Research letter

Osteoporosis

Association between air pollution and bone mineral density: a Mendelian randomization study

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Submitted: 6 August 2024; **Accepted:** 26 August 2024
Online publication: 28 August 2024

Arch Med Sci 2024; 20 (4): 1334–1338
DOI: https://doi.org/10.5114/aoms/192628

Abstract

Introduction: The association of air pollution with bone mineral density (BMD) has attracted increasing attention. However, establishing a causal relationship remains uncertain.
Methods: We conducted a Mendelian randomization (MR) study employing $PM_{2.5}$, $PM_{2.5-10}$, PM_{10}, nitrogen dioxide, and nitrogen oxides as exposures and BMD as the outcome to explore the causality between air pollution and the occurrence of decreased BMD.
Results: By employing the IVW method, we identified a negative causality between air pollution ($PM_{2.5}$, PM_{10}, and nitrogen oxides) and BMD.
Conclusions: Our findings demonstrate that $PM_{2.5}$, PM_{10} and nitrogen oxides exposure may contribute to decreased BMD.

Key words: air pollution, osteoporosis, bone mineral density, Mendelian randomization, causal relationship.

Osteoporosis (OP) is a widespread chronic condition characterized by a reduction in bone mineral density (BMD), compromised bone strength, and an elevated susceptibility to fractures [1]. In the USA, over 10.2 million individuals are affected by OP, and over 3 million cases of fractures associated with OP are expected annually, leading to a projected treatment cost of approximately $25.3 billion [2]. OP is strongly linked to aging, and it is worrisome that as the world's population continues to age, the prevalence of osteoporosis will also increase [3].

According to the 2016 data provided by the WHO, around 91% of the global population resided in areas with low air quality [4]. Common air pollutants are usually divided into particulate matter (PM) and various gases, such as nitrogen dioxide, nitrogen oxides and more. PM is categorized according to its size, with particles smaller than 10 µm classified as PM_{10}, those smaller than 2.5 µm as $PM_{2.5}$, and particles with diameters between 2.5 µm and 10 µm as $PM_{2.5-10}$ [5].

Observational studies have provided some indications of the connection between air pollution and BMD. A study found a negative association between BMD in the femoral neck and exposure to air pollutants like $PM_{2.5}$ and PM_{10} [6]. Likewise, another study demonstrated a correlation between exposure to $PM_{2.5}$ and PM_{10} and reduced BMD in a group of 590 men aged 75 years and older [7].

Although numerous studies have shown a connection between air pollution and BMD, the question of causality is still being actively researched. In this study, we conducted an MR study using publicly available GWAS data, employing $PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, nitrogen dioxide, and nitrogen oxides as exposures and BMD as the outcome. The study aimed to clarify the potential causal relationship between air pollution and BMD.

Methods. ***Study design.*** In our study, air pollution served as the exposure factor, and IVs consisting of single nucleotide polymorphisms (SNPs) displayed a strong correlation with air pollution ($PM_{2.5}$, $PM_{2.5–10}$, PM_{10}, nitrogen dioxide, and nitrogen oxides). BMD served as the outcome variable in this study. Therefore, we employed an MR investigation to analyze the causal relationship between air pollution and BMD.

GWAS data sources. GWAS data related to SNPs were obtained from publicly available GWAS. Summary-level genetic data for $PM_{2.5}$, $PM_{2.5–10}$, PM_{10}, nitrogen dioxide, and nitrogen oxides were obtained from the UK Biobank (http://www.nealelab.is/uk-biobank), including 423,796; 423,796; 455,314; 456,380; 456,380 individuals of European ancestry, respectively. Summary-level genetic data for BMD were obtained from a meta-GWAS study, including 365,403 individuals of European ancestry. Additional data details are listed in Table I.

