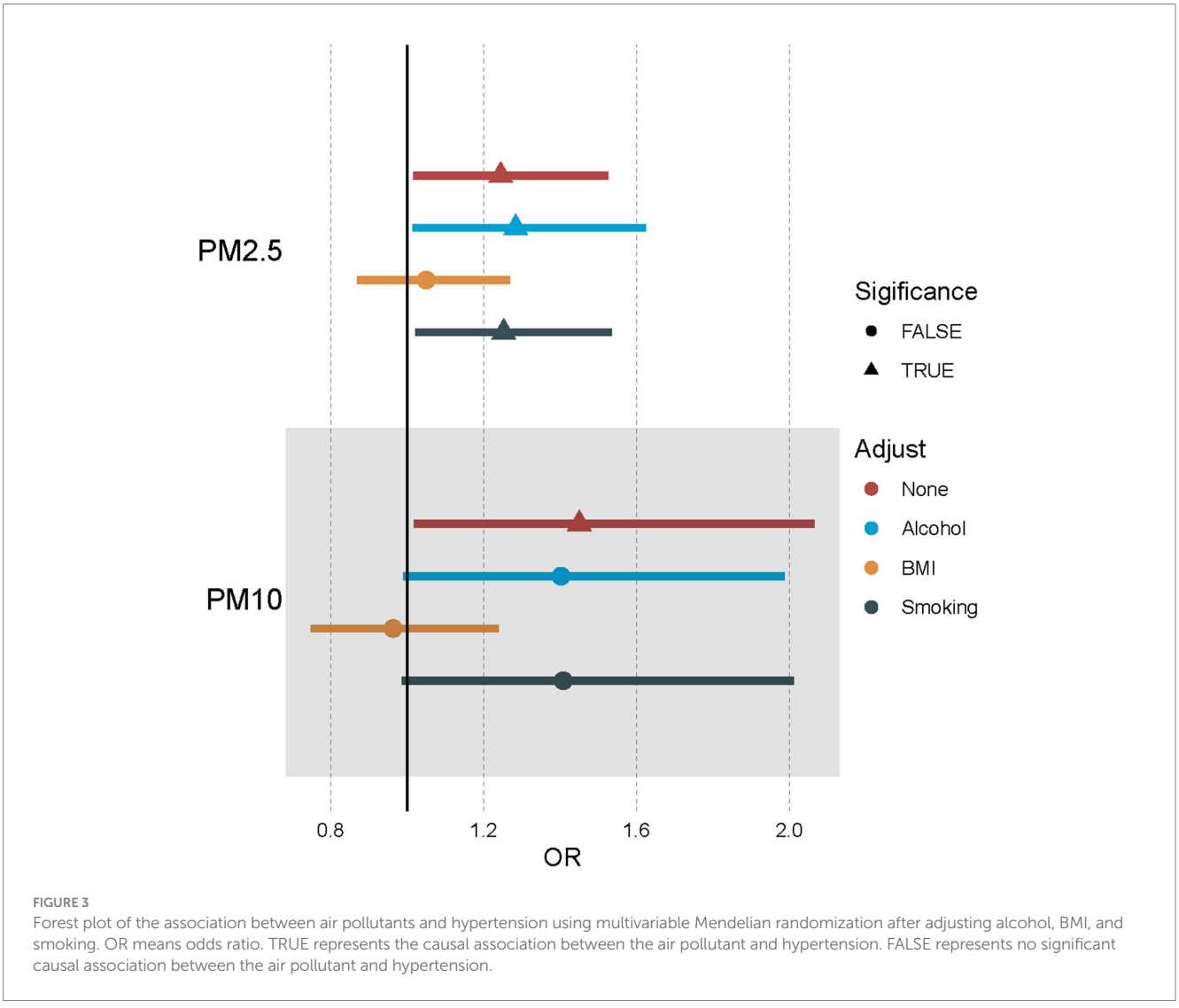

FIGURE 3
Forest plot of the association between air pollutants and hypertension using multivariable Mendelian randomization after adjusting alcohol, BMI, and smoking. OR means odds ratio. TRUE represents the causal association between the air pollutant and hypertension. FALSE represents no significant causal association between the air pollutant and hypertension.

