

Multi-omics Mendelian Randomization Reveals the Causal Association and Mediating Mechanisms of PM2.5 with Depression: A Systematic Study Integrating Transcriptomics, Metabolomics, and Radiomics

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Research Article

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Abstract

Background

PM_{2.5} exposure has been associated with major depressive disorder (MDD), but causal evidence remains inconclusive, and the underlying multilevel mechanisms are poorly understood.

Objective

To investigate the causal effect of PM_{2.5} on MDD and to systematically explore potential mediators across multiple biological layers, including gene expression in blood and brain regions, peripheral and central metabolites, and brain imaging traits, using a multi-omics Mendelian randomization (MR) framework.

Methods

We first confirmed a significant genetic overlap between PM_{2.5} and MDD using LD score regression, and taking this as a premise, we then conducted a multi-omics MR study to assess the causal effect of genetically predicted PM_{2.5} on MDD. A two-step MR approach was used to evaluate mediation effects through blood and brain-region gene expression, blood and cerebrospinal fluid metabolites, and brain imaging-derived phenotypes.

Results

LD score regression revealed significant genetic overlap ($r_g = 0.3338$, $p = 1.92E-11$). Genetically predicted PM_{2.5} causally increased MDD risk (OR = 1.27, 95% CI: 1.07–1.51, $p = 5.95E-03$). Mediation analyses identified five blood genes (enriched in antigen presentation and xenobiotic metabolism), six brain-region genes (involved in autophagy, proteostasis, and immune response), and two blood fatty acid ratio metabolites as significant mediators. No significant mediation was found for cerebrospinal fluid metabolites or brain imaging traits.

Significance: This study provides robust genetic evidence for a causal role of PM_{2.5} in MDD. By integrating multi-omics data, it delineates a multilevel mechanistic landscape—spanning peripheral immunometabolic disturbances and region-specific autophagy, ER stress, and adaptive immunity—thereby advancing our understanding of how air pollution contributes to depression and offering potential molecular targets for future prevention and intervention.

Impact Statement

This is the first multi-tissue Mendelian randomization study to establish a causal link between PM_{2.5} and major depressive disorder through genetic evidence. By integrating blood and brain-region transcriptomes, peripheral metabolites, and imaging phenotypes, we uncover a dual-pathway mechanism: peripheral immunometabolic dysregulation (antigen presentation and xenobiotic

metabolism) coupled with brain-specific disruptions (autophagy, ER stress, and immune activation). These findings shift the understanding from single-level associations to a systemic-central nervous system interplay, offering tissue-specific molecular targets for future prevention and intervention strategies against pollution-related depression.

1. Introduction

Fine particulate matter with diameter $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) poses a major global health threat. Due to its small aerodynamic diameter, $\text{PM}_{2.5}$ can penetrate deep into the respiratory system. It enters the circulatory system via gas exchange and subsequently crosses the blood-brain barrier (BBB), exerting direct effects on the central nervous system (CNS). In recent years, multiple large-scale epidemiological studies have provided strong evidence for the association between $\text{PM}_{2.5}$ and depression [1, 2]. A nationwide population-based study in Nepal found that long-term exposure to $\text{PM}_{2.5}$ was significantly associated with increased depression risk [3]. Another large-scale, long-term follow-up study (median follow-up 10.9 years) based on the UK Biobank confirmed this association. It demonstrated that long-term exposure to relatively low $\text{PM}_{2.5}$ levels (median $\sim 10 \mu\text{g}/\text{m}^3$) is a risk factor for depression onset [4]. Although these observational studies have revealed correlations, they face two main limitations. First, traditional epidemiological studies struggle to avoid interference from residual confounding factors such as socioeconomic status and lifestyle. This makes establishing clear causal relationships difficult. Second, observational studies cannot elucidate the biological mechanisms by which $\text{PM}_{2.5}$ induces depression.

The biological mechanisms linking $\text{PM}_{2.5}$ exposure to depression likely involve complex, multidimensional, and multi-pathway processes. These encompass a series of changes from peripheral inflammation to the CNS. Firstly, $\text{PM}_{2.5}$ may influence gene expression. By stimulating immune cells to release pro-inflammatory cytokines such as interleukin-6 (IL-6), these molecules can compromise BBB integrity. This subsequently affects gene expression profiles in both peripheral and central nervous systems [5]. Secondly, $\text{PM}_{2.5}$ can alter the composition of blood metabolites, particularly those related to fatty acid, amino acid, and glucose metabolism [6–9]. These metabolic disturbances may indirectly contribute to brain dysfunction. They do so by altering neurotransmitter synthesis and precursor availability [7, 10, 11]. Thirdly, neuroimaging studies have found that $\text{PM}_{2.5}$ exposure may be associated with structural alterations and functional connectivity abnormalities in specific brain regions [12, 13]. However, evidence from different omics levels remains fragmented, lacking systematic integration. Currently, there is no definitive causal evidence establishing these factors as exact mediating mechanisms through which $\text{PM}_{2.5}$ leads to depression.

Mendelian randomization (MR) analysis is an epidemiological method that uses genetic variants as instrumental variables (IVs) to infer causal relationships between exposures and outcomes. Its core principle is based on Mendel's law of independent assortment. Genotypes are determined early in life and are generally not influenced by postnatal environmental or lifestyle confounders. They also avoid

reverse causation. Therefore, this method has become a powerful tool for exploring causal relationships between exposures and diseases. A limited number of recent studies have applied MR to explore the association between PM_{2.5} and major depressive disorder (MDD) [14–17]. However, these studies have the following two limitations. First, as PM_{2.5} is a non-biological exposure factor, it is necessary to verify the heritability of its associated genetic variants and their genetic correlation with the disease, which is a prerequisite for establishing causality. Second, they have largely been confined to confirming causal relationships without delving into the underlying biological mechanisms. Zhang et al. (2025) suggested a potential mediating role for neurotrophin-3 [17]. Yet, this study relied solely on plasma metabolite data to infer mechanisms within the brain. Since many metabolite macromolecules cannot cross the BBB, this approach cannot systematically and accurately reflect the pathogenic mechanisms of PM_{2.5}.

To address the above limitations, this study proposes a framework for analyzing the relationship between PM_{2.5} exposure and MDD, incorporating both an analysis of their genetic architecture and a multi-level, complementary multi-omics MR approach. Unlike the traditional strategy of constructing a single linear causal chain, we will first evaluate the heritability of single nucleotide polymorphisms (SNPs) associated with the exposure and disease, and assess whether they share a partial genetic architecture. Subsequently, we simultaneously incorporated expression quantitative trait loci (eQTL) data from blood and multiple brain tissues, metabolomic data from blood and cerebrospinal fluid (CSF), and brain imaging data. This allows for parallel testing across multiple biological levels: gene expression, metabolic pathways, and neural structure/function. This design enables direct investigation of the molecular changes PM_{2.5} induces within the CNS, effectively avoiding misjudgments due to incorrect tissue localization. Through multiple independent MR and mediation analyses, we aim to test in parallel whether PM_{2.5} influences depression risk via these mediating variables. This approach is expected to provide robust, multidimensional mechanistic evidence for the causal link between PM_{2.5} and depression. It thereby advances etiological and preventive research in environmental psychiatry.

2. Materials and methods

2.1 Data sources

This study utilized publicly available GWAS summary data for analysis. PM_{2.5} exposure data were obtained from the IEU OpenGWAS database (n = 423,796). Depression outcome data were sourced from the FinnGen consortium (n = 406,986). To explore underlying mechanisms, we further incorporated multi-omics mediator data. Blood eQTL data were obtained from the eQTLGen consortium (n = 31,684). eQTL data for 13 brain tissues were obtained from Genotype-Tissue Expression Project version 7 (GTEx V7) (n = 635). Data for 249 blood metabolites were obtained from Richardson et al. [18] (n: 110,051 to 115,082). Data for 338 CSF metabolites were sourced from Panyard et al. [19] (n = 291). Additionally, based on 3,935 brain imaging features provided by Smith et al. [20], we selected 398 features associated with depression-related core brain regions based on prior literature. These regions include the amygdala,

hippocampus, and prefrontal cortex (n: 18,412 to 22,133). Detailed identifiers and sample size information for each dataset are provided in Supplementary Tables S1–S2.

2.2 Analysis of heritability and genetic correlation

Linkage disequilibrium score regression (LDSC) is a method used to estimate genetic correlations between phenotypes or diseases. We referred to the LD scores from the 1000 Genomes Project and removed SNPs that did not match the reference panel ($MAF \leq 0.01$ or $INFO \text{ score} \leq 0.9$). First, using GWAS data for $PM_{2.5}$ exposure and MDD, we calculated the heritability (h^2) of SNPs associated with each trait. Subsequently, we performed LDSC analysis to assess the genetic relationship (r_g) between $PM_{2.5}$ exposure and MDD, thereby determining whether causal effects might be influenced by shared genetic architecture. A threshold of $P < 0.05$ was used to determine statistical significance. LDSC analyses were conducted using Python (v 2.7).

2.3 Instrumental variable selection

To ensure the reliability of MR analysis results, we screened for appropriate genetic IVs (SNPs) for each exposure and mediator. From the GWAS summary statistics of each exposure or mediator, we extracted SNPs that reached genome-wide significance (significance threshold set at $p < 1.00 \times 10^{-5}$). To eliminate bias due to linkage disequilibrium (LD), we clumped these SNPs using the European 1000 Genomes Project data as the reference panel. Parameters were set as $clump_r^2 = 0.001$ and $clump_kb = 10,000$ kilobases. We retained only the independent SNP with the strongest association to the exposure within each clump. Subsequently, we calculated the F-statistic for each IV to assess its strength. We excluded SNPs with $F < 10$, thereby effectively avoiding weak instrument bias. Furthermore, we harmonized the exposure and outcome data to ensure consistent allele directions. We removed any palindromic SNPs. For the final set of selected SNPs, their corresponding effect sizes and standard errors were extracted from the outcome GWAS summary data for use in subsequent MR analyses. For eQTLs, the selection criteria were set to include only cis-eQTLs using the aforementioned parameters.

2.4 Mendelian randomization (MR) analysis

2.4.1 Primary analysis

A two-sample MR framework was employed to assess the potential causal relationship between $PM_{2.5}$ exposure and depression. To enhance robustness, this study utilized multiple statistical methods. The core causal estimation method was selected based on the number of available instrumental variables (IVs). When only one independent IV was available, the Wald ratio method was applied. When two or more IVs were present, the Inverse Variance Weighted (IVW) method was primarily used for estimation. For analyses with three or more IVs, we further applied various sensitivity analysis methods to test result reliability and identify potential biases. These methods included MR-Egger regression, the Weighted Median method, the Simple Mode method, the Weighted Mode method, and the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) test. Causal effect sizes are expressed as Odds Ratios (ORs) with 95% confidence intervals (CIs). We used Cochran's Q test to assess heterogeneity among genetic

instruments. When no significant heterogeneity was detected ($p \geq 0.05$), results from the fixed-effects IVW model were reported. Otherwise, results from the random-effects IVW model were reported, which provides more conservative estimates. The statistical significance threshold was set at $p < 0.05$. All analyses were performed using the "TwoSampleMR" and "MR-PRESSO" packages in R software.

2.4.2 Mediation analysis

A two-step MR approach was used to explore the potential mediating roles of transcriptomic, metabolomic, and radiomic phenotypes in the causal relationship between $PM_{2.5}$ exposure and MDD. In the first step, we treated $PM_{2.5}$ as the exposure and used two-sample MR with the IVW method to estimate its causal effect (β_a) on each potential mediator. In the second step, these candidate mediators were treated as exposures to estimate their causal effect (β_b) on MDD. The mediation effect (indirect effect β_{ab}) was calculated using the product of coefficients method ($\beta_a \times \beta_b$), and its standard error was estimated using the Delta method.

Because this study involved a large number of potential mediators (thousands of phenotypes across multiple omics layers), using a conventional $p < 0.05$ threshold would inflate the false positive rate due to multiple hypothesis testing. Therefore, to control the false discovery rate, we applied the Benjamini-Hochberg method to adjust the p -values of all mediators in the first step. Only those mediators with an FDR-adjusted p -value (q -value) < 0.05 in the first step were retained as candidate mediators for the second step. The statistical significance of the mediation effect was also determined using $FDR < 0.05$. All analyses were performed using the "TwoSampleMR" and "Rmediation" packages in R.

2.4.3 Sensitivity analysis

To mitigate the influence of horizontal pleiotropy, outliers, and heterogeneity, and to validate the robustness of causal inferences, this study integrated multiple sensitivity analysis methods. First, we used MR-Egger regression to test for horizontal pleiotropy. This method relaxes the assumption of a zero intercept in the traditional IVW model. Its intercept quantifies the average pleiotropic effect of instruments on depression not mediated through $PM_{2.5}$ exposure. Second, we applied the MR-PRESSO method to address potential outliers. This method follows a three-stage process: Global Test, Outlier Identification and Removal, and Effect Re-estimation. It corrects bias caused by pleiotropy or genotyping errors. Cochran's Q statistic was employed in both MR-Egger and IVW methods to test for heterogeneity. Simultaneously, we conducted leave-one-out sensitivity tests. Individual SNPs were sequentially removed and analyses were repeated. This assessed whether overall results were driven by any single influential SNP, thereby verifying stability.

2.5 Gene functional annotation

Tissue-specific Gene Ontology (GO) enrichment analysis was performed on genes exhibiting significant mediating effects between $PM_{2.5}$ and MDD. This aimed to elucidate specific potential biological functions in different tissues. Significant mediator genes identified via expression quantitative trait loci

(eQTLs) were grouped into independent gene lists based on tissue origin. When a tissue had very few significant mediator genes, we first used the STRING online database to construct a protein-protein interaction network. GO enrichment analysis (covering Biological Process, Molecular Function, and Cellular Component ontologies) was then performed on protein-coding genes within this network. Enrichment significance was assessed using the hypergeometric test. GO terms with $p < 0.05$ were defined as significantly enriched in that tissue.

3. Results

3.1 Estimation of genetic correlations between PM_{2.5} exposure and MDD

Heritability estimates showed that the h^2 values for both the PM_{2.5} exposure cohort and the MDD cohort were significantly greater than zero (Table 1). Specifically, the heritability of SNPs associated with PM_{2.5} exposure was $h^2 = 0.0145$ (SE = 0.0016, $p = 1.32E-19$). In the MDD cohort, the heritability was $h^2 = 0.0349$ (SE = 0.0019, $p = 1.93E-75$). The LDSC analysis revealed a genetic correlation (r_g) of 0.3338 between PM_{2.5} exposure and MDD risk (SE = 0.0497, $p = 1.92E-11$), indicating that PM_{2.5} exposure and MDD share 33.38% of their genetic variants, reflecting a positive and significant genetic correlation.

Table 1
Analysis of heritability and genetic correlation of PM_{2.5} exposure and MDD-related SNPs.

	h^2/r_g	SE	p -value
Heritability estimation (h^2)			
PM _{2.5} exposure	0.0145	0.0016	1.32E-19
MDD	0.0349	0.0019	1.93E-75
Genetic correlation (r_g)			
	0.3338	0.0497	1.92E-11

3.2 Overall causal effect of PM_{2.5} on MDD

After stringent filtering, 100 SNPs significantly associated with PM_{2.5} exposure were included as genetic IVs. The F-statistic for all instruments exceeded 10 (range: 19.56–69.92, Table S3), indicating no weak instrument bias. Using these 100 instruments, we employed six methods, including IVW, MR-Egger, Weighted Median, and MR-PRESSO, to assess the overall causal effect of PM_{2.5} on MDD.

Initial analysis suggested the presence of outlier IVs and significant heterogeneity (Table S4). Therefore, we removed two SNPs identified as outliers (rs72642437 and rs1372504). The random-effects IVW

model was used as the primary analysis method. Results showed that genetically predicted higher PM_{2.5} exposure levels were associated with increased MDD risk (OR = 1.27, 95% CI: 1.07–1.51, $p = 5.95E-03$; Table S4, Fig. 1A). MR-PRESSO analysis after outlier correction yielded consistent results (OR = 1.27, 95% CI: 1.07–1.51, $p = 7.10E-03$, Table S4).

