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Association between air pollution and osteoporosis

A Mendelian randomization study

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Abstract

Osteoporosis (OP) is a significant disease in the aging society, which poses a threat to the physical well-being of older adults. Some studies suggest that air pollution may contribute to an increased incidence of OP; however, this causal relationship has not been firmly established. To address this gap, we conducted Mendelian randomization (MR) analysis to assess the potential causal association between air pollution (including nitrogen dioxide [N = 456,380], nitrogen oxides [N = 456,380], particulate matter [PM]2.5 [N = 423,796], and PM10 [N = 455,314]) and total-body bone mineral density (BMD) (N = 56,284). We utilized summary data from IEU Open GWAS on the database of genome-wide association studies (GWAS) and employed inverse variance weighting (IVW) as our primary analytical approach. The findings from our MR study in the European population using the IVW method indicated a potential causal link between nitrogen oxides: $\beta = -0.59$, confidence interval (CI) = (−1.03 to −0.16), $P = 0.008$; PM2.5: $\beta = -0.60$, CI = (−1.12 to −0.08), $P = .025$. These results suggest that there might be a causative relationship between nitrogen oxides, PM2.5, and BMD with regards to OP development among individuals exposed to air pollution. Importantly, the observed associations passed all statistical tests without any evidence of heterogeneity or pleiotropy. Furthermore, the presence of air pollution was found to be associated with an elevated risk of developing OP. This study provides compelling evidence for a causal connection between nitrogen oxides, PM2.5, and OP, suggesting that reducing air pollution could play a crucial role in preventing OP development.

Abbreviations: BMD = bone mineral density, CI = confidence interval, GWAS = genome-wide association study, IV = instrumental variable, IVW = inverse variance weighted, MR = Mendelian randomization, OP = osteoporosis, PM = particulate matter, SNP = single nucleotide polymorphism, WM = weight median.

Keywords: air pollution, Mendelian randomization study, nitrogen oxides, osteoporosis, PM2.5

1. Introduction

OP is a disease characterized by osteopenia, microarchitectural deterioration, and fragility fractures.[1] OP is a common systemic bone disease in clinical practice, affecting over 30 million people in Europe alone.[2] OP is 1 of the most important diseases facing the aging population.[3] The World Health Organization reports that population aging is a growing problem and it is estimated that by 2050, 22% of the world's population will be over the age of 60.[4] As the world's population ages, OP is becoming more prevalent.[5] OP causes approximately 2 million hip, spine, wrist, and other fractures each year.[6] At the same time, OP-induced fractures are a common cause of death among older adults.[7] As a result of population growth and increased life expectancy, the total number of people aged 50 and over with hip fractures alone is projected to increase to twice its current level by 2050.[8] In addition, the direct (fracture-related) and indirect costs of

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The datasets generated during and/or analyzed during the current study are publicly available.

The summary GWAS data used in this study are publicly available and no specific ethical approval was required.

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OP are enormous, with studies showing that the costs associated with OP in Europe alone amounted to €56.9 billion in 2019. Countries around the world face increasing challenges in reducing the burden caused by OP.[9] Air pollution can pose a serious threat to human health and can cause a wide range of systemic diseases in the human body, including respiratory diseases, cardiovascular diseases, and central nervous system diseases.[10] Air pollution can lead to adverse pregnancies, negatively affecting the health of pregnant women and fetuses.[11] The World Health Organization reports that approximately 2.4 million people die each year from diseases attributable to air pollution.[12]

A study from the UK Biobank containing 422,955 subjects showed that long-term exposure to PM2.5, nitrogen dioxide, and nitrogen oxides increases the risk of OP.[13] In a cross-sectional analysis from India, exposure to PM2.5 decreased bone mineral content in humans.[14] In addition, 2 articles published in The Lancet Planet Health suggest that air pollution contributes to bone loss and causes OP.[15,16] However, some studies suggest that the evidence between air pollution causes OP is heterogeneous.[17,18]