The possible mechanisms by which air pollution increases the risk of hypertension have been widely studied (50). As the most critical air pollutant, PM has a complex mechanism related to hypertension. The most important are oxidative stress and inflammatory reactions, which are closely related and mutually induced (51). The former will promote vascular dysfunction, damage endothelial homeostasis, increase vascular permeability, and raise blood pressure (52). PM exposure has been found to result in an elevation of inflammatory cytokines and ROS levels (53), along with cellular infiltration that results in either local or systemic inflammation mediated via air-blood barrier breakdown at alveolar level (54). Additionally, hormones like cortisol, adrenaline, and noradrenaline get raised through PM, increasing the likelihood of developing hypertension (55–57). However, the mechanism by which PM2.5 and PM10 increase the risk of hypertension is currently unclear, and further research is needed to clarify it.

Our findings provided novel research insights and experimental evidence for understanding the adverse effects of air pollution on human well-being. They demonstrated the relationship between several air pollutants and primary hypertension while minimizing confounding factors and reverse causality. This could guide the screening of susceptible populations and the prevention of hypertension. Individuals with hypertension usually have a significantly higher risk of developing potentially life-threatening conditions such as heart disease and stroke (58). Consequently, we believe that our study can suggest the effect of air pollution on cardiovascular diseases to a certain degree. Additionally, conducting MVMR studies incorporating other confounding factors such as BMI, smoking, and alcohol can help inform targeted prevention strategies for cardiovascular disease in air-polluted populations.

There are some strengths to our research. Firstly, we used Mendelian randomization to establish an association between air pollution and hypertension. Secondly, we replicated the MR analysis to increase the validation. The sample size was large enough (Finn: 42,857 cases and 162,837 controls; UKB: 54,358 cases and 408,652 controls), making the estimated results as close to the actual values as possible (59).

However, some things could be improved in our study. First, we only included European ancestry, limiting the expansion of our conclusion to other races. Second, the potential bias of sample overlapping in our validated MR exists. Third, more mediators and mechanisms in which air pollutants cause hypertension must be revealed in the future. Last, genetic variants and health outcomes within UKB were associated with birth location, which could not be accounted for routine adjustments (60). This geographic structure of populations might produce biased associations for the genetic instruments.

Data availability statement

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

Author contributions

JW and YL wrote the manuscript. ZX and HZ supervised the study and revised the manuscript. CL, ZD, XL, NZ, and WW revised the manuscript. WW checked the language of the mansucript. 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.2024.1247149/full#supplementary-material

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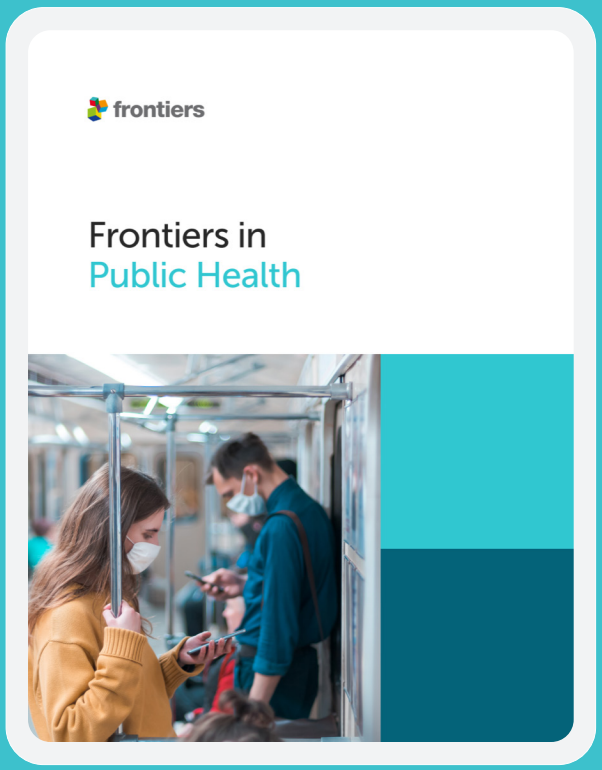

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