Impact of Particulate Matter Air Pollution on 25-Hydroxyvitamin D Levels: A Mendelian Randomization Study

Yi Zhang
Zhejiang Chinese Medical University
Zan Shen
Zhejiang Chinese Medical University
Hang Pei
Zhejiang Chinese Medical University
Guanyin Wang
Zhejiang Chinese Medical University
Ziyue Wang
Zhejiang Chinese Medical University
xinshi Wei
Zhejiang Chinese Medical University
Jinsheng Yu
Zhejiang Chinese Medical University
chao Wang
Anji County Hospital of Chinese Medicine
Jiang Hua
The First Affiliated Hospital of Zhejiang Chinese Medical University
Bangjian He
hebangjian@163.com

The First Affiliated Hospital of Zhejiang Chinese Medical University

Research Article

Keywords: 25-hydroxyvitamin D, particulate matter air pollution, osteoporosis, metabolism, mendelian randomization

Posted Date: October 17th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3437692/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Public Health on May 1st, 2024. See the published version at https://doi.org/10.1016/j.puhe.2024.03.002.

Abstract

Background

In observational studies, the 25-hydroxyvitamin D (25(OH)D) level in body has been found to be closely related to Particulate matter air pollution (PM). In this study, we employed the two-sample Mendelian randomization method (MR) to investigate and discuss the potential causal relationship and mode of influence.

Methods

PM data (PM_{10}, $PM_{2.5–10}$, $PM_{2.5,}$ $PM_{2.5}$ absorbance) came from the UKBiobank database and 25(OH)D data came from the EBI database. The analysis was conducted utilizing three prominent methods (Inverse-variance weighted (IVW), MR-Egger, weighted median, weighted mode, and simple mode). The primary emphasis was placed on IVW (random effects), accompanied by heterogeneity and horizontal pleiotropy tests. Furthermore, sensitivity analysis was undertaken.

Results

The Mendelian randomization analysis revealed a significant association between exposure to PM_{10} and a decrease in levels of 25(OH)D (OR: 0.878, 95%CI: 0.789–0.977). However, no significant relationship was observed between $PM_{2.5}$ exposure and 25(OH)D (OR: 0.858, 95%CI: 0.728–1.012). Further analysis indicated that the main contributor to the decline in 25(OH)D levels is linked to $PM_{2.5–10}$ exposure (OR: 0.840, 95%CI: 0.751–0.940) and $PM_{2.5}$ absorbance (OR: 0.875, 95%CI: 0.824–0.929). No heterogeneity and horizontal pleiotropy existed.

Conclusions

The MR results suggest that PM exposure lowers VD levels by reducing UV rays, and no significant PM2.5 impact on VD within the human body has been found. Considering the important mediator of VD in osteoporosis, we recommend that people in highly polluted areas supplement appropriate amounts of VD.

Introduction

Vitamin D (VD) is an essential fat-soluble steroid that plays a critical role in maintaining the balance of calcium and phosphate levels within the human body [1]. VD has two primary sources: vitamin D2 (ergocalciferol) obtained from dietary intake, and vitamin D3 (cholecalciferol) synthesized in the skin upon exposure to ultraviolet radiation which is the primary source of VD in the body [2]. After entering the

bloodstream, VD is transported to the liver where it is converted to 25-hydroxyvitamin D (25(OH)D), the main blood marker for assessing VD levels in the body [3]. VD plays a crucial role in maintaining skeletal health by promoting calcium absorption in the intestines and regulating bone mineralization, thereby preventing bone-related conditions such as rickets and osteomalacia [4]. In addition to its classical role in bone metabolism, extensive research suggests that VD exerts pleiotropic effects in various aspects, including the immune, cardiovascular, and endocrine systems [5–7].

Particulate matter (PM) is a complex mixture of tiny solid and liquid particles suspended in the air, considered one of the major air pollutants [8]. It is categorized into fine particles ($PM_{2.5}$, diameter ≤ 2.5μm) and coarse particles (PM_{10}, diameter ≤ 10μm). The sources of PM including both human activities (industrial production, transportation, residential heating) and natural processes (dust storms, forest fires, volcanic eruptions) [9]. Therefore, the composition of PM varies in space and time, comprising various chemical components like organic compounds, metals, sulfates, nitrates, and carbonaceous particles [10]. PM poses a global threat to the environment and public health: $PM_{2.5}$ can deeply penetrate the respiratory system and enter the bloodstream, causing severe health risks; $PM_{2.5-10}$ primarily affect the upper respiratory tract and have milder health impacts [11, 12].

VD deficiency continues to pose a significant global health challenge, particularly in populations residing at higher latitudes with limited access to sunlight and individuals with certain medical conditions [13, 14]. Additionally, emerging observational research has associated reduced vitamin D levels with PM pollution in specific regions [15–17]. Nevertheless, the complexity of these studies underscores the importance of addressing confounding factors to ensure the accuracy and validity of the findings. Therefore, the causal relationship between PM and VD is unclear and we need stronger evidence to support it.