Mendelian randomization (MR) is a method used to assess a causal relationship between genetic variants that alter exposure or biological intermediates and clinically relevant outcomes,[19] which effectively avoids the confounding bias of traditional epidemiologic studies.[20] MR has also been used in previous articles to study atmospheric pollution and disease.[21,22]

Therefore, to further investigate whether there is an association between air pollution and OP, we used large-scale publicly available genome-wide association studies (GWAS) data for MR studies with nitrogen dioxide, nitrogen oxides, PM2.5, and PM10 as exposures and total-body bone mineral density (BMD) as outcomes. BMD can be used to diagnose OP,[23] so it was used in place of OP in MR studies.[24] The results of the study may have a positive impact on the generation of new OP prevention measures and policies related to air quality improvement. We hope that these policies can target effective interventions for those who are most at risk of OP in the future, to reduce the burden of OP, minimize the number of deaths among the elderly, and enhance the well-being of the population in an aging society in the years to come.

2. Method

2.1. Study design

We selected data from the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/datasets) for 2-sample MR analysis. Exposure data were nitrogen dioxide, nitrogen oxides, PM2.5, and PM10 datasets. The outcome data were the total-body BMD dataset. We performed a 2-sample MR analysis of the exposure data with the outcome data to estimate the causal effect of air pollution and OP. Three core assumptions were met: the instrumental variables (IVs) and the exposure (air pollution) were strongly associated; no correlation between IVs and confounders; the instrumental variable is not directly related to the outcome and its effect on the outcome can only be reflected by exposure. Figure 1 is a flowchart of the study design and the MR analysis process.

2.2. Data sources

We selected air pollution (including nitrogen dioxide, nitrogen oxides, PM2.5, and PM10) as the exposure, with data on all air pollution coming from UK Biobank, a large prospective study with more than half a million participants in the UK, and its phenotype, genetic information, and genome-wide genotyping data have been published.[25] We used the GWAS air pollution summary database for the European population. In European populations, the nitrogen dioxide (GWAS ID: ukb-b-9942), nitrogen oxides (GWAS ID: ukb-b-12,417), PM2.5 (GWAS ID: ukb-b-10,817), PM10 (GWAS ID: ukb-b-589), GWAS summary datasets included 456,380, 456,380, 423,796, and 455,314 participants, respectively.

We used total-body BMD as the outcome, and data were obtained from the European Bioinformatics Institute.[26] In European populations, the total-body BMD (GWAS ID: ebi-a-GCST005348) GWAS summary datasets included 56,284 participants as shown in Table 1.

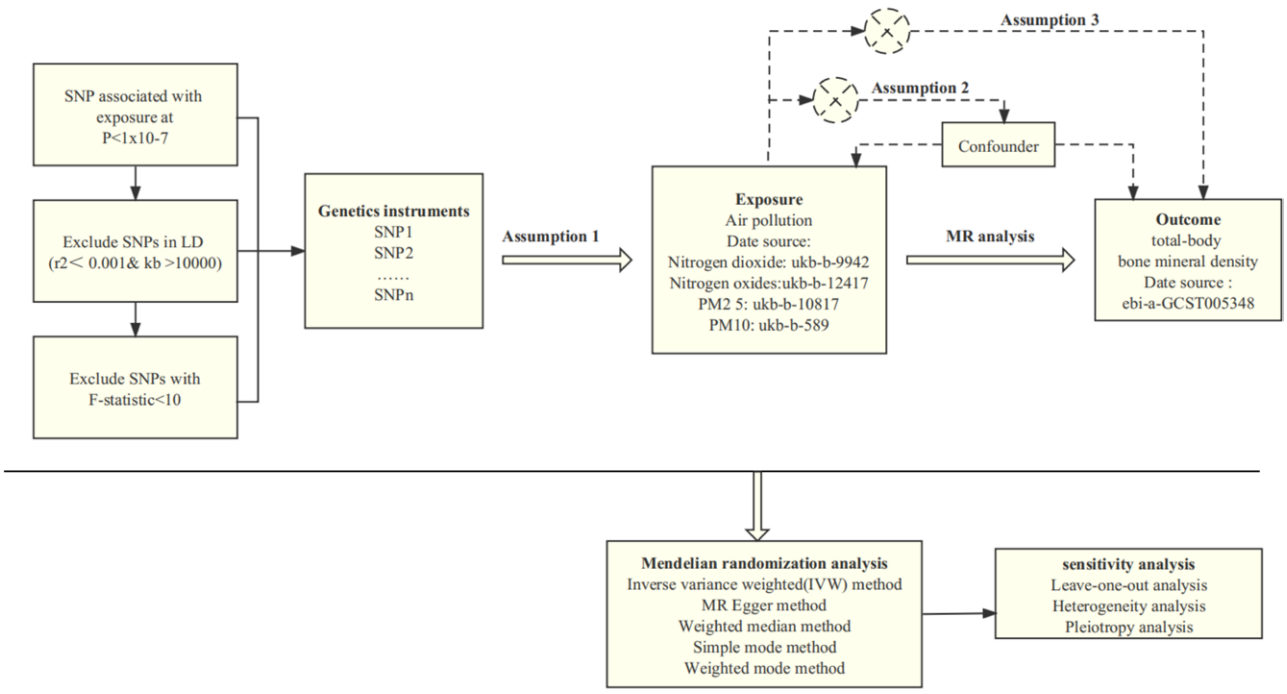

Figure 1. The flow chart of this study.

Table 1

Summary of the GWAS included in this MR study.

Exposures/outcomes	Dataset	Sample size	Number of SNPs	Population	Consortium	Sex	Year
Nitrogen dioxide	ukb-b-9942	456,380	9,851,867	European	MRC-IEU	Males and females	2018
Nitrogen oxides	ukb-b-12417	456,380	9,851,867	European	MRC-IEU	Males and females	2018
PM2.5	ukb-b-10817	423,796	9,851,867	European	MRC-IEU	Males and females	2018
PM10	ukb-b-589	455,314	9,851,867	European	MRC-IEU	Males and females	2018
Total-body bone mineral density	ebi-a-GCST005348	56,284	16,162,733	European	NA	NA	2018

GWAS = genome-wide association studies, MR = Mendelian randomization, PM = particulate matter, SNPs = single nucleotide polymorphisms.

2.3. Selection of instrumental variables

We used $P < 5 \times 10^{-8}$ as the genome-wide significance threshold for exposure to satisfy assumption 1, but the single nucleotide polymorphisms (SNPs) obtained in this way were limited. Therefore, we took a more relaxed *P*-value ($P < 1 \times 10^{-7}$) to obtain SNPs suitable for this MR analysis, and this relaxed threshold has also been applied in many studies.[27,28] To remove SNPs with linkage disequilibrium, $r^2 < 0.001$ and kb > 10,000 were set when extracting IVs. Then, we calculated the *F*-statistic ($F=\beta^2/SE^2$) for each SNP and eliminated SNPs with $F < 10$ to avoid weak instrumental bias.[29] We used the PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/phenoscanner) website to determine whether IV was significantly associated with risk factors for OP and associated SNPs were culled[30] (Table S1, Supplemental Digital Content, http://links.lww.com/MD/O387).

2.4. MR analysis

We used the inverse variance weighting (IVW) method as the primary analytical method for assessing the causal effects of nitrogen dioxide, nitrogen oxides, PM2.5, and PM10 on total-body BMD, which provides reliable estimates of the causal effects.[31] The weighted median, MR-Egger regression, simple mode, and weighted mode were used as auxiliary analysis methods to further improve the credibility and accuracy of the research results.[32]

2.5. Sensitivity analysis

To avoid heterogeneity in IV, we used Cochran *Q*-test, and $P > .05$ indicated no significant heterogeneity.[33] We performed pleiotropic tests using MR-Egger regression and MR-PRESSO global testing to ensure that IV did not compromise the accuracy of the results by other pathways. It was judged that there was no effect of pleiotropy in IVs if the MR–Egger intercept was close to 0 or $P > .05$.[34] MR-PRESSO enables a systematic assessment of the role of pleiotropy.[35] In MR-PRESSO, $P > .05$ proved no pleiotropy. Finally, the "leave-one-out "method was used to examine the sensitivity of the remaining SNPs 1 by 1. To avoid having specific SNPS influencing our results.[36]

2.6. Statistical analysis

All analyses were performed using the packages "Two Sample MR"[37] and "MR-PRESSO"[35] in R version 4.3.1. The threshold of statistical significance for evidence is $P < .05$.

3. Results

To assess the causal effect of air pollution (including nitrogen dioxide, nitrogen oxides, PM2.5, and PM10,) on OP, we performed MR Analysis in a European population. After removing SNPs with linkage imbalances and culling SNPs with confounders, nitrogen dioxide, nitrogen oxides, PM2.5, and PM10 were left with 8, 7, 6, and 14 SNPs (Table S1, Supplemental Digital Content, http://links.lww.com/MD/O387). The *F*-statistics for the exposure-related IVs were all >10, virtually ruling out the influence of weak IVs on the results.

Here are the results of our IVW analysis: nitrogen dioxide: $\beta = -2.88$, confidence interval (CI) = −5.68 to −0.07, $P = .182$; nitrogen oxides: $\beta = -0.59$, CI = −1.03 to −0.16, $P = .008$; PM2.5: $\beta = -0.60$, CI = 1.12 to −0.08, $P = .025$; PM10: $\beta = -0.08$, CI = −0.74 to 0.57, $P = .803$. Based on the IVW results, we found that nitrogen oxides and PM2.5 were negatively correlated with total-body BMD. The weighted median method also revealed the association between nitrogen oxides, PM2.5, and the risk of total-body BMD. Nitrogen oxides: $\beta = -0.77$, CI = −1.37 to −0.17, $P = .011$; PM2.5: $\beta = -0.73$, CI = −1.39 to −0.06, $P = .032$ (Fig. 2). The results of the MR-Egger, weighted model and simple model were not significant (Fig. 2). These results suggested a causal relationship between nitrogen dioxides, PM2.5, and increased risk of OP.

However, the results of the various analyses of nitrogen dioxide and PM10 were not significant, and there was no evidence of an association between nitrogen dioxide, PM10, and OP (Figs. 2–4).

Cochran *Q*-test showed no evidence of heterogeneity ($P > .05$). The results of MR-PRESSO analysis and MR-Egger intercept analysis indicated no horizontal pleiotropy in this analysis ($P > .05$). And conclusions were supported by leave-one-out sensitivity (Fig. 4). In conclusion, our MR analysis proved to be reliable and robust.

4. Discussion

Our MR study revealed a causal relationship between air pollution and OP.MR analysis showed that nitrogen oxides and PM2.5 had an effect on OP, and nitrogen dioxide and PM10 had no effect on OP. Our findings confirmed some epidemiologic studies that air pollution is a risk factor for OP. For example, a prospective observational study of air pollution and decreased BMD in postmenopausal women in the United States showed that nitrogen oxides can severely affect bone density in postmenopausal women.[38] Another study on outdoor air pollution and MD in older men, Oslo Health, also showed a statistically significant negative correlation between air pollution indicators and total-body BMD.[39] In addition, a cross-section study reported that long-term exposure to PM2.5 increased the prevalence of OP among participants in Hubei,[40] and a meta-analysis by Liu et al also showed an increased risk of OP with PM2.5 exposure,[41] which is similar to the results of our study. There is a lack of studies on the causal relationship between air pollution and OP risk. This study is the first to investigate the relationship between air pollution and OP using two sample MR (TSMR). Our findings were similar to traditional observational studies, further supporting the causal relationship between nitrogen oxides, PM2.5, and OP.

The molecular mechanisms by which nitrogen oxides and PM2.5 increase the risk of OP are unknown. Some studies suggest that it may be related to 3 mechanisms: air pollution promotes low-grade systemic inflammation, causes oxidative stress, and leads to vitamin D deficiency. Exposure to air pollutants

Mendelian randomization (MR) analysis of air pollution (nitrogen dioxide , nitrogen oxides, pm2.5 and pm10) with total-body bone mineral density in European population.

Exposures	Outcomes	Nsnp	Method	Beta (95% CI)	P	P(Cochran's Q heterogeneity test)	P(MR-Egger intercept test)	P(MR-PRESSO global test)
NO2	Tb BMD	4	MR Egger	-2.88 (-5.68,-0.07)	0.182	0.752	0.207	0.389
			Weighted median	-0.34 (-0.92,0.24)	0.253			
			IVW	-0.28 (-0.82,0.27)	0.316			
			Simple mode	-0.54 (-1.52,0.43)	0.355			
			Weighted mode	-0.56 (-1.45,0.32)	0.301			
NO	Tb BMD	5	MR Egger	-0.26 (-2.71, 2.19)	0.850	0.801	0.367	0.015
			Weighted median	-0.77 (-1.37, -0.17)	0.011			
			IVW	-0.59 (-1.03, -0.16)	0.008			
			Simple mode	-0.91 (-1.75, -0.06)	0.103			
			Weighted mode	-0.90 (-1.81,0.01)	0.124			
PM2.5	Tb BMD	3	MR Egger	-1.08 (-3.24, 1.08)	0.506	0.326	0.730	---
			Weighted median	-0.73 (-1.39, -0.06)	0.032			
			IVW	-0.60 (-1.12, -0.08)	0.025			
			Simple mode	-0.79 (-1.58, -0.01)	0.187			
			Weighted mode	-0.79 (-1.57, -0.01)	0.187			
PM10	Tb BMD	7	MR Egger	-5.69 (-10.0, -1.32)	0.051	0.053	0.200	0.389
			Weighted median	-0.18 (-0.76,0.41)	0.555			
			IVW	-0.08 (-0.74,0.57)	0.803			
			Simple mode	-0.54 (-1.39,0.31)	0.258			
			Weighted mode	-0.37 (-1.17,0.43)	0.403			

Figure 2. Inverse variance weighting (IVW) was used as the main method to analyze the air pollution (nitrogen dioxide, nitrogen oxides, PM2.5, and PM10) with total-body BMD in the European population. Beta: risk index; 95% CI. BMD = bone mineral density, CI = confidence interval, PM = particulate matter.

increases the levels of pro-inflammatory mediators in the human circulation[42] and bone loss in the elderly may be associated with low-grade systemic inflammation.[43] Air pollution causes oxidative stress in bones, which increases with age and causes OP in the elderly.[44] In addition, air pollution has been shown to cause kidney damage.[45] The kidneys are involved in vitamin D metabolism, and vitamin D deficiency leads to decreased bone mineral density and an increased risk of osteoporosis-related fractures.[46]

Our MR Study has the following strengths. We used TSMR to analyze the causal relationship between air pollution and OP. Previous epidemiological studies have shown a controversial relationship between air pollution and OP, which may be affected by confounding factors and reverse causality. Our

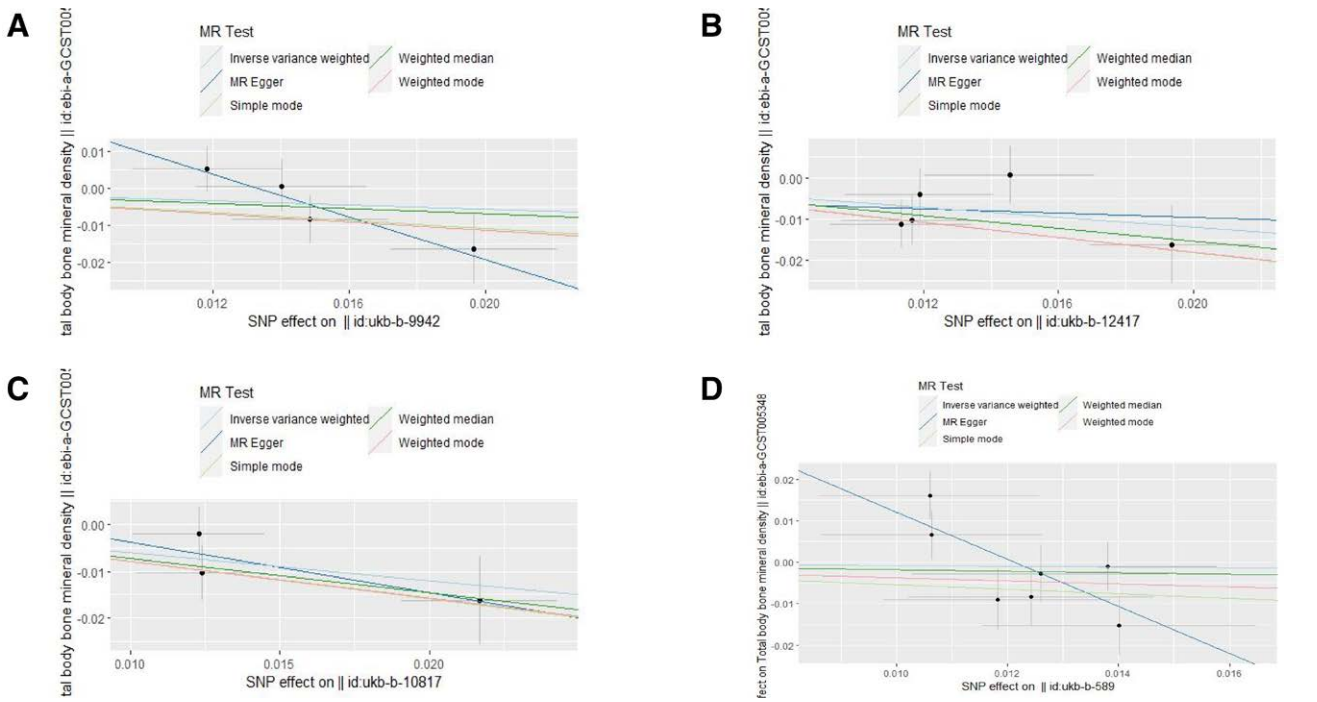

Figure 3. Scatter plot of air pollution and total-body BMD. Horizontal ordinate: SNP effect on "exposure"; vertical coordinates: SNP effect on "outcome." (A) Exposure: nitrogen dioxide, outcome: total-body BMD; (B) exposure: nitrogen oxides, outcome: total-body BMD; (C) exposure: PM2.5, outcome: total-body BMD; (D) exposure: PM10, outcome: total-body BMD. BMD = bone mineral density, PM = particulate matter, SNP = single nucleotide polymorphisms.

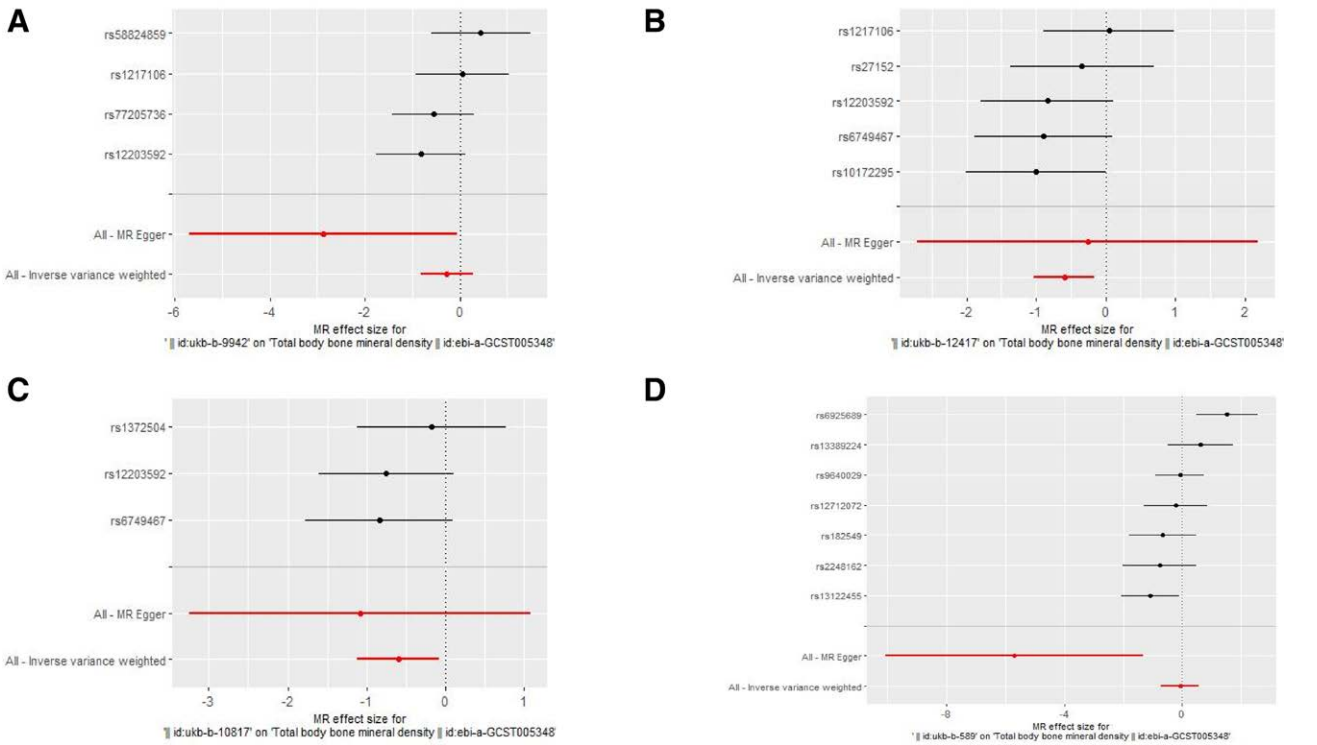

Figure 4. Forest plots of air pollution and total-body BMD. Horizontal ordinate: SNP effect on "exposure"; vertical coordinates: SNP effect on "outcome." (A) Exposure: nitrogen dioxide, outcome: total-body BMD; (B) exposure: nitrogen oxides, outcome: total-body BMD; (C) exposure: PM2.5, outcome: total-body BMD; (D) exposure: PM10, outcome: total-body BMD. BMD = bone mineral density, PM = particulate matter, SNP = single nucleotide polymorphisms.

study makes up for the shortcomings of traditional observational studies and the results are more reliable. Exposure and individual outcome data are European descent, can effectively reduce the effects of population stratification caused by potential association.

Of course, our study has some limitations. Our TSMR analyses are based on European ancestry, which has some limitations. This relationship may change in individuals of other ancestries, and may not apply to other regions and countries, so it is prudent to generalize to racially and ethnically diverse populations.

We performed MR analyses using only summary statistics of air pollution and total-body BMD, which only tentatively determined that there was a causal relationship between air pollution and OP. The mechanism of how air pollution further affects OP still needs further investigation. In addition, our results were based on a significance level of $1 \times 10^{-7,}$ which may require expanding the sample size to further validate our conclusions. The relatively small number of SNPS for some pollutants after screening (e.g., 6 SNPS for PM2.5) may have limited the statistical power of the analyses.

5. Conclusion

In summary, air pollution is a modifiable risk factor for OP, and these studies may guide the prevention of OP and fractures due to fragility and help contribute to an aging society by significantly reducing the costs associated with it.

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