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*Original Article*

# PM2.5 is linked to Alzheimer's syndrome and delirium: a mendelian randomization analysis

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**Abstract:** Background: Increasing air pollution has drawn our attention to particulate matter (PM2.5), which has been shown to correlate significantly with respiratory and cardiovascular systems. However, whether PM2.5 is causally associated with Alzheimer's syndrome or delirium is unclear. Methods: We retrieved the genetic summary data of PM2.5 from genome-wide association studies (GWAS). The genetic information for Alzheimer's disease was obtained from the IEU OpenGWAS project, and that for delirium was obtained from FinnGen. We used two-sample Mendelian randomization analysis (MR) to associate PM2.5 with Alzheimer's disease or delirium. Results: The odds ratio (OR) for Alzheimer's disease was 0.996 with a *p-value* of 0.443 using the inverse variance weighted algorithm, and the OR associated with the outcome variable of delirium was 0.393 with a *p-value* of 0.343. Conclusion: With the exclusion of confounding factors, our findings do not support a genetic association between PM2.5 and Alzheimer's disease or delirium. Further population-based and experimental studies are needed to dissect the complex correlation between PM2.5 and Alzheimer's disease or delirium.

**Keywords:** PM2.5, Alzheimer's syndrome, delirium, two-sample Mendelian randomization analysis, GWAS, SNP

## Introduction

Air pollution is a major global health concern, with the World Health Organization (WHO) reporting approximately 4.2 million deaths annually due to its effects [1]. Fine particulate matter (PM2.5), an essential component of air pollution, consists of particles with an aerodynamic equivalent diameter of ≤ 2.5 μm [2]. These particles have a larger surface area relative to their size, allowing them to adsorb toxic substances and remain suspended in the atmosphere for extended periods [3]. Consequently, PM2.5 can be transported over long distances, exerting a significant impact on human health. Numerous studies have established a clear association between long-term PM2.5 exposure and public health risks, particularly in the respiratory and cardiovascular systems [4]. However, there is limited research on the effects of PM2.5 on organic and functional brain lesions.

Alzheimer's disease, a typical example of an organic brain lesion, is characterized by the progressive worsening of symptoms that significantly affect the daily lives of elderly patients, making it a substantial cause of disability and mortality in this population [5]. Currently, 44 million people worldwide suffer from dementia, and this number is projected to triple by 2050 due to the increasing aging population [6]. Despite advancement in understanding the pathogenesis and treatment of Alzheimer's disease since its first reported case in 1907, there remains a lack of accurate knowledge regarding the factors that may influence its development [7]. Delirium, one of the most common functional brain disorders, refers to a group of syndromes also known as acute brain syndromes [8]. It is characterized by disturbances in consciousness, sensory perception, and memory [9]. The onset of delirium is typically acute, with marked fluctuations in symptoms [10]. A combination of predisposing and precipi-

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tating factors can trigger the development of delirium. The increasing levels of air pollution have raised concerns about a potential association between PM2.5 exposure and the occurrence of Alzheimer's disease or delirium. However, evidence supporting these correlations is currently lacking.

Mendelian Randomization (MR) is a data analysis technique employed in epidemiologic studies to evaluate causal inference [11]. By using genetic variants strongly associated with exposure factors as instrumental variables, MR analyses are considered less susceptible to the influence of potential confounding factors, as these genetic variants are fixed at birth [12]. In observational studies, distinguishing between a causal and reverse causal relationship between exposure and outcome can be challenging [13]. However, the instrumental variables selected in MR are randomly allocated, analogous to randomized controlled experiments, thereby mitigating the impact of disease status on an individual's sensitivity to exposure factors [13]. While MR cannot completely replace randomized controlled trials, it offers a robust method to assess a potential causal relationship between PM2.5 and Alzheimer's disease and delirium without the need for population interventions. This approach holds significant implications for the formulation of public health policies [14].

In this study, we utilized genome-wide association study (GWAS) summary statistics for PM2.5, Alzheimer's disease, and delirium to investigate the common genetic background between these traits. We quantified genome-wide genetic correlations and performed MR analyses to unravel possible causal relationships between PM2.5 and Alzheimer's disease and delirium.

## Methods

### *Study design*

We conducted a two-sample Mendelian randomization (MR) analysis to determine causal associations between particulate matter (PM2.5) and Alzheimer's disease or delirium using publicly available pooled datasets from three genome-wide association studies (GWAS). Previous observational studies have shown a correlation between long-term exposure to environmental pollution and Alzheimer's disease, but no studies have linked it to delirium. Therefore, we further conducted MR analyses, which were used to estimate the direct causal effect of PM2.5 on the risk of developing Alzheimer's disease or delirium.