To validate result robustness, we performed a series of sensitivity analyses. The CI of the MR-Egger regression line (red line) covered both sides of zero, suggesting no significant directional pleiotropy among all instruments (intercept = 0.0028, $p = 3.26E-01$; Table S4, Fig. 1A). Leave-one-out sensitivity analysis indicated that after sequentially removing any single IV, combined effect estimates from remaining variables were consistent in direction. Their CIs overlapped with the total effect, demonstrating robustness. Results were not driven by any single instrument (Fig. 1B). Furthermore, the scatter plot displayed the association strength between each IV and PM_{2.5} exposure as well as depression risk. Fitted lines from different analytical methods (e.g., IVW, MR-Egger) all showed positive trends, further supporting that PM_{2.5} exposure increases depression risk (Fig. 1C). The distribution of effect estimates for each instrument in the funnel plot was largely symmetrical, suggesting low likelihood of potential pleiotropy (Fig. 1D). Together, these results support the robustness of the conclusion that a positive causal association exists between PM_{2.5} and MDD.

3.3 Blood transcriptomic mediation analysis

In this study, we employed a two-step MR approach to systematically investigate whether PM_{2.5} influences MDD by affecting blood gene expression. The first step assessed the causal association between PM_{2.5} exposure and eQTLs across tissues. In blood, we identified 369 genes whose expression levels had a significant causal association with PM_{2.5} (FDR < 0.05, Table S5). These genes significantly associated with PM_{2.5} served as candidate mediators for the second step analysis.

In the second step, we evaluated the causal association between candidate gene expression levels identified in step one and MDD. Results showed that in blood, expression of 20 genes had a significant causal relationship with MDD (FDR < 0.05, Table S6).

We further calculated the mediation effect of each gene in the association between PM_{2.5} exposure and MDD. The mediation effect test showed that this effect reached statistical significance for only 5 genes, *C6orf48*, *CERKL*, *CITED4*, *POR* and *SPATA5L1* (FDR < 0.05, Fig. 2, Table S7). The mediated effect via gene expression (β_{ab}) ranged from 0.11 (95% CI: 0.02 to 0.20) to 0.22 (95% CI: 0.05 to 0.39).

3.4 Brain transcriptomic mediation analysis

To investigate whether PM_{2.5} influences major depressive disorder (MDD) by regulating gene expression in specific brain regions, we first analyzed the causal association between PM_{2.5} exposure and gene expression levels in 13 brain tissues. Results showed that PM_{2.5} had widespread significant effects on gene expression across multiple brain regions (FDR < 0.05, Table S8). The numbers of genes significantly

affected by PM_{2.5} exposure in the 13 brain tissues were as follows: 54 in amygdala, 46 in anterior cingulate cortex BA24, 41 in caudate basal ganglia, 56 in cerebellar hemisphere, 49 in cerebellum, 46 in cortex, 50 in frontal cortex BA9, 38 in hippocampus, 40 in hypothalamus, 39 in nucleus accumbens basal ganglia, 57 in putamen basal ganglia, 51 in spinal cord cervical c-1, and 48 in substantia nigra (Table S8).

Next, we assessed the causal association between the expression levels of PM_{2.5}-affected brain tissue genes and MDD risk. Results revealed significant causal relationships between certain gene expression levels and MDD (FDR < 0.05, Table S9). In the 13 brain tissues, the numbers of genes significantly associated with MDD were: 12 in amygdala, 8 in anterior cingulate cortex BA24, 10 in caudate basal ganglia, 20 in cerebellar hemisphere, 15 in cerebellum, 13 in cortex, 8 in frontal cortex BA9, 8 in hippocampus, 4 in hypothalamus, 12 in nucleus accumbens basal ganglia, 13 in putamen basal ganglia, 6 in spinal cord cervical c-1, and 7 in substantia nigra. Genes significant in both analytical steps were identified as potential candidate mediators.

Finally, we tested the mediation effect of each candidate gene in the association between PM_{2.5} and MDD (Table S10). Results revealed that only six genes across five brain regions exhibited significant mediation effects (FDR < 0.05, Fig. 3). Specifically, in the amygdala, the gene *HCG20* showed a mediation effect of 0.16 (95% confidence interval [CI]: 0.03 to 0.29, Fig. 3A). In the anterior cingulate cortex BA24, *ATG10* had an effect of 0.16 (95% CI: 0.02 to 0.31, Fig. 3B). In the nucleus accumbens basal ganglia, *HSPA1L* had an effect of 0.21 (95% CI: 0.03 to 0.39, Fig. 3C). In the putamen basal ganglia, two genes were identified: *AS3MT* (0.23, 95% CI: 0.03 to 0.43, Fig. 3D) and *HLA-B* (0.12, 95% CI: 0.00 to 0.24, Fig. 3E). In the spinal cord cervical c-1, *BMP7* had an effect of 0.16 (95% CI: 0.03 to 0.28, Fig. 3F). These findings suggest that PM_{2.5} may primarily exert its impact on MDD risk through altered expression of these key genes in specific brain regions.

3.5 Gene ontology analysis of genes with significant mediation effects in each tissue

Gene Ontology (GO) enrichment analysis was performed on genes with significant mediation effects in blood and five brain regions. Analysis revealed that these genes were significantly enriched in three interrelated biological layers. To highlight the most core biological findings, the top three entries for each category, ranked by p-value, were selected for presentation (Fig. 4).

Mediation genes in blood were significantly enriched in immune- and metabolism-related pathways. The most significant Biological Process (BP) terms included "antigen processing and presentation of peptide antigen via major histocompatibility complex (MHC) class I", "xenobiotic metabolic process", and "immune response". In Cellular Component (CC), genes were primarily located in "MHC class I protein complex", "lumenal side of endoplasmic reticulum membrane", and "external side of plasma membrane". Their core Molecular Functions (MF) involved "MHC class I protein binding", "heme binding", and "peptide antigen binding". The enrichment of MHC class I-related terms suggests that PM_{2.5} components might be recognized as non-self antigens by the immune system, thereby triggering neuroinflammation.

Concurrently, enrichment of "xenobiotic metabolic process" directly corresponds to the biotransformation of chemicals within PM_{2.5}. These results collectively indicate that PM_{2.5} may contribute to MDD pathogenesis through antigen mimicry and interference with xenobiotic metabolic processes.

In amygdala tissue, the only gene with a significant mediation effect was the non-coding ribonucleic acid gene *HCG20*; therefore, standard GO enrichment analysis was not performed.

Mediation genes in the anterior cingulate cortex BA24 were highly specifically enriched in cellular autophagy processes. The most significant BP terms were "autophagosome assembly", "mitophagy", and functions related to autophagosome membranes. The CC terms focused on autophagy regulation processes, such as "protein lipidation" and its regulation. MF terms were enriched in "endoplasmic reticulum membrane" and "protein-membrane adaptor activity".

Mediation genes in the nucleus accumbens basal ganglia were mainly enriched in protein structure and localization-related terms, including "unfolded protein binding", "response to unfolded protein", and "protein folding". At the CC and MF levels, they were involved in "cytoplasm", "extracellular exosome", and "COP9 signalosome". This indicates that PM_{2.5} might induce endoplasmic reticulum stress in this reward center, disrupting its normal neural signaling function.

Mediation analysis in the putamen basal ganglia revealed strong adaptive immune-related signatures. The most significant BP and CC terms were highly concentrated on processes such as "MHC class I protein complex", "CD8-positive alpha-beta T cell activation", and "regulation of dendritic cell differentiation". Molecular functions also involved "antigen processing and presentation via MHC class II". This pattern suggests that PM_{2.5} may trigger a specific T-cell-mediated neuroimmune response in this brain region.

Mediation genes in the spinal cord cervical c-1 were significantly enriched in bone morphogenetic protein (BMP) signaling pathways and related regulation. The core BP terms all pointed to "BMP signaling pathway", "positive regulation of bone mineralization", and "cellular response to BMP stimulus". This provides a new clue that PM_{2.5} might affect organismal state by interfering with conserved developmental and repair signaling pathways within the central nervous system.

Taken together, these tissue-specific enrichment results collectively demonstrate that the effect of PM_{2.5} on MDD risk does not operate through a single pathway but rather constitutes a multi-layered mechanistic network.

3.6 Blood metabolite mediation analysis

Blood metabolites are key carriers of the body's metabolic state. Their alterations are closely related to MDD pathogenesis, reflecting pathological processes such as neurotransmitter synthesis, neuroinflammation, and energy metabolism, and also hold potential as biomarkers. This study first

assessed the causal relationship between PM_{2.5} exposure and 248 blood metabolites via MR analysis (Table S11). A total of 9 metabolites were identified as having significant causal associations with PM_{2.5}. Using these metabolites as exposures, their causal effects on MDD were further analyzed (Table S12). Analysis found that only two of these metabolites, “ratio of polyunsaturated fatty acids to monounsaturated fatty acids” and “ratio of polyunsaturated fatty acids to total fatty acids” had significant associations with MDD. They were included in subsequent mediation analysis.

The mediation effect test results showed that both of the above two fatty acid ratio-related metabolites significantly mediated the effect of PM_{2.5} on MDD ($\beta = 0.01$, 95% CI: 0.00 to 0.02, FDR < 0.05, Fig. 5, Table S13). These findings suggest that PM_{2.5} may mediate its potential impact on MDD risk by affecting the metabolism and relative levels of unsaturated fatty acids in blood.

3.7 CSF metabolite mediation analysis

CSF metabolites provide a direct window into changes in the central nervous system microenvironment. We first evaluated the causal relationship between PM_{2.5} exposure and 294 CSF metabolites. Results showed that two metabolites had significant causal associations with PM_{2.5} (Table S14). Next, we assessed the causal effect of the above PM_{2.5}-influenced CSF metabolites on MDD risk. Results showed that the levels of these two metabolites had no significant causal associations with MDD (Table S15).

Therefore, within the MR framework of this study, there is no evidence to support that these PM_{2.5}-influenced metabolites in the cerebrospinal fluid changes represent a significant mediating pathway leading to MDD.

3.8 Brain imaging feature mediation analysis

Brain imaging features can objectively reflect brain structure and microstructure changes associated with MDD. We first assessed the causal relationship between PM_{2.5} exposure and 390 brain imaging features. Results showed that only five features had significant causal associations with PM_{2.5}, IDP T1 FIRST left hippocampus volume, IDP T1 FIRST left amygdala volume, IDP T1 FAST ROIs L juxtapos lobule cortex, IDP T1 FAST ROIs L temp fusif cortex post and aseg global intensity CC-Posterior (Table S16).

Subsequently, we evaluated the independent causal effect of the above PM_{2.5}-influenced brain imaging features on MDD risk (Table S17). Analysis results showed no significant causal association between any brain imaging feature and MDD. Therefore, based on the design of this study, it was not necessary to further conduct a mediation analysis of brain structural or white matter microstructure.

4. Discussion

This study is the first to systematically evaluate the causal association between PM_{2.5} exposure and MDD and its potential mediating mechanisms. It integrates a two-sample and two-step MR analytical

framework with multi-tissue, multi-dimensional omics data. We first conducted LDSC analysis on PM_{2.5} and MDD, and the results confirmed that PM_{2.5}-associated SNPs have significant heritability and that PM_{2.5} exposure shares 33.38% of its genetic architecture with MDD risk, indicating a significant genetic correlation. We further performed MR analysis, and the findings provide strong genetic support for a causal link between PM_{2.5} and MDD. Recently, some studies have provided genetic-level causal evidence using MR in the Psychiatric Genomics Consortium cohort (OR = 1.33, 95% CI: 1.11 to 1.55; OR = 1.02, 95% CI: 1.01 to 1.03, respectively) [15, 17]. This study independently replicated this causal relationship in the Finnish population cohort. The effect size was comparable (OR = 1.27, 95% CI: 1.07–1.51), further enhancing the generalizability and reliability of the conclusion. This genetically reinforces the urgency of incorporating air pollution control into mental illness prevention.

We must acknowledge the methodological limitation: the issue of socio-spatial confounding in environmental exposure MR. It should be frankly noted that individual differences in PM_{2.5} exposure are largely determined by socio-spatial factors such as residential location, socioeconomic status, and urban-rural spatial structure. Consequently, genetic instruments for PM_{2.5} may partially capture the genetic propensities related to these factors rather than purely reflecting intrinsic biological susceptibility to pollutant toxicity, which poses a potential challenge to the exclusion restriction assumption of MR. However, three points merit attention. First, current PM_{2.5} GWAS data (e.g., exposure estimates from UK Biobank) have been adjusted for socioeconomic indicators including the Townsend deprivation index, which mitigates the influence of social confounding to some extent[3]. Second, and more importantly, the mediation pathways identified in this study (e.g., “xenobiotic metabolism” in blood, “autophagy” and “MHC class I antigen presentation” in brain regions) exhibit a high degree of biological specificity that is closely consistent with the known toxicological effects of PM_{2.5}. If the instruments affected MDD solely through socio-spatial allocation, it would be impossible to observe such a systematic enrichment of molecular mediators linked to particulate matter toxicity. Third, sensitivity analyses showed that the MR-Egger intercept was non-significant, arguing against the instruments influencing MDD through major confounding pathways independent of PM_{2.5} exposure (e.g., direct socioeconomic deprivation). In summary, while residual socio-spatial confounding cannot be completely excluded, the multi-omics mediation evidence together with the sensitivity analyses supports the biological plausibility of our causal inference. Future research should further independently validate the conclusions of this study using quasi-experimental designs (e.g., natural experiments from air pollution policy changes) or negative control methods in exposure MR.

Prevailing theories suggest PM_{2.5} affects the brain by inducing systemic inflammation, oxidative stress, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation [21, 22]. However, Zhang et al. (2025)¹⁵ attempted to use 199 blood proteins (covering pathways like neuroinflammation and oxidative stress) as mediators but failed to confirm their significant role. In contrast, our results from blood transcriptomics data clearly point to two synergistic pathways: immune antigen presentation and xenobiotic metabolism, rather than generalized inflammatory markers.

Previous studies often speculated that PM_{2.5}'s effects require breaching the blood-brain barrier or causing central neuroinflammation, but lacked direct central evidence. Zhang et al. (2025)[17] was also limited to blood biomarkers. Our study is the first to extend mediation analysis directly to multiple brain tissues, revealing noteworthy region-specific mechanisms. First, mediating genes in the anterior cingulate cortex Brodmann area 24 (BA24) were enriched in autophagy-related pathways. Autophagy is a crucial biological process for maintaining cellular homeostasis by degrading cytoplasmic proteins and damaged organelles. Autophagy impairment has been observed in lipopolysaccharide-induced depressive mouse models [23]. Our findings suggest PM_{2.5} may impair the cellular "cleaning" function in this region, leading to neuronal homeostasis imbalance and subsequent depression. Second, mediating genes in the nucleus accumbens basal ganglia were enriched in protein structure and localization-related terms. The nucleus accumbens is a core target of the mesolimbic dopamine pathway. Its function highly depends on normal dopamine signaling and receptor transduction [24, 25]. The endoplasmic reticulum is crucial for the correct folding and processing of secretory proteins. The enriched functional terms in the accumbens indicate that PM_{2.5} may induce endoplasmic reticulum stress in this reward hub. This potentially interferes with the synthesis, folding, and membrane localization of key signaling proteins like dopamine receptors, impairing dopaminergic signaling and thereby contributing to core depressive symptoms like anhedonia. Third, mediating genes in the putamen basal ganglia were highly enriched in T cell activation and major histocompatibility complex (MHC) class I/II molecular pathways. Typically, this brain region in neurological diseases is thought to exhibit a microglia-mediated innate immune inflammation model [26, 27]. However, our discovery suggests PM_{2.5} may directly activate a peripheral-like adaptive immune response mediated by MHC I/II molecules and T cells within the putamen.

Particularly noteworthy is the significant enrichment of the biological process "antigen processing and presentation of peptide antigen via MHC class I" in both blood and the putamen basal ganglia. MHC class I molecules are key regulators of normal synaptic plasticity, memory, and reward behavior. Their dysfunction may lead to abnormal synaptic pruning, impaired long-term depression (LTD), and imbalance in reward circuits. These are all potential cellular and circuit-level pathological bases of depression[28–31]. The enrichment of "antigen processing and presentation of peptide antigen via MHC class I" suggests PM_{2.5} may promote depression through a dual mechanism. On one hand, it induces MHC class I molecules to participate in abnormal, immunogenic antigen presentation, triggering neuroinflammation. On the other hand, this competitively interferes with the physiological synaptic pruning and plasticity regulatory functions of MHC class I molecules. Ultimately, this may lead to dysfunctional neural networks in localized brain regions, manifesting as depressive symptoms.

Mediation analysis of blood metabolites identified three significant mediators related to unsaturated fatty acid ratios. Systemic oxidative stress and low-grade inflammation induced by PM_{2.5} exposure can disrupt the metabolic balance of polyunsaturated fatty acids (e.g., ω -3 and ω -6 series). These are precursors for inflammatory mediators like prostaglandins and leukotrienes. An imbalance in their ratios is itself a marker of a pro-inflammatory state. Meanwhile, unsaturated fatty acids (especially

polyunsaturated fatty acids) are vital for neuronal membrane structure and function [32]. Their metabolic dysregulation is closely linked to white matter abnormalities in depressed patients, constituting a known pathological association [33, 34]. Our results indicate that unsaturated fatty acids may be involved in the process by which PM_{2.5} induces depression. However, compared to the effect sizes of mediating genes, the mediating role of these three fatty acid metabolites is considerably smaller. Therefore, considering the aforementioned relationship between oxidative stress, inflammation, and unsaturated fatty acid metabolism, this fatty acid metabolic disturbance is more likely a downstream concomitant phenomenon. It reflects the systemic immunometabolic disruption triggered by PM_{2.5}, rather than a dominant pathogenic pathway.

Brain imaging features did not show significant mediating effects in this study. This may reflect that these metrics represent more downstream or concomitant phenotypes. It highlights that gene expression changes are likely more upstream and direct mediating events. Our findings resonate with those of Li et al. (2021) [35], who suggested that individuals with high genetic risk might be more sensitive to pollution. Our study directly points to the potential molecular mechanisms underlying this sensitivity.

It is noteworthy that some genes and metabolites showing significant associations in the stepwise analyses did not reach statistical significance in the mediation effect test. This likely stems from the mediation test itself being more stringent. The mediation test examines whether the "product" $\beta_a \times \beta_b$ is significantly different from zero. Its standard error (usually calculated via the Delta method) is considerably larger than the standard errors from the first two steps individually. This means that even if β_a and β_b are each significant, their product may become non-significant due to the expanded error margin. The mediation test is inherently a more conservative joint test. The overall "signal strength" of the mediation effect depends on the product of β_a and β_b . If the absolute value of one effect is small or if the directions of the two effects are inconsistent (one positive, one negative, which itself may suggest a suppressor effect), the absolute value of the product will be smaller. This makes it harder to achieve statistical significance. Even if both are individually significant, the "strength of evidence" for their product may be insufficient. Therefore, the ultimately identified significant mediating genes represent potential mechanisms with relatively stronger and more stable evidence in the pathway through which PM_{2.5} exposure influences MDD.

5. Conclusion

This study first identified a significant genetic overlap between PM_{2.5} exposure and MDD ($r_g = 0.3338$, $p = 1.92E-11$). Subsequently, it confirmed that long-term PM_{2.5} exposure is a causal risk factor for MDD (odds ratio [OR] = 1.27, 95% confidence interval [CI]: 1.07–1.51). Integrative multi-omics analyses further revealed tissue-specific mediating mechanisms underlying this association. In blood, the pathogenic effect is likely mediated via antigen presentation and xenobiotic metabolism pathways. Within distinct brain regions, PM_{2.5} disrupts key cellular functions, including autophagy processes in the anterior

cingulate cortex, proteostasis in the nucleus accumbens, and local immune activation in the putamen. These findings collectively suggest that PM_{2.5} may contribute to depression through a combination of systemic immunometabolic disruption and central nervous system-specific cellular dysfunction.

This study, of course, has limitations. First, the analysis is primarily based on transcriptomics and phenotypic databases of European ancestry. The generalizability of the conclusions to other populations requires verification. Second, MR reflects the lifelong exposure effect determined by genetic predisposition. It cannot capture exposure windows in early life or specific critical periods. Finally, the mediating mechanisms revealed are based primarily on statistical genetic inference. The specific details of their molecular regulation require validation through functional experiments in cellular or animal models. Therefore, future research should focus on the following aspects. First, conducting trans-ancestry MR validations in different populations. Second, utilizing spatial transcriptomics or single-cell sequencing technologies to elucidate the mechanisms of the identified genes at a cell-type-specific level. Third, establishing prospective environmental monitoring cohorts combined with dynamic multi-timepoint, multi-omics data collection to uncover the complete process from early perturbation by PM_{2.5} exposure to the onset of disease. Fourth, combine quasi-experimental designs (e.g., natural experiments from air pollution policy changes) or negative control methods in exposure Mendelian randomization to further validate the robustness of our causal inference, thereby more effectively addressing the concern that genetic instruments may be confounded by socio-spatial factors.

Declarations

Author Contribution Statement

Conceptualization, H.W., S.Z., and Y.Y.; methodology, H.W., and Y.Y.; software, Z.Z., J.X., H.L., and R.W.; validation, Z.Z., Z.Z., Y.Y., and L.Z.; formal analysis, H.W., Z.Z., L.Z., and Z.Z.; visualization, S.W.; data curation, Z.Z., J.X., H.L., and R.W.; writing—original draft preparation, H.W. and Z.Z.; writing—review and editing, D.G., and S.Z. All authors have read and approved the published version of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data Availability Statement

The data required for the article has been provided in the supplementary materials.

References

1. Braithwaite I, Zhang S, Kirkbride JB, Osborn DPJ, Hayes JF (2019) Air Pollution (Particulate Matter) Exposure and Associations with Depression, Anxiety, Bipolar, Psychosis and Suicide Risk: A Systematic Review and Meta-Analysis. *Environ Health Perspect* 127(12):126002. <http://doi.org/10.1289/ehp4595>
2. Zhang Z, Zhao D, Hong YS, Chang Y, Ryu S, Kang D, Monteiro J, Shin HC, Guallar E, Cho J (2019) Long-Term Particulate Matter Exposure and Onset of Depression in Middle-Aged Men and Women. *Environ Health Perspect* 127(7):77001. <http://doi.org/10.1289/ehp4094>
3. Acharya SR, Bhatta J, Timilsina D, Ray N, Pahari S (2025) Long-term exposure to air pollutants, meteorological factors, and mental health status: a nationwide population-based study with multilevel regression analysis. *Arch Public Health* 83(1):81. <http://doi.org/10.1186/s13690-025-01570-y>
4. Yang T, Wang J, Huang J, Kelly FJ, Li G (2023) Long-term Exposure to Multiple Ambient Air Pollutants and Association With Incident Depression and Anxiety. *JAMA Psychiatry* 80(4):305–313. <http://doi.org/10.1001/jamapsychiatry.2022.4812>
5. Nguyen HD (2025) Effects of a mixture of ambient air pollution and its metabolites on depression: From epidemiology to molecular mechanisms. *J Environ Sci (China)* 158:405–419. <http://doi.org/10.1016/j.jes.2025.02.015>
6. Si H, Gao T, Yang J, Zhu J, Han Y, Li C, Wang J, Li J, Zhao Y, Chen L, Zheng Y, Jiang M (2023) Multi-omics reveals hypertrophy of adipose tissue and lipid metabolism disorder via mitochondria in young mice under real-ambient exposure to air pollution. *Front Pharmacol* 14:1122615. <http://doi.org/10.3389/fphar.2023.1122615>
7. Kim HJ, Kim JH, Lee S, Do PA, Lee JY, Cha SK, Lee J (2024) PM_{2.5} Exposure Triggers Hypothalamic Oxidative and ER Stress Leading to Depressive-like Behaviors in Rats. *Int J Mol Sci* 25(24). <http://doi.org/10.3390/ijms252413527>

8. Liu C, Xu X, Bai Y, Wang TY, Rao X, Wang A, Sun L, Ying Z, Gushchina L, Maisseyeu A, Morishita M, Sun Q, Harkema JR, Rajagopalan S (2014) Air pollution-mediated susceptibility to inflammation and insulin resistance: influence of CCR2 pathways in mice. *Environ Health Perspect* 122(1):17–26. <http://doi.org/10.1289/ehp.1306841>
9. Lu Y, Qiu W, Liao R, Cao W, Huang F, Wang X, Li M, Li Y (2025) Subacute PM_{2.5} Exposure Induces Hepatic Insulin Resistance Through Inflammation and Oxidative Stress. *Int J Mol Sci* 26(2). <http://doi.org/10.3390/ijms26020812>
10. Yuan T, Cheng M, Ma Y, Zou H, Kan H, Meng X, Guo Y, Peng Z, Xu Y, Lu L, Ling S, Dong Z, Wang Y, Yang Q, Xu W, Shi Y, Liu C, Lin S (2024) PM_{2.5} Exposure as a Risk Factor for Optic Nerve Health in Type 2 Diabetes Mellitus. *Toxics* 12(11). <http://doi.org/10.3390/toxics12110767>
11. Xu MX, Zhu YF, Chang HF, Liang Y (2016) Nanoceria restrains PM_{2.5}-induced metabolic disorder and hypothalamus inflammation by inhibition of astrocytes activation related NF- κ B pathway in Nrf2 deficient mice. *Free Radic Biol Med* 99:259–272. <http://doi.org/10.1016/j.freeradbiomed.2016.08.021>
12. Burnor E, Cserbik D, Cotter DL, Palmer CE, Ahmadi H, Eckel SP, Berhane K, McConnell R, Chen JC, Schwartz J, Jackson R, Herting MM (2021) Association of Outdoor Ambient Fine Particulate Matter With Intracellular White Matter Microstructural Properties Among Children. *JAMA Netw Open* 4(12):e2138300. <http://doi.org/10.1001/jamanetworkopen.2021.38300>
13. Younan D, Petkus AJ, Widaman KF, Wang X, Casanova R, Espeland MA, Gatz M, Henderson VW, Manson JE, Rapp SR, Sachs BC, Serre ML, Gaussoin SA, Barnard R, Saldana S, Vizuite W, Beavers DP, Salinas JA, Chui HC, Resnick SM, Shumaker SA, Chen JC (2020) Particulate matter episodic memory decline mediated early neuroanatomic biomarkers Alzheimer's disease *Brain* 143(1):289–302. <http://doi.org/10.1093/brain/awz348>
14. Liu Y, Xu F, Lv Z, Li K, Dong X (2025) Causal relationship between PM_{2.5} exposure and population-level antidepressant medication use: A Mendelian randomization study using GWAS data from multi-biobank. *Environ Res* 283:122192. <http://doi.org/10.1016/j.envres.2025.122192>
15. Bai Y, Liang X, Xia L, Yu S, Wu F, Li M (2024) Association between air pollutants and four major mental disorders: Evidence from a Mendelian randomization study. *Ecotoxicol Environ Saf* 283:116887. <http://doi.org/10.1016/j.ecoenv.2024.116887>
16. Jing Z, Ding X, Zhang X, Qi X, Wang Y (2026) Using genetic instruments to predict the causal relationship between air pollution and mental disorders: A multi-model Mendelian randomization analysis. *J Affect Disord* 120429 394(Pt A). <http://doi.org/10.1016/j.jad.2025.120429>
17. Zhang Y, Wang W, Zhang X, Jing R, Wen X, Xiao P, Liu X, Zhao Z, Chang T, Li Y, Liu W, Sun C, Yang X, Yang L, Lu M (2025) Neurotrophin-3 as a mediator in the link between PM_{2.5} exposure and psychiatric disorders: A Mendelian randomization study. *Ecotoxicol Environ Saf* 289:117658. <http://doi.org/10.1016/j.ecoenv.2024.117658>
18. Richardson TG, Leyden GM, Wang Q, Bell JA, Elsworth B, Davey Smith G, Holmes MV (2022) Characterising metabolomic signatures of lipid-modifying therapies through drug target mendelian

- randomisation. PLoS Biol 20(2):e3001547. <http://doi.org/10.1371/journal.pbio.3001547>
19. Panyard DJ, Kim KM, Darst BF, Deming YK, Zhong X, Wu Y, Kang H, Carlsson CM, Johnson SC, Asthana S, Engelman CD, Lu Q (2021) *Cerebrospinal fluid metabolomics identifies 19 brain-related phenotype associations*. Commun Biol, 4(1): p. 63. <http://doi.org/10.1038/s42003-020-01583-z>
 20. Smith SM, Douaud G, Chen W, Hanayik T, Alfaro-Almagro F, Sharp K, Elliott LT (2021) An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank. Nat Neurosci 24(5):737–745. <http://doi.org/10.1038/s41593-021-00826-4>
 21. Hahad O, Lelieveld J, Birklein F, Lieb K, Daiber A, Münzel T (2020) Ambient Air Pollution Increases the Risk of Cerebrovascular and Neuropsychiatric Disorders through Induction of Inflammation and Oxidative Stress. Int J Mol Sci 21(12). <http://doi.org/10.3390/ijms21124306>
 22. Hajipour S, Farbood Y, Gharib-Naseri MK, Goudarzi G, Rashno M, Maleki H, Bakhtiari N, Nesari A, Khoshnam SE, Dianat M, Sarkaki B, Sarkaki A (2020) Exposure to ambient dusty particulate matter impairs spatial memory and hippocampal LTP by increasing brain inflammation and oxidative stress in rats. Life Sci 242:117210. <http://doi.org/10.1016/j.lfs.2019.117210>
 23. Ali T, Rahman SU, Hao Q, Li W, Liu Z, Ali Shah F, Murtaza I, Zhang Z, Yang X, Liu G, Li S (2020) Melatonin prevents neuroinflammation and relieves depression by attenuating autophagy impairment through FOXO3a regulation. J Pineal Res 69(2):e12667. <http://doi.org/10.1111/jpi.12667>
 24. Corkrum M, Covelo A, Lines J, Bellocchio L, Pisansky M, Loke K, Quintana R, Rothwell PE, Lujan R, Marsicano G, Martin ED, Thomas MJ, Kofuji P, Araque A (2020) Dopamine-Evoked Synaptic Regulation in the Nucleus Accumbens Requires Astrocyte Activity. Neuron 105(6):1036–1047e1035. <http://doi.org/10.1016/j.neuron.2019.12.026>
 25. Kutlu MG, Zachry JE, Melugin PR, Tat J, Cajigas S, Isiktas AU, Patel DD, Siciliano CA, Schoenbaum G, Sharpe MJ, Calipari ES (2022) Dopamine signaling in the nucleus accumbens core mediates latent inhibition. Nat Neurosci 25(8):1071–1081. <http://doi.org/10.1038/s41593-022-01126-1>
 26. Wang Y, Fasching L, Wu F, Suvakov M, Huttner A, Berretta S, Roberts R, Leckman JF, Fernandez TV, Abyzov A, Vaccarino FM (2025) Interneuron Loss and Microglia Activation by Transcriptome Analyses in the Basal Ganglia of Tourette Disorder. Biol Psychiatry 98(3):260–270. <http://doi.org/10.1016/j.biopsych.2024.12.022>
 27. Rocha NP, Charron O, Latham LB, Colpo GD, Zanotti-Fregonara P, Yu M, Freeman L, Furr E, Stimming, Teixeira AL (2021) Microglia Activation in Basal Ganglia Is a Late Event in Huntington Disease Pathophysiology. Neurol Neuroimmunol Neuroinflamm 8(3). <http://doi.org/10.1212/nxi.0000000000000984>
 28. Huh GS, Boulanger LM, Du H, Riquelme PA, Brotz TM, Shatz CJ (2000) Functional requirement for class I MHC in CNS development and plasticity. Science 290(5499):2155–2159. <http://doi.org/10.1126/science.290.5499.2155>
 29. Nelson PA, Sage JR, Wood SC, Davenport CM, Anagnostaras SG, Boulanger LM (2013) MHC class I immune proteins are critical for hippocampus-dependent memory and gate NMDAR-dependent

- hippocampal long-term depression. *Learn Mem* 20(9):505–517.
<http://doi.org/10.1101/lm.031351.113>
30. Elmer BM, McAllister AK (2012) Major histocompatibility complex class I proteins in brain development and plasticity. *Trends Neurosci* 35(11):660–670.
<http://doi.org/10.1016/j.tins.2012.08.001>
31. Edamura M, Murakami G, Meng H, Itakura M, Shigemoto R, Fukuda A, Nakahara D (2014) Functional deficiency of MHC class I enhances LTP and abolishes LTD in the nucleus accumbens of mice. *PLoS ONE* 9(9):e107099. <http://doi.org/10.1371/journal.pone.0107099>
32. Vazquez GH, Camino S, Tondo L, Baldessarini RJ (2017) Potential Novel Treatments for Bipolar Depression: Ketamine, Fatty Acids, Anti-inflammatory Agents, and Probiotics. *CNS Neurol Disord Drug Targets* 16(8):858–869. <http://doi.org/10.2174/1871527316666170728165648>
33. Liu J, Liu Z, Wei Y, Zhang Y, Womer FY, Jia D, Wei S, Wu F, Kong L, Jiang X, Zhang L, Tang Y, Zhang X, Wang F (2022) Combinatorial panel with endophenotypes from multilevel information of diffusion tensor imaging and lipid profile as predictors for depression. *Aust N Z J Psychiatry* 56(9):1187–1198. <http://doi.org/10.1177/00048674211031477>
34. Cao B, Lu C, Yan L, McIntyre RS, Teopiz KM, Zhan L (2025) The dysbiosis of gut microbiota in major depressive disorder and comorbidity with overweight/obesity: unraveling biomarkers and metabolic pathways from a microbial perspective. *BMC Psychiatry* 25(1):1069. <http://doi.org/10.1186/s12888-025-07388-w>
35. Li Z, Yan H, Zhang X, Shah S, Yang G, Chen Q, Han S, Zhang D, Weinberger DR, Yue W, Tan HY (2021) Air pollution interacts with genetic risk to influence cortical networks implicated in depression. *Proc Natl Acad Sci U S A* 118(46). <http://doi.org/10.1073/pnas.2109310118>

Figures

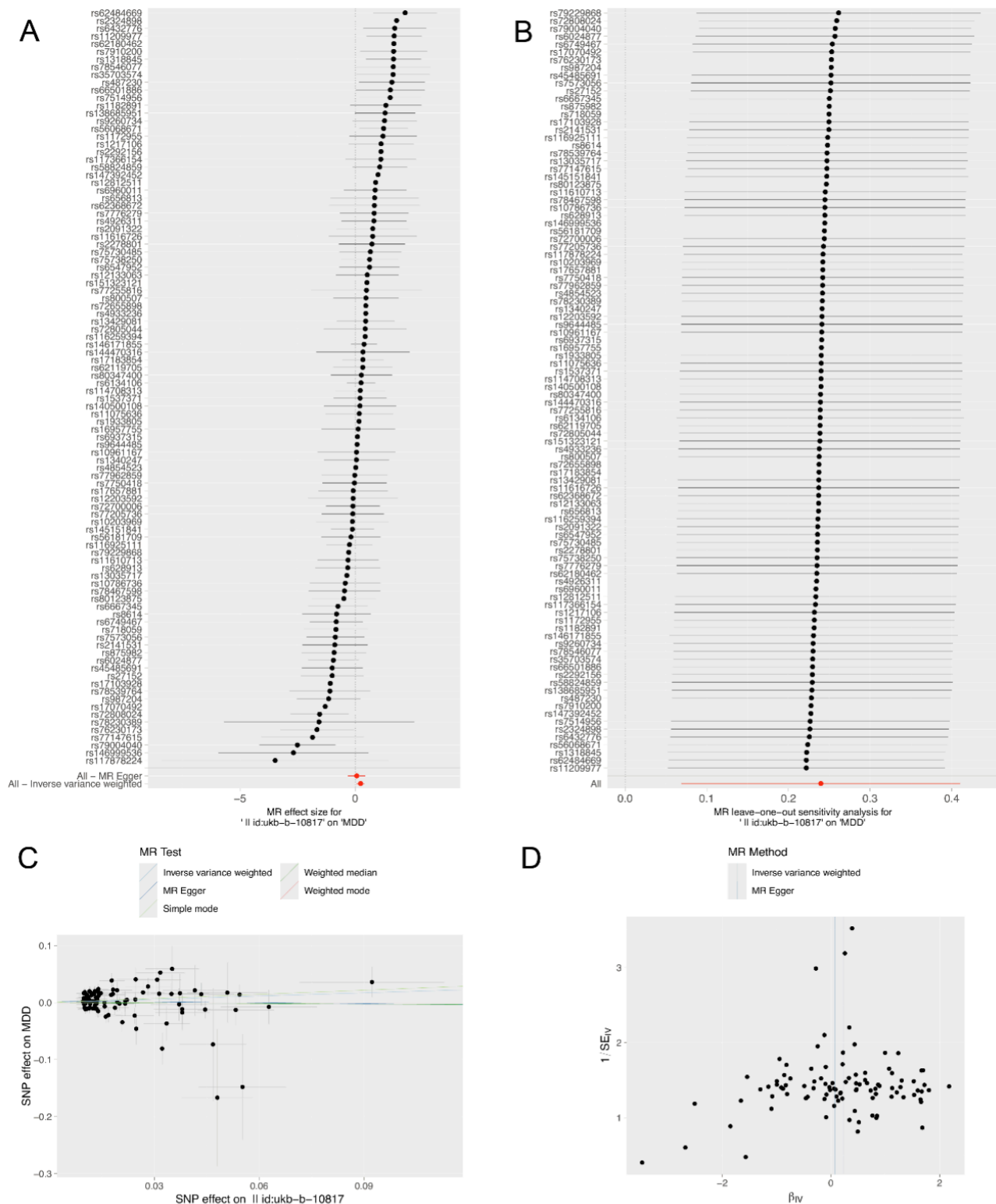


Figure 1

Sensitivity analyses for the causal relationship between $PM_{2.5}$ and depression. A. Forest plot. The CI of the MR-Egger regression line (red line) covered both sides of zero, suggesting no significant directional pleiotropy among all instruments. B. Leave-one-out sensitivity analysis plot. After sequentially removing any single instrumental variable, combined effect estimates from remaining variables were consistent in direction. C. Scatter plot. Fitted lines from different analytical methods all showed positive trends. D.

Funnel plot. The distribution of effect estimates for each instrument in the funnel plot was largely symmetrical, suggesting low likelihood of potential pleiotropy.

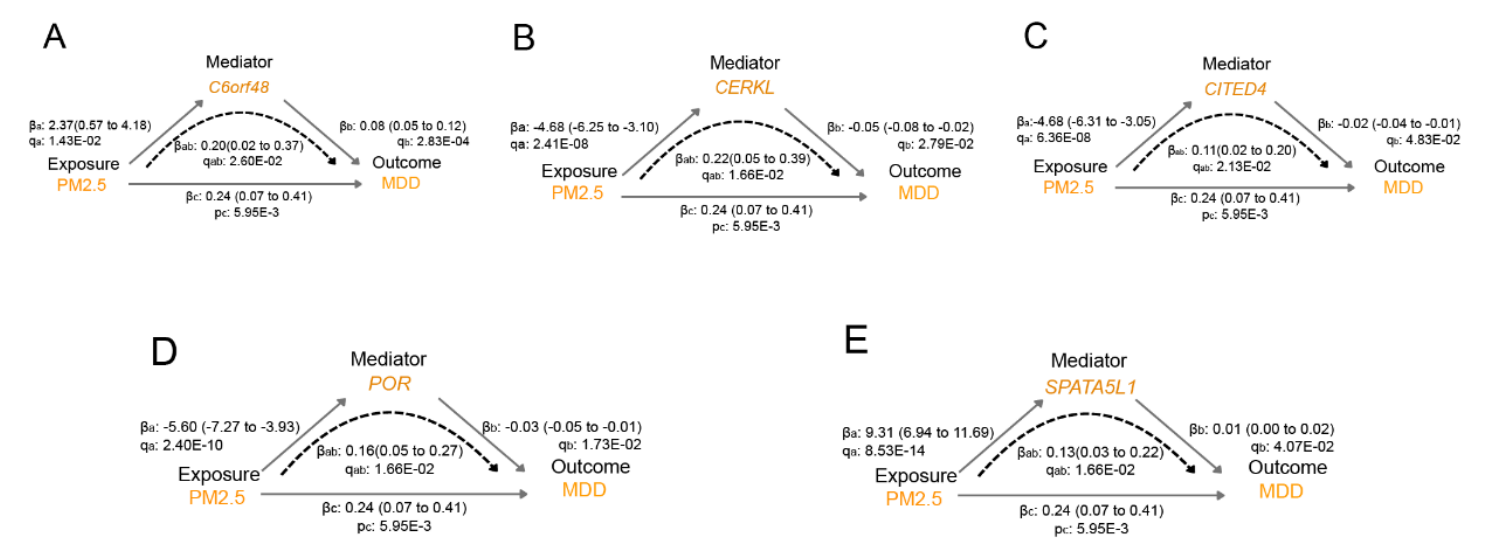


Figure 2

Mediating role of nine genes expressed in blood in the effect of PM_{2.5} on MDD.

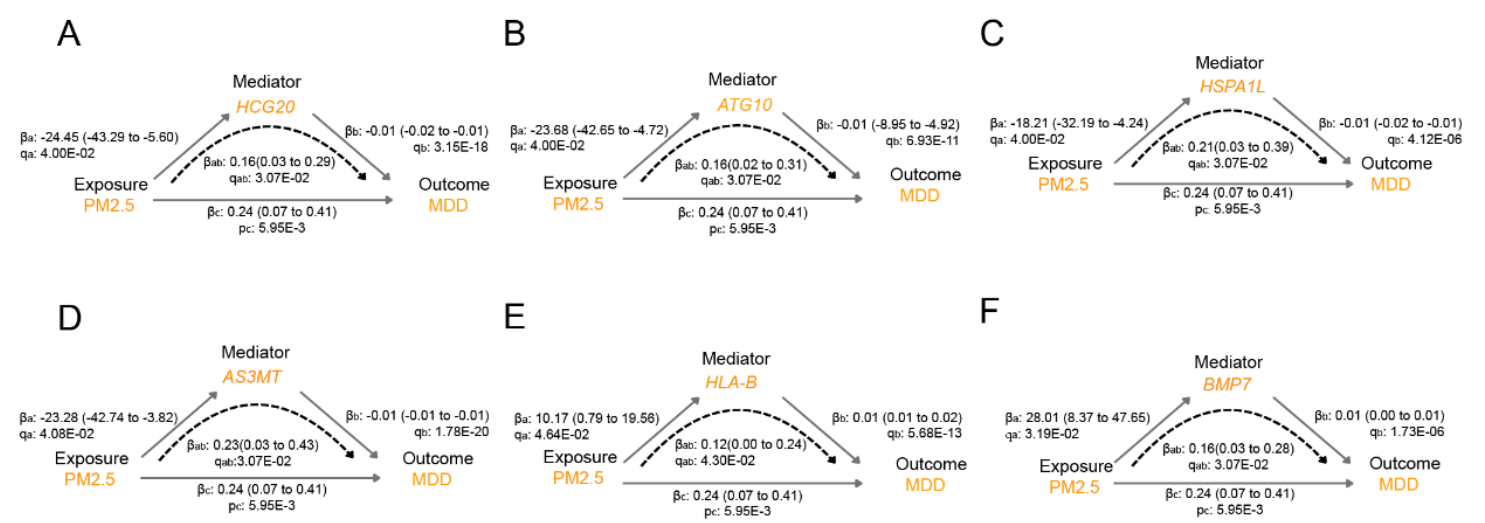


Figure 3

Mediating role of six genes expressed in specific brain tissues in the effect of PM_{2.5} on MDD. A. The gene *ATG10* in anterior cingulate. B. The gene *HSPA1L* in nucleus accumbens basal ganglia. C and D. Two genes *AS3MT* and *HLA-B* in putamen basal ganglia. E. The gene *BMP7* in spinal cord cervical c-1.

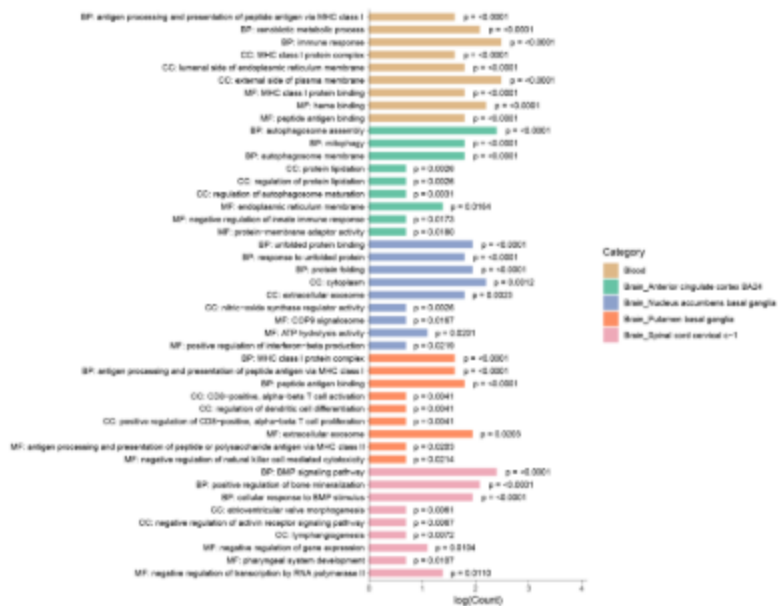


Figure 4

Gene Ontology (GO) analysis of genes with significant mediation effects in each tissue.

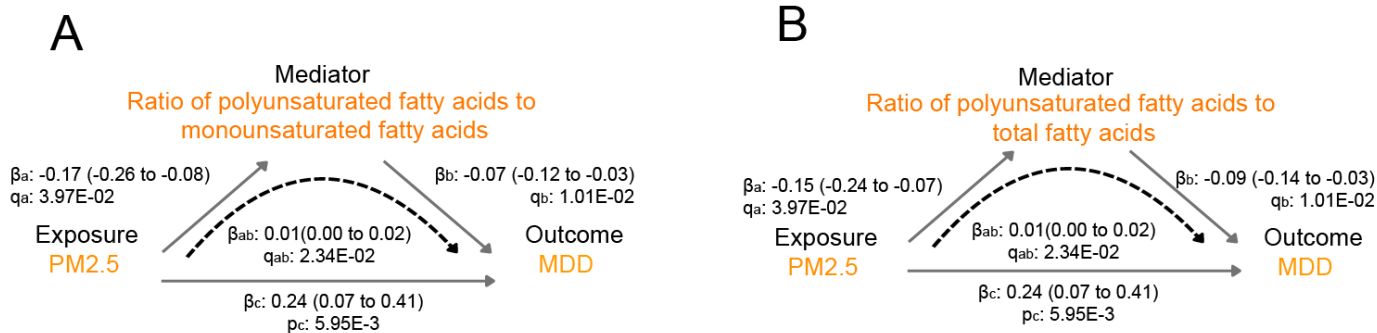


Figure 5

Mediating role of three blood metabolites in the effect of PM_{2.5} on MDD.

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