Mendelian randomization (MR) is a method that utilizes single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to infer causal relationships between exposure and outcome, minimizing biases caused by confounding and reverse causality [18]. In this study, we employed a two-sample MR design to investigate the potential relationship between PM exposure and 25(OH)D levels. Meanwhile, based on MR results and related literature, we discussed the ways in which PM affects 25(OH)D if the results support observational studies.

Methods

Study design

This study utilized a two-sample Mendelian randomization to investigate the causal relationship between PM and 25(OH)D. PM was the exposure factor, and the outcome variable was the level of 25(OH)D. The complete process is shown in Fig. 1.

Data source

The PM data used in this study was obtained from the UK Biobank database in 2018, comprising a sizable sample of 423,796 individuals and a total of 9,851,867 SNPs [19]. The 25(OH)D data, crucial for our analysis, was sourced from a publication by Revez JA in 2020, involving 496,946 samples and a total of 6,896,093 SNPs [20].

Instrumental variable

IVs must satisfy the three crucial assumptions of MR: 1) the relevance assumption: strong correlation between SNP and exposure factor; 2) the independence assumption: SNP is unrelated to confounding factors; 3) the exclusion restriction assumption: SNP affects the outcome solely through the exposure factor.

To fulfill the assumption of relevance, we curated SNPs highly correlated with PM (including PM_{10}, $PM_{2.5-10}$, $PM_{2.5}$, and $PM_{2.5}$ absorbance) from the GWAS dataset. To obtain enough SNPs to ensure the robustness of the analysis, we set the significance threshold at $P < 5*10^{-6}$ [21, 22]. Additionally, we identified independent SNPs through linkage disequilibrium pruning ($R^2 < 0.001$, kb > 10,000) [23]. Following that, we extracted SNPs and their corresponding statistical data for 25(OH)D from the GWAS dataset, SNPs with minor allele frequency (MAF) < 0.01 were excluded [24]. To ensure data coherence between PM and 25(OH)D, we eliminated all palindromic SNPs. To satisfy the independence assumption, we rigorously examined the characteristics of each SNP using the PhenoScanner database (www.phenoscanner.medschl.cam.ac.uk/) to eliminate any potential confounding factors [25]. Subsequently, we performed F-statistic ($F = [(N - k - 1)/k] \times [R^2/ (1 - R^2)]$) for each SNP to assess their instrumental variable strength [26]. SNPs which F < 10 indicate insufficient instrumental variable strength, which may introduce bias into the results. Therefore, we will exclude such SNPs from our analysis.

MR analysis strategy

In this section, we employed three different analysis methods, namely inverse variance weighted (IVW), MR-Egger, and weighted median (weighted mode and simple mode as supplementary analysis), to estimate the potential causal relationship between PM and 25(OH)D. The IVW method employed a meta-analysis approach, assuming that all SNPs are valid instrumental variables and that there is no evidence of directional pleiotropy [24]. It is considered the most powerful and precise estimation method and served as the primary analysis approach in this study [27]. The other four analysis methods were used as supplementary approaches.

Additionally, we conducted heterogeneity, pleiotropy, and sensitivity analyses to ensure the robustness of our results. We assessed heterogeneity quantitatively using Q-values and I^2 statistics for SNPs ($p < 0.05$ indicates significant heterogeneity) [23]. Furthermore, the leave-one-out analysis was conducted to gauge the influence of individual SNPs on the overall estimate. MR-Egger intercept was used to evaluate pleiotropy, and MR-presso analysis was employed to identify and adjust for any pleiotropic outlier SNPs

[24]. These comprehensive analyses helped address potential sources of bias and provided a more comprehensive evaluation of the causal relationship between PM and 25(OH)D.

All statistical analyzes and visualization of results were performed using R statistical software (version 4.1.0, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org); using the “TwoSampleMR” and “LDlinkR” software packages. The statistical results were estimated using β-values and their 95% confidence intervals (CI) to assess the degree of causality. $P < 0.05$ is considered statistically significant.

Results

Criteria-compliant SNPs

After excluding SNPs in linkage disequilibrium (LD) or with minor allele frequency (MAF) < 0.01 and removing palindrome structures and SNPs associated with confounding factors, we retained 18 SNPs (PM_{10}), 42 SNPs ($PM_{2.5}$), 16 SNPs ($PM_{2.5-10}$), and 44 SNPs ($PM_{2.5}$ absorbance) as valid instrumental variables. (Supplementary material 1) Subsequently, we calculated the strength of these instrumental variables using the formula, and no weak instruments ($F < 10$) were found.

MR analysis results

As shown in Fig. 2 and Fig. 3. Utilizing the IVW method, our analysis revealed a noteworthy connection between exposure to PM_{10} and $PM_{2.5-10}$ environments and a reduction in intracellular 25(OH)D levels. Nevertheless, the statistical disparities were absent when examining the impact of $PM_{2.5}$ exposure. Remarkably, our supplementary investigations highlighted a correlation between the decline in intracellular 25(OH)D concentrations and the concurrent elevation in $PM_{2.5}$ absorbance levels.