### *Data sources*

For the PM2.5 exposure dataset, pooled genetic data for PM2.5 were obtained from the United Kingdom Biospecimen Bank (UKB) GWAS, which included 423,796 European participants. The study was based on the ESCAPE project (European Cohort Study on the Effects of Air Pollution), which used the LUR model to estimate PM2.5 pollution concentrations at the study participants' home addresses. The mean (± standard deviation) PM2.5 value was 9.99 (±1.06) $\mu g/m^3$ in the GWAS. The dataset is publicly available from the UKB database (https://www.ukbiobank.ac.uk/) with GWAS-ID ukb-b-10817.

Data on genetic variants associated with Alzheimer's disease were obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/datasets/ieu-b-5067/). The GWAS-ID is ieu-b-5067. The dataset consisted of 488,285 cases, of which 487,331 were healthy controls and 954 patients with Alzheimer's disease. The cases in the dataset consisted exclusively of Europeans. The instances in the dataset consisted exclusively of Europeans.

Data on genetic variants associated with delirium were obtained from the FinnGen consortium (https://risteys.finregistry.fi/endpoints/O15_PRE_OR_ECLAMPSIA). The GWAS-ID is finngen_R9_F5_DELIRIUM. The dataset consists of 377,277 cases, of which 375,219 were healthy controls, and patients with delirium included 2,058 cases. The instances in the dataset consisted exclusively of Europeans.

### *Genetic variation*

The MR analysis screened single nucleotide polymorphisms (SNPs) as IVs from the exposure dataset. The IVs had to fulfill three major assumptions: 1) strong correlation with PM2.5, 2) independence from confounders, and 3) only two outcome variables could be affected by PM2.5. Based on the three assumptions, we used $P$ value < 5e-08 as the genome-wide threshold and obtained 20 SNPs. Considering the effect of chain instability, we eliminated 15

out of 20 SNPs. After filtering by removing the weak variable tool, we finally obtained 5 PM2.5-related SNPs. There were 12,321,875 SNPs for the ending variable I Alzheimer's disease and 18,709,281 SNPs for the ending variable II delirium.

*Mendelian randomization analysis*

For the analysis of PM2.5 with two outcome variables. In the first step, we normalized the SNPs of the exposure and outcome factors using a coordinated effects tool, with no sieve reduction in the SNPs of either outcome variable. In the second step, the function defaulted to five algorithms for MR analysis (MR Egger, Weighted median, Inverse variance weighted, Simple mode, Weighted mode) OR greater than one represents that the exposure factor is an unfavorable factor for the outcome; OR less than one means that the exposure factor is a favorable factor for the outcome. In the third step, heterogeneity was assessed by the MR-Egger test after correction for outliers. The inverse variance weighted method was used to determine whether the results were positive. In the fourth step, the MR egger_intercept algorithm was used to detect the data's diversity and assess the robustness of the results.

All analyses were performed using the TwoSampleMR package (https://github.com/MRCIEU/TwoSampleMR) and R Foundation version 4.2.0. Statistical significance was set at $P < 0.05$.

## Results

*Instrumental variables*

We obtained 20 single nucleotide polymorphisms (SNPs) associated with particulate matter (PM2.5) from the UK Biobank (UKB) database by applying a filter condition of *P-value* < 5e-08. Genetic variants with similar genomic locations are more likely to be co-inherited, resulting in a higher probability of alleles belonging to two or more loci appearing together on a chromosome simultaneously than the frequency by random occurrence. This phenomenon is known as linkage disequilibrium (LD). To ensure the independence of the selected SNPs from confounding factors, we eliminated 15 SNPs with an $r^2$ value of 1 using the chain instability tool. The $r^2$ value is a measure of LD, with a value of 1 indicating complete LD between two SNPs. By removing SNPs with high LD, we minimized any potential influence of confounding factors on the association between the selected SNPs and PM2.5 exposure.

Furthermore, to satisfy the assumption that the exposure factor (PM2.5) only interacts with the outcome variable (Alzheimer's disease or delirium), we validated the remaining 5 SNPs using the weak variable tool. This tool assesses the strength of the association between the SNPs and the exposure factor. We calculated the F-test value for each SNP and retained only those with an F-test value greater than 10, indicating a strong association between the SNP and PM2.5 exposure.

After applying these filtering steps, we obtained a final set of 5 SNPs that were strongly correlated with PM2.5 exposure and independent of confounding factors. These SNPs were used as instrumental variables in the subsequent Mendelian randomization analyses to investigate a potential causal relationship between PM2.5 exposure and Alzheimer's disease and delirium.

*Mendelian randomization (MR) analysis*

Identification of SNPs Associated with Alzheimer's Disease and Delirium. We obtained SNPs associated with Alzheimer's disease from the IEU OpenGWAS project database and SNPs related to delirium from the FinnGen database. After normalization using the coordinated effects tool, no further screening was performed on these SNPs.