Selection of IVs. First, we established uniform filtering criteria ($p < 5 \times 10^{-8}$) for the IVs to ensure statistical significance [8]. However, insufficient SNPs were identified. Drawing upon the correlation analysis findings of relatively reliable thresholds in the existing literature, we relaxed the criteria to 5×10^{-6} for screening IVs [9]. For each corresponding SNP of each IV, we considered the linkage disequilibrium correlation coefficient ($r^2 < 0.001$) and base pair distance between the two SNPs (kb > 10,000). Then, we excluded those with intermediate allele frequencies, palindrome SNPs, incompatible SNPs, and confounder-related SNPs. Finally, we set a stringent threshold for statistical strength, with $F > 10$ as the criterion for strong correlation, minimizing the potential for weak instrument bias.

MR analysis method. In our study, we employed the inverse variance weighted (IVW) approach as the main methodology to evaluate the potential causality between air pollution and BMD. Additionally, we incorporated additional validation through MR-Egger and weighted median analyses. Then, we utilized MR-Egger regression and Cochran's Q test to ascertain the presence of pleiotropy and heterogeneity.

Statistical analysis. All MR analyses were executed using the R package "Two Sample MR". Furthermore, we computed the false discovery rate (FDR) adjusted *p*-values to address multiple testing, considering findings with $p < 0.05$ as statistically significant.

Results. In our research, 32 SNPs robustly linked to $PM_{2.5}$, 18 SNPs strongly related to $PM_{2.5\text{-}10}$, 156 SNPs robustly associated with PM_{10}, 70 SNPs robustly correlated with nitrogen dioxide, and 53 SNPs strongly related to nitrogen oxides. F-statistics of all IVs surpassed a threshold of 10. Detailed information about these IVs is provided in Supplementary Table SI.

The IVW method showed that the Beta and corresponding 95% confidence intervals (CI) for various exposures are as follows: $PM_{2.5}$: Beta = –0.135, 95% CI = [–0.201, –0.070], $p = 8.23 \times 10^{-5}$; $PM_{2.5\text{-}10}$: Beta = –0.006, 95% CI = [–0.006, 0.085], $p = 9.03 \times 10^{-1}$; PM_{10}: Beta = –0.091, 95% CI = [–0.124, –0.058], $p = 3.3 \times 10^{-7}$; nitrogen dioxide: Beta = –0.056, 95% CI = [–0.113, 0.001], $p = 6.59 \times 10^{-2}$; nitrogen oxides: Beta = –0.137, 95% CI = [–0.191, –0.083], $p = 1.52 \times 10^{-6}$ (Figure 1). All significance levels are FDR-adjusted. As indicated by the finding, we identified a causality linking air pollution ($PM_{2.5}$, PM_{10}, nitrogen oxides) with BMD. Other methods demonstrated that these relationships persisted (Figure 1). Furthermore, this study did not observe any evidence of causality between $PM_{2.5\text{-}10}$, nitrogen dioxide, and BMD (Figure 1).

This study showed no evidence of pleiotropy (Table II), indicating IVs do not affect the outcome via the confounding factors. No heterogeneity was observed in our study for $PM_{2.5}$, $PM_{2.5\text{-}10}$, PM_{10}, and nitrogen oxides, except for nitrogen dioxide

Table I. Overview of the data sources of phenotypes used in the MR study

Phenotype	Sample size	Number of SNPs	Consortium	Ancestry	Sex	GWAS ID	Year
$PM_{2.5}$	423,796	9,851,867	MRC-IEU	European	Both sexes	ukb-b-10817	2018
$PM_{2.5\text{-}10}$	423,796	9,851,867	MRC-IEU	European	Both sexes	ukb-b-12963	2018
PM_{10}	455,314	9,851,867	MRC-IEU	European	Both sexes	ukb-b-589	2018
Nitrogen dioxide	456,380	9,851,867	MRC-IEU	European	Both sexes	ukb-b-2618	2018
Nitrogen oxides	456,380	9,851,867	MRC-IEU	European	Both sexes	ukb-b-12417	2018
BMD	365,403	10,783,906	NA	European	Both sexes	ebi-a-GCST90014022	2021

PM – particulate matter, MR – Mendelian randomization, SNPs – single nucleotide polymorphisms, MRC-IEU – Medical Research Council Integrative Epidemiology Unit, NA – not available.

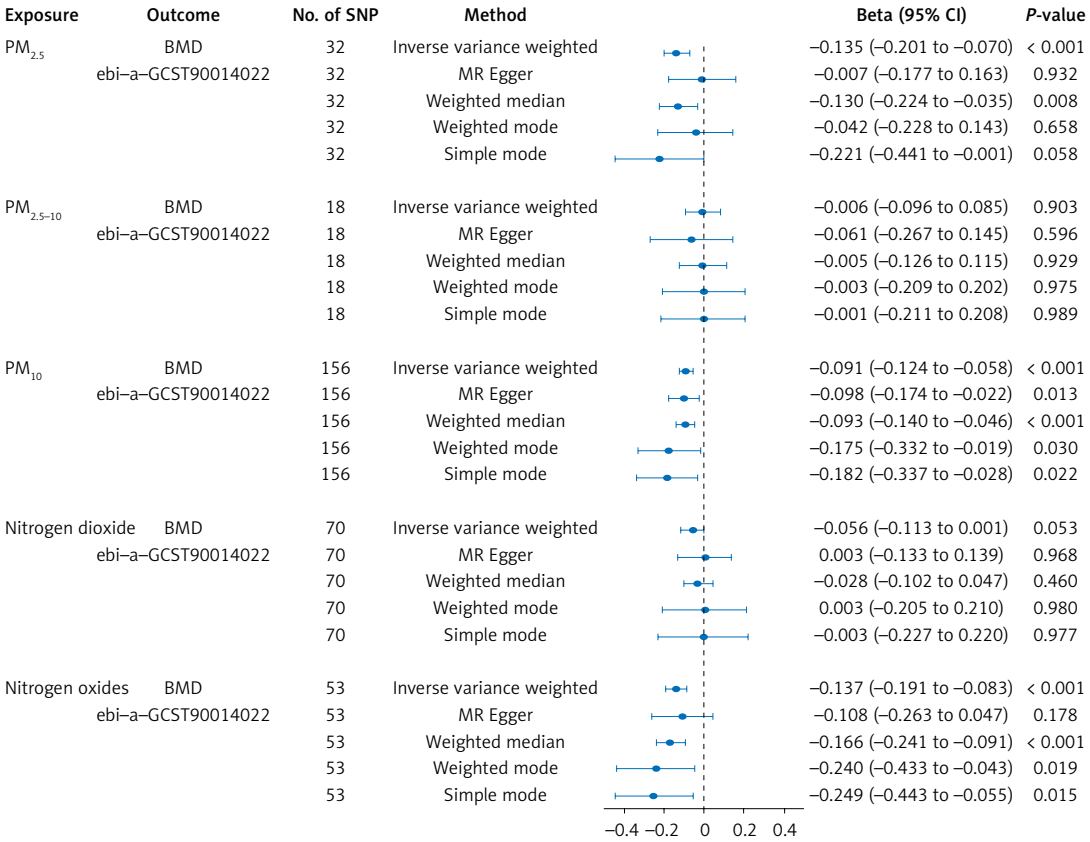

Figure 1. The causal relationship between exposure to air pollution and outcomes in BMD

Table II. Pleiotropy and heterogeneity test of air pollution genetic instrumental variables in GWAS for BMD

Exposure	Pleiotropy test			Heterogeneity test		
	P-value	SE	Intercept	*P*-value	Q	Q-df
$PM_{2.5}$	0.120	0.001	-0.002	0.708	26.276	31
$PM_{2.5-10}$	0.566	0.002	0.001	0.810	11.831	17
PM_{10}	0.849	0.000	0.000	0.845	137.163	155
Nitrogen dioxide	0.352	0.001	-0.001	0.034	91.968	69
Nitrogen oxides	0.697	0.001	0.000	0.700	46.204	52

GWAS – genome-wide association study, PM – particulate matter.

(p = 0.034, Q = 91.968) (Table II). The "leave-one-out" analysis indicated that findings remained consistent even with the exclusion of any individual SNP.

Discussion. The connection between air pollutants and bone mineral metabolism is not fully comprehended due to the complexity of the biological processes involved. However, an increasing amount of proof suggests that increased inflammatory reactions caused by air pollution exposure can be considered a contributing element [10]. Exposure to air pollutants can increase overall inflammation by triggering certain proinflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-17. These cytokines, in turn, influence the differentiation and function of osteoblasts and osteoclasts [11]. Additionally, air pollution is likely to induce cellular oxidative stress, which is one of the pathogenic mechanisms. Studies suggest that bone loss in estrogen-deficient mice is caused by oxidative stress, which activates T cells through increased activation of bone marrow dendritic cells [12]. Besides, vitamin D (Vit D) deficiency serves as an additional factor connecting air pollution to OP. Low levels of Vit D can lead to decreased serum calcium levels, which can then increase osteoclast activity and the transfer of calcium from the bones to the outside of cells [13]. Air pollution might be associated with a decrease in outdoor activities, leading to reduced exposure to solar ultraviolet B (UVB) radiation. Insufficient absorption of UVB by the skin is a significant contributor to Vit D deficiency [14]. Additional studies are needed to elucidate

the biological mechanisms linking air pollutant exposure and reduced BMD.

This study presents several advantages. Firstly, our study harnessed Mendel's principle of independent assortment, opting for IVs as the exposure in MR analysis. This choice greatly boosts the reliability of our results as we investigate the cause-and-effect connection between air pollution and BMD. Secondly, reverse causality is precluded as genes precede the onset of the disease. Thirdly, our study leveraged data from publicly available GWAS pooled investigations, benefiting from a substantial sample size that enhances the robustness of our analysis. Additionally, our study offers a novel theoretical and practical groundwork to address the hazards posed by air pollution to bone health.

Nevertheless, our study comes with inherent limitations. Firstly, it is noteworthy that the population under investigation for air pollution and BMD predominantly comprises individuals of European descent. This potential ethnic homogeneity may limit the broader applicability of our findings to the entire population. Secondly, due to our reliance solely on summary statistics from the MR study, our conclusions are limited to finding that air pollution ($PM_{2.5}$ and nitrogen oxides) is negatively correlated with BMD. Further research is imperative to elucidate the specific mechanisms.

In conclusion, this MR study has robust evidence affirming a causal relationship between air pollution-related indicators ($PM_{2.5}$, PM_{10} and nitrogen oxides) and decreased BMD. The outcomes of this study offer the potential to guide clinical decision-making and shape public health strategies. Ultimately, these findings can contribute to the formulation of targeted interventions and alleviate the impact of air pollution on bone health, thereby enhancing the quality of life for individuals affected by this condition.

Data availability

The GWAS summary statistics used in this MR study are available in Open GWAS. The R scripts applied in the two-sample MR analysis and shell codes used in genetic correlation analysis are available from the author (Jiang Rui 2426758230@qq.com) upon request.

$PM_{2.5}$: (https://gwas.mrcieu.ac.uk/datasets/ukb-b-10817/),

$PM_{2.5-10}$: (https://gwas.mrcieu.ac.uk/datasets/ukb-b-12963/),

PM_{10}: (https://gwas.mrcieu.ac.uk/datasets/ukb-b-589/),

Nitrogen dioxide: (https://gwas.mrcieu.ac.uk/datasets/ukb-b-2618/),

Nitrogen oxides: (https://gwas.mrcieu.ac.uk/datasets/ukb-b-12417/),

BMD: (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90014022/).

Acknowledgments

Rui Jiang, Qi Qu, Zhiyu Wang contributed equally to this work.

We sincerely thank all the participants for their valuable contributions to this study, which utilized publicly available data from prior research studies.

Funding

No external funding.

Ethical approval

The data were obtained from a publicly accessible database, and no human subjects were involved; therefore, the ethical parameters were not applicable.

Conflict of interest

The authors declare no conflict of interest.

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