Validation analysis

To ensure the robustness and reliability of our findings, we undertook rigorous analyses to assess the stability of the obtained results. We conducted MR-Egger test on the selected SNP, which yielded no significant indications of potential horizontal pleiotropy ($P > 0.05$); furthermore, the adjusted Q and I^2 statistic underscored the absence of heterogeneity ($P > 0.05$). A funnel plot of the relationship between the causal effect of PM2.5 on GDM was shown in Fig. 4.

Additionally, we executed a leave-one-out sensitivity analysis to ascertain the potential impact of each individual SNP on the overarching causal association (Fig. 5). This scrutiny revealed that systematically excluding individual SNPs and subsequently reiterating the MR analysis did not yield any pronounced deviations from the observed causal relationship.

Discussion

In this study, we employed a robust two-sample MR approach to elucidate the intricate relationship between exposure to PM and human 25(OH)D concentrations. Our findings underscore a discernible association where in elevated concentrations of $PM_{2.5-10}$, as well as heightened $PM_{2.5}$ absorbance, correlate with a concomitant reduction in circulating 25(OH)D levels. It is noteworthy that no statistically significant impact was observed pertaining to $PM_{2.5}$ exposure. These outcomes contribute to our comprehension of the complex interplay between PM and VD metabolism within the human biological milieu.

Observational and cohort studies have indeed demonstrated a decline in 25(OH)D within the human body because of exposure to PM [17, 28, 29]. However, a persistent debate surrounds the specific constituents and pathways responsible for this effect. While some studies argue that both $PM_{2.5}$ and $PM_{2.5-10}$ exert an impact on 25(OH)D [28, 30], others contend that the influence is limited to $PM_{2.5-10}$ alone [31]. In the above literature, there is ongoing dispute regarding the precise mechanisms through which PM disrupts 25(OH)D, encompassing both internal metabolic processes and its potential to alter atmospheric UV radiation intensity.

Following metabolism in the liver, 25(OH)D becomes activated VD ($25(OH)_2D$) in the kidneys [1]. Some research suggests that specific immune cells (macrophages and T cells) possess the capability to synthesize $25(OH)_2D$ under inflammatory conditions, thus orchestrating localized immune modulation [32]. Owing to minute particle size, $PM_{2.5}$ could through the human body via the respiratory system triggers a systemic inflammatory response [8]. Meanwhile, cohort studies also indicated that $PM_{2.5}$ may exert detrimental effects on kidney, potentially leading to disruptions in VD metabolism [33]. Hence, we postulated that $PM_{2.5}$ could impact 25(OH)D. But our MR analysis didn't reveal a link between them.

In contrast to $PM_{2.5}$, PM_{10} lacks the ability to permeate the human body. However, its physical properties grant it the capacity to reflect UV in the atmosphere [34]. Consequently, PM_{10} emerges as a prospective influencer of 25(OH)D. Building upon this premise, our MR analysis elucidated a correlation between PM_{10} exposure and a decline in 25(OH)D. While $PM_{2.5}$ is encompassed within PM_{10}, we refrained from multivariate MR analysis due to potential bias arising from data transformations. Instead, we opted for direct collection and analysis of $PM_{2.5-10}$ data, consistently revealing affirmative results. To further substantiate PM's influence on 25(OH)D via UV, we incorporated $PM_{2.5}$ absorbance data for supplementary analysis, corroborating a corresponding decline in 25(OH)D with heightened $PM_{2.5}$ absorbance.

Osteoporosis is a bone metabolic disorder characterized by a decrease in bone density, and particularly prevalent among postmenopausal women [35]. VD pathways is one of the most important pathways for osteoporosis, it plays a crucial role in bone metabolism by mediating calcium absorption and is one of the fundamental medications for preventing and treating osteoporosis [36]. Fragility fractures are the most severe complications of osteoporosis, and cohort studies in Taiwan have indicated that prolonged exposure to PM can elevate the risk of fractures [37, 38]. Therefore, we recommend that postmenopausal

women and osteoporosis patients residing in PM polluted areas should pay attention to their VD levels, ensure adequate VD supplementation, and reduce the risk of osteoporotic fractures.

This study has certain limitations. Firstly, it exclusively included individuals of European ancestry, thus the findings may not be generalizable to different ethnicities, nations, or regions due to potential genetic variations. Secondly, variations in PM2.5 composition across different regions could introduce potential bias [10]. Finally, our study focused on observational data, which may entail inherent limitations in establishing causation. Further research involving diverse populations and controlled experiments is essential to validate these findings and provide a more comprehensive understanding of the relationship between PM exposure and 25(OH)D levels.

Conclusion

In summary, this study supports that PM's impact on VD is mediated through UV, but we have not yet found evidence of $PM_{2.5}$'s direct effect on VD within the human body, however, we cannot entirely rule out the potential impact of $PM_{2.5}$. Meanwhile, we recommend that postmenopausal women in areas with high air pollution should consider timely VD supplementation to prevent osteoporosis.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: All authors agree to publish.

Availability of data and materials: All data are available.

Author contributions: YZ, XSW and JSY conducted the preliminary literature search and constructed the article idea; YZ, ZS and HP conducted data collection and processing; YZ, GYW and ZYW wrote the article; CW, JH and BJH reviewed the overall article review.

Competing interests: All authors declare no potential competing interests.

Funding: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: 2023 Medical Rookie——He Bangjian (1S22317). Natural Science Foundation of Zhejiang Province (LY21H270008). National Natural Science Foundation of China (82074469). Zhejiang Administration of Traditional Chinese Medicine (2023ZF019). Hua Jiang Famous Expert Inheritance Studio of Traditional Chinese Medicine (GZS2021020)

Availability of data and material: The datasets used or analyzed during the current study are available from the corresponding.

Acknowledgements: All authors agreed to publish.

References

1. Khazai N, Judd SE, Tangpricha V (2008) Calcium and vitamin D: skeletal and extraskeletal health. Curr Rheumatol Rep 10:110-117
2. Urena-Torres P, Souberbielle JC (2014) Pharmacologic role of vitamin D natural products. Curr Vasc Pharmacol 12:278-285
3. Tripathi A, Ansari M, Dandekar P, Jain R (2022) Analytical methods for 25-hydroxyvitamin D: advantages and limitations of the existing assays. J Nutr Biochem 109:109123
4. Bikle DD (2012) Vitamin D and bone. Curr Osteoporos Rep 10:151-159
5. Prietl B, Treiber G, Pieber TR, Amrein K (2013) Vitamin D and immune function. Nutrients 5:2502-2521
6. Latic N, Erben RG (2020) Vitamin D and Cardiovascular Disease, with Emphasis on Hypertension, Atherosclerosis, and Heart Failure. Int J Mol Sci 21:
7. Savastio S, Cinquatti R, Tagliaferri F, Rabbone I, Bona G (2020) Vitamin D effects and endocrine diseases. Minerva Pediatr 72:326-339
8. Kim KH, Kabir E, Kabir S (2015) A review on the human health impact of airborne particulate matter. Environ Int 74:136-143
9. Daellenbach KR, Uzu G, Jiang J, et al. (2020) Sources of particulate-matter air pollution and its oxidative potential in Europe. Nature 587:414-419
10. Mukherjee A, Agrawal M (2018) A Global Perspective of Fine Particulate Matter Pollution and Its Health Effects. Rev Environ Contam Toxicol 244:5-51
11. Ottone M, Broccoli S, Parmagnani F, et al. (2020) Source-related components of fine particulate matter and risk of adverse birth outcomes in Northern Italy. Environ Res 186:109564
12. Donaldson K, MacNee W (2001) Potential mechanisms of adverse pulmonary and cardiovascular effects of particulate air pollution (PM10). Int J Hyg Environ Health 203:411-415
13. Holick MF (2017) The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 18:153-165
14. Woo J, Giurgescu C, Wagner CL (2019) Evidence of an Association Between Vitamin D Deficiency and Preterm Birth and Preeclampsia: A Critical Review. J Midwifery Womens Health 64:613-629
15. Zhao Y, Wang L, Liu H, Cao Z, Su X, Cai J, Hua J (2019) Particulate Air Pollution Exposure and Plasma Vitamin D Levels in Pregnant Women: A Longitudinal Cohort Study. J Clin Endocrinol Metab 104:3320-3326
16. Mousavi SE, Amini H, Heydarpour P, Amini Chermahini F, Godderis L (2019) Air pollution, environmental chemicals, and smoking may trigger vitamin D deficiency: Evidence and potential mechanisms. Environ Int 122:67-90
17. Calderon-Garciduenas L, Franco-Lira M, D'Angiulli A, et al. (2015) Mexico City normal weight children exposed to high concentrations of ambient PM2.5 show high blood leptin and endothelin-1, vitamin

D deficiency, and food reward hormone dysregulation versus low pollution controls. Relevance for obesity and Alzheimer disease. Environ Res 140:579-592

18. Bowden J, Holmes MV (2019) Meta-analysis and Mendelian randomization: A review. Res Synth Methods 10:486-496
19. Eeftens M, Beelen R, de Hoogh K, et al. (2012) Development of Land Use Regression models for PM(2.5), PM(2.5) absorbance, PM(10) and PM(coarse) in 20 European study areas; results of the ESCAPE project. Environ Sci Technol 46:11195-11205
20. Revez JA, Lin T, Qiao Z, et al. (2020) Genome-wide association study identifies 143 loci associated with 25 hydroxyvitamin D concentration. Nat Commun 11:1647
21. Davies NM, Holmes MV, Davey Smith G (2018) Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 362:k601
22. Zou XL, Wang S, Wang LY, Xiao LX, Yao TX, Zeng Y, Zhang L (2021) Childhood Obesity and Risk of Stroke: A Mendelian Randomisation Analysis. Front Genet 12:727475
23. Shen J, Zhou H, Liu J, Zhang Y, Zhou T, Yang Y, Fang W, Huang Y, Zhang L (2021) A modifiable risk factors atlas of lung cancer: A Mendelian randomization study. Cancer Med 10:4587-4603
24. Cui Z, Hou G, Meng X, Feng H, He B, Tian Y (2020) Bidirectional Causal Associations Between Inflammatory Bowel Disease and Ankylosing Spondylitis: A Two-Sample Mendelian Randomization Analysis. Front Genet 11:587876
25. Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, Butterworth AS, Staley JR (2019) PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics 35:4851-4853
26. Burgess S, Thompson SG, Collaboration CCG (2011) Avoiding bias from weak instruments in Mendelian randomization studies. Int J Epidemiol 40:755-764
27. Yuan S, Tang B, Zheng J, Larsson SC (2020) Circulating Lipoprotein Lipids, Apolipoproteins and Ischemic Stroke. Ann Neurol 88:1229-1236
28. Yang C, Li D, Tian Y, Wang P (2021) Ambient Air Pollutions Are Associated with Vitamin D Status. Int J Environ Res Public Health 18:
29. Baiz N, Dargent-Molina P, Wark JD, Souberbielle JC, Slama R, Annesi-Maesano I, Group EM-CCS (2012) Gestational exposure to urban air pollution related to a decrease in cord blood vitamin d levels. J Clin Endocrinol Metab 97:4087-4095
30. Mousavibaygei SR, Bisadi A, ZareSakhvidi F (2023) Outdoor air pollution exposure, bone mineral density, osteoporosis, and osteoporotic fractures: A systematic review and meta-analysis. Sci Total Environ 865:161117
31. Torkashvand J, Jonidi Jafari A, Pasalari H, Shahsavani A, Oshidari Y, Amoohadi V, Kermani M (2022) The potential osteoporosis due to exposure to particulate matter in ambient air: Mechanisms and preventive methods. J Air Waste Manag Assoc 72:925-934

32. Fakhoury HMA, Kvietys PR, AlKattan W, Anouti FA, Elahi MA, Karras SN, Grant WB (2020) Vitamin D and intestinal homeostasis: Barrier, microbiota, and immune modulation. J Steroid Biochem Mol Biol 200:105663
33. Zhang Y, Liu D, Liu Z (2021) Fine Particulate Matter (PM(2.5)) and Chronic Kidney Disease. Rev Environ Contam Toxicol 254:183-215
34. Schikowski T, Huls A (2020) Air Pollution and Skin Aging. Curr Environ Health Rep 7:58-64
35. Wang L, Yu W, Yin X, et al. (2021) Prevalence of Osteoporosis and Fracture in China: The China Osteoporosis Prevalence Study. JAMA Netw Open 4:e2121106
36. Liao EY, Zhang ZL, Xia WB, et al. (2018) Calcifediol (25-hydroxyvitamin D) improvement and calcium-phosphate metabolism of alendronate sodium/vitamin D(3) combination in Chinese women with postmenopausal osteoporosis: a post hoc efficacy analysis and safety reappraisal. BMC Musculoskelet Disord 19:210
37. Yang Y, Li R, Cai M, et al. (2023) Ambient air pollution, bone mineral density and osteoporosis: Results from a national population-based cohort study. Chemosphere 310:136871
38. Chiu YC, Lin YT, Hsia YF, Jung CR, Lo YC, Chen TM, Chan JC, Wang YC, Kuo CC, Hwang BF (2021) Long-term exposure to fine particulate matter and osteoporotic fracture: A case-control study in Taiwan. Environ Res 196:110888

Figures

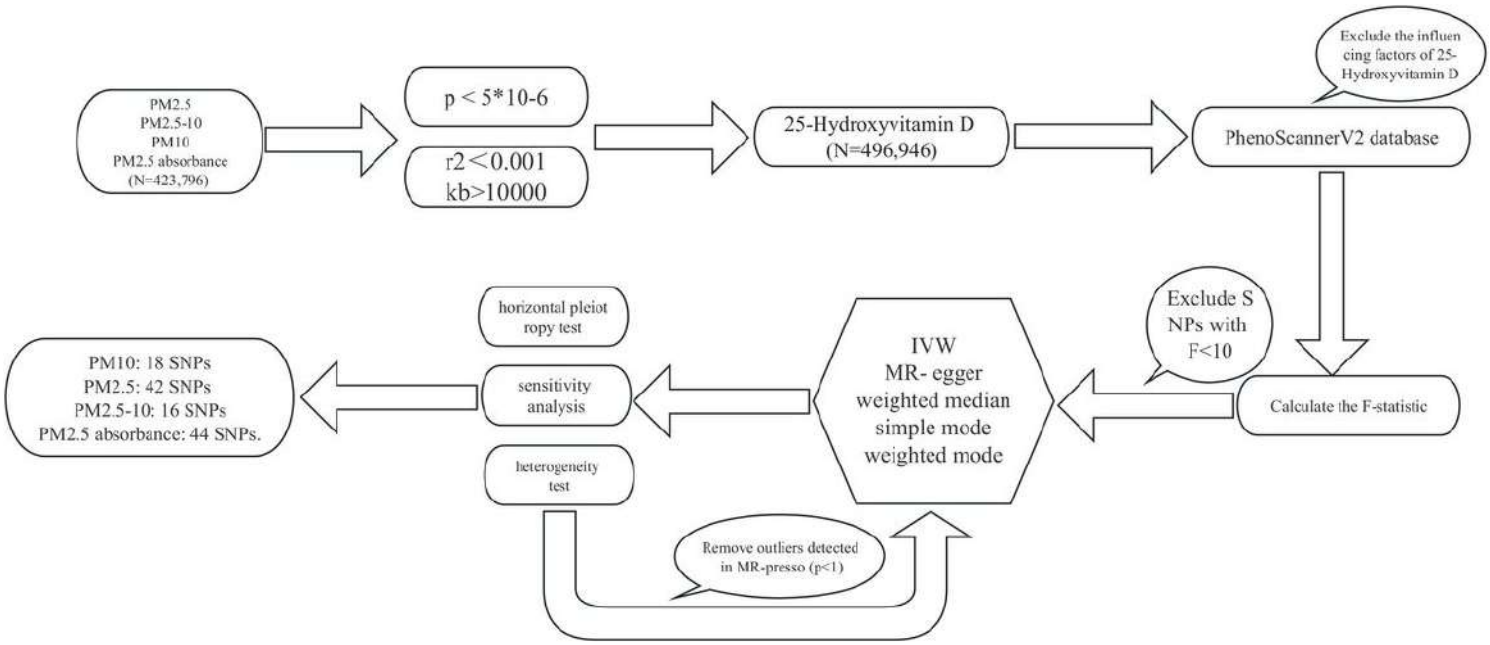

Figure 1

Flowchart of MR randomization analysis

Exposure	nSNP	Method	P_value	OR(95%CI)
PM2.5	36	MR Egger	0.5687	0.903(0.638-1.278)
	36	Weighted median	0.6242	0.977(0.895-1.069)
	36	IVW	0.2238	0.943(0.858-1.037)
PM2.5-10	16	MR Egger	0.1113	0.738(0.520-1.048)
	16	Weighted median	0.2791	0.925(0.803-1.065)
	16	IVW	0.0024	0.840(0.751-0.940)
PM10	17	MR Egger	0.1622	0.830(0.647-1.064)
	17	Weighted median	0.0818	0.885(0.772-1.015)
	17	IVW	0.0171	0.878(0.789-0.977)
PM2.5 absorbance	41	MR Egger	0.0632	0.861(0.738-1.004)
	41	Weighted median	0.0069	0.888(0.815-0.968)
	41	IVW	1.39E-05	0.875(0.824-0.929)

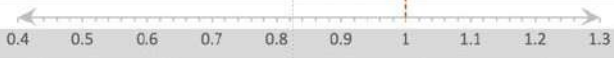

Figure 2

Flowchart of MR randomization analysis. OR: odds ratio; CI, confidence interval.

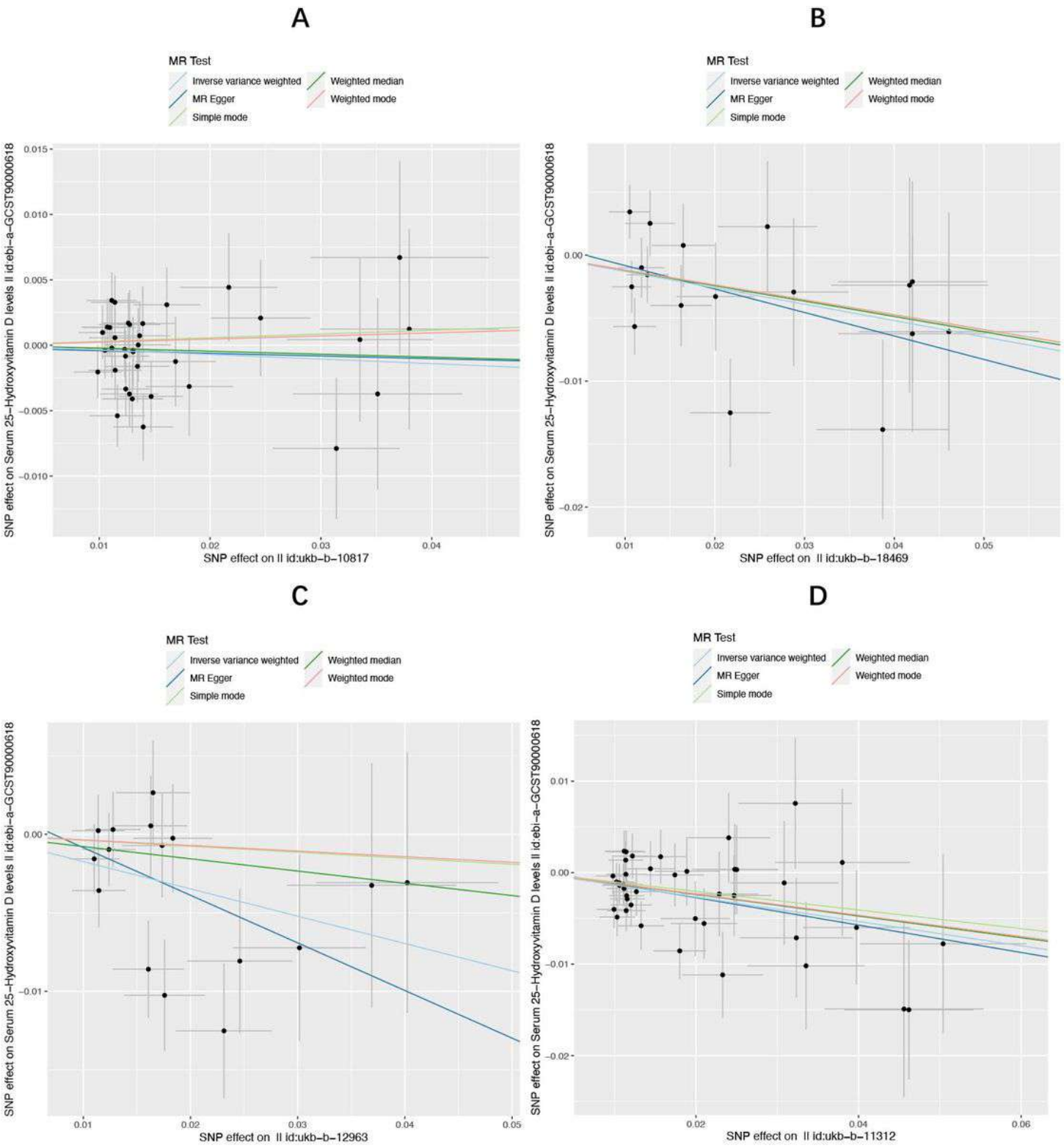

Figure 3

A scatter plot is employed to visually represent the causal relationship between PM and 25(OH)D. A: $PM_{2.5}$; B: PM_{10}; C: $PM_{2.5\text{-}10}$; D: $PM_{2.5}$ absorbance. As evidenced by the scatter plots of various methods including the inverse-variance weighted (IVW) method, MR–Egger regression method, weighted median, weighted mode, and simple mode, the slope of the linear regression line signifies the strength of the causal connection.

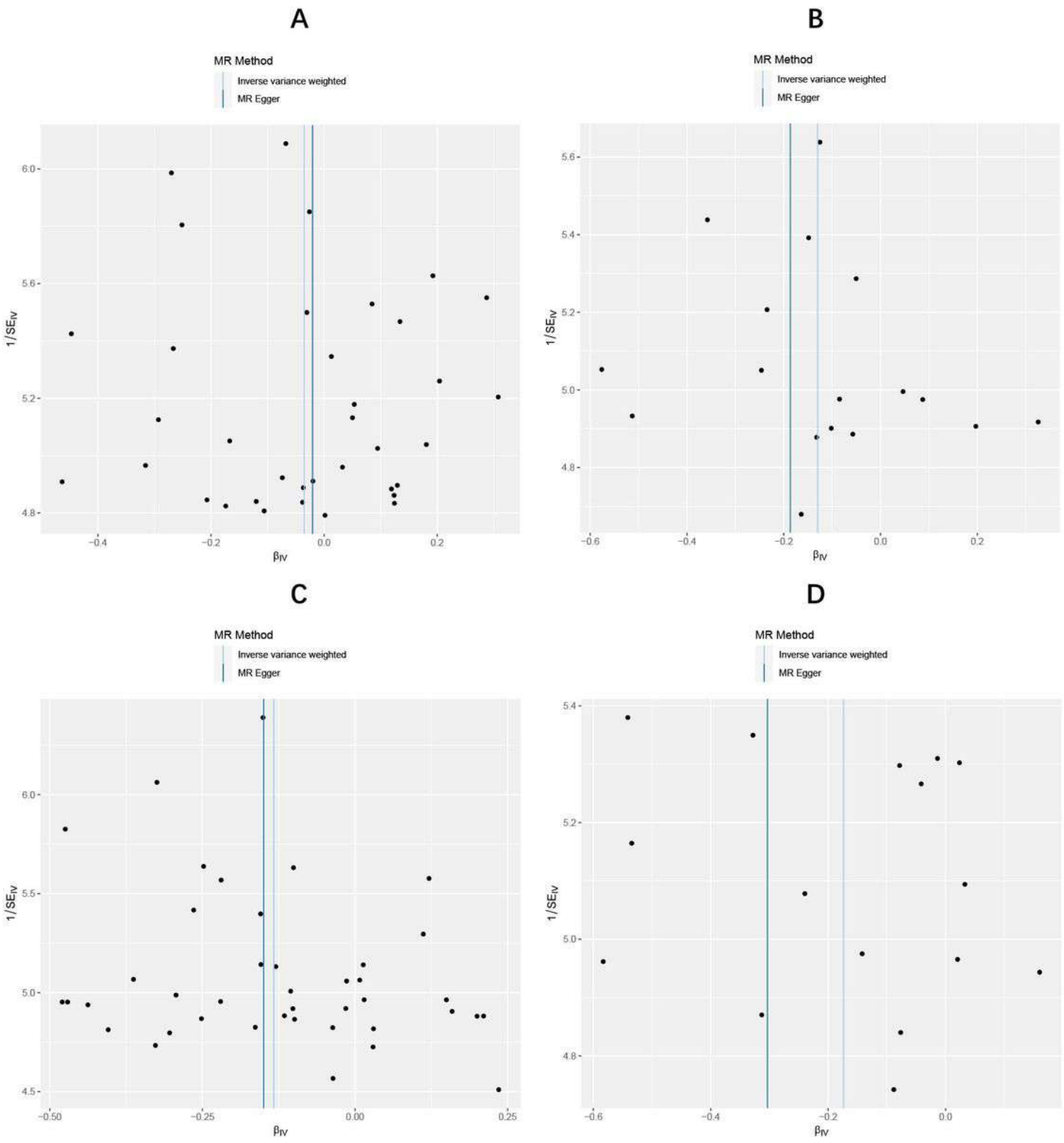

Figure 4

A funnel plot illustrating the relationship between PM's causal effect on 25(OH)D. A: $PM_{2.5}$; B: PM_{10}; C: $PM_{2.5}$ absorbance; D: $PM_{2.5-10}$. These plots display the connection between PM's causal impact on GDM, estimated using individual SNPs as separate instruments, and the reciprocal of the standard error of the causal estimate. Each black point signifies a valid instrumental SNP. The vertical line represents the estimated causal effect resulting from all instrumental SNPs using the two different methods.

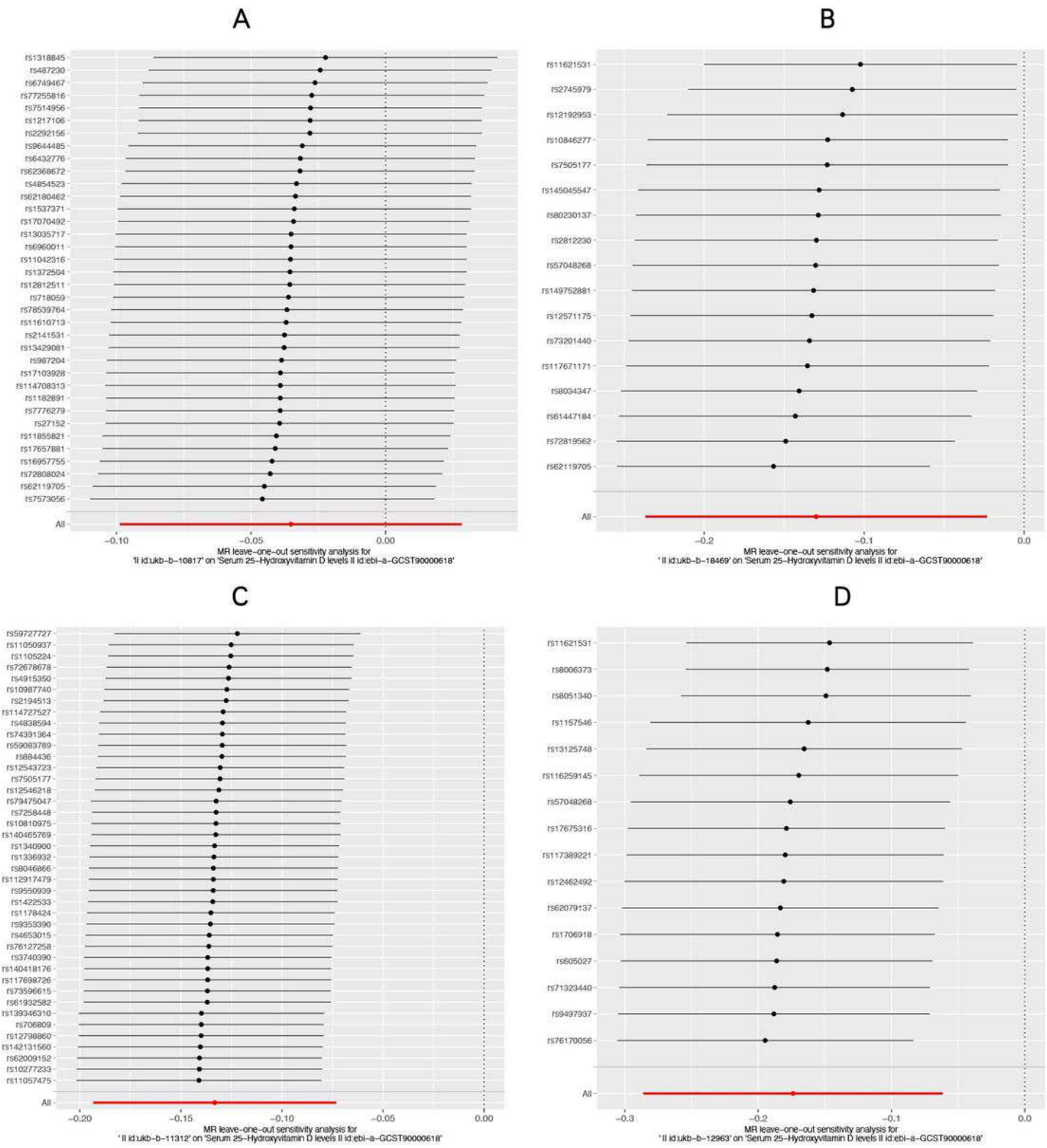

Figure 5

A forest plot depicting the 'leave-one-out' sensitivity analysis method to illustrate the impact of individual SNPs on the outcomes. A: $PM_{2.5}$; B: PM_{10}; C: $PM_{2.5}$ absorbance; D: $PM_{2.5-10}$. The red data point represents the IVW estimates obtained using all SNPs.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- file.pdf