To investigate the potential correlation between PM2.5 exposure and the two outcome variables (Alzheimer's disease and delirium), we performed Mendelian randomization (MR) analyses using five algorithms: MR-Egger, weighted median, inverse variance weighted (IVW), simple mode, and weighted method (**Figures 1A**, **2A**). The IVW method was used as the primary criterion to determine the presence of a positive result. The odds ratio (OR) for Alzheimer's disease was 0.9960713, and the OR for delirium was 0.3931085, suggesting that PM2.5 exposure in our environment was not associated with the occurrence of Alzheimer's disease or delirium (**Table 1**). To exclude possible heterogeneity of instrumental variables arising from different analytic platforms, experiments, or populations, we assessed heteroge-

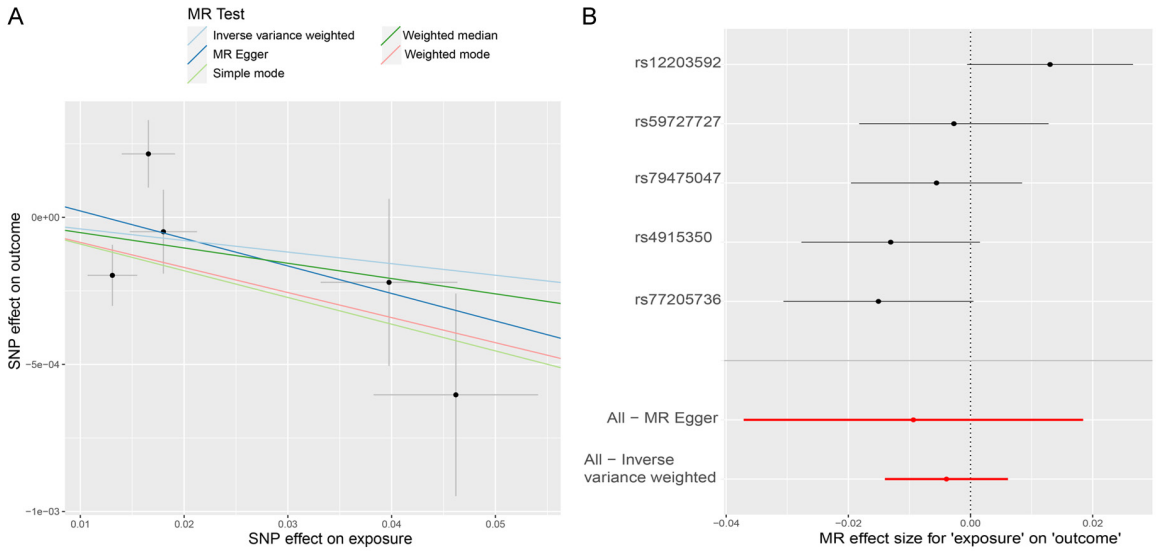


**Figure 1.** Mendelian randomization analysis of Alzheimer's syndrome and particulate matter (PM2.5). Five default algorithms (MR Egger, Weighted median, Inverse variance weighted, Simple mode, Weighted mode) for Mendelian randomization analysis on the link between PM2.5 and Alzheimer's syndrome (A). Heterogeneity was assessed by Inverse variance weighted (IVW) and MR-Egger tests (B).

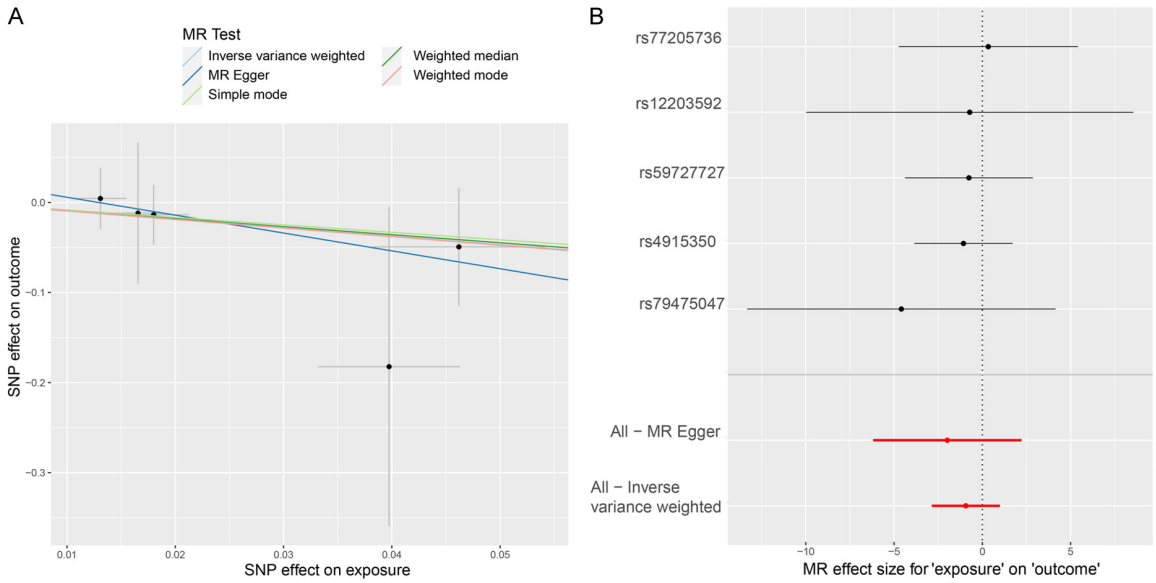


**Figure 2.** Mendelian randomization analysis of delirium and PM2.5. Five default algorithms (MR Egger, Weighted median, Inverse variance weighted, Simple mode, Weighted mode) for Mendelian randomization analysis on the link between PM2.5 and delirium (A). Heterogeneity was assessed by Inverse variance weighted (IVW) and MR-Egger tests (B).

neity using the IVW and MR-Egger tests (**Figures 1B**, **2B**). In the case of Alzheimer's disease, the *p-value* for both tests was < 0.05, indicating the presence of heterogeneity in the study. Conversely, for delirium, the *p-value* was > 0.05, suggesting an absence of heterogeneity (**Table 2**).

Given the presence of heterogeneity in the Alzheimer's disease data, we applied the outlier algorithm to evaluate potential outliers. The results indicated no outliers in our dataset. To verify that the exposure factor (PM2.5) does not influence the occurrence of the outcome variables through other factors, we employed

**Table 1.** Results of Mendelian analysis of PM2.5 and Alzheimer's syndrome & delirium

| Outcome | Method | Nsnp | Beta | SE | *p*-value | OR | OR_lci95 | OR_uci95 |
|---|---|---|---|---|---|---|---|---|
| Alzheimer's syndrome | MR Egger | 5 | -0.009 | 0.014 | 0.557 | 0.991 | 0.964 | 1.019 |
| | Weighted median | 5 | -0.005 | 0.005 | 0.269 | 0.995 | 0.986 | 1.004 |
| | Inverse variance weighted | 5 | -0.004 | 0.005 | 0.444 | 0.996 | 0.986 | 1.006 |
| | Simple mode | 5 | -0.009 | 0.007 | 0.251 | 0.991 | 0.978 | 1.004 |
| | Weighted mode | 5 | -0.009 | 0.007 | 0.282 | 0.992 | 0.978 | 1.005 |
| Delirium | MR Egger | 5 | -1.983 | 2.146 | 0.424 | 0.138 | 0.002 | 9.239 |
| | Weighted median | 5 | -0.895 | 1.153 | 0.438 | 0.409 | 0.043 | 3.860 |
| | Inverse variance weighted | 5 | -0.934 | 0.985 | 0.343 | 0.393 | 0.057 | 2.710 |
| | Simple mode | 5 | -0.829 | 1.426 | 0.592 | 0.436 | 0.025 | 7.591 |
| | Weighted mode | 5 | -0.948 | 1.243 | 0.488 | 0.388 | 0.037 | 4.028 |

An OR greater than 1 represents the exposure factor as an unfavorable factor for the outcome; an OR less than 1 represents the exposure factor as a favorable factor for the outcome.

**Table 2.** Heterogeneity assessed by IVW and MR-Egger test

| Outcome | Method | Q | Q_df | Q-value |
|---|---|---|---|---|
| Alzheimer's syndrome | MR Egger | 9.011 | 3 | 0.029 |
| | Inverse variance weighted | 9.536 | 4 | 0.049 |
| Delirium | MR Egger | 0.630 | 3 | 0.889 |
| | Inverse variance weighted | 0.933 | 4 | 0.920 |

Q-value < 0.05 indicates heterogeneity in the study.

**Table 3.** Multivariate validity test

| Outcome | Method | *p* value |
|---|---|---|
| Alzheimer's syndrome | Egger_intercept | 0.704 |
| Delirium | Egger_intercept | 0.620 |

*p* value < 0.05, indicating the presence of multiple validity of the data.

the MR-Egger intercept algorithm. The *p-value* was found to be > 0.5 for both Alzheimer's disease (*p*-value = 0.7041215) and delirium (*p-value* = 0.6203764), confirming the absence of directional pleiotropy (**Table 3**). This finding strengthens the validity of our MR analysis results, indicating that PM2.5 exposure does not have a causal effect on the occurrence of Alzheimer's disease or delirium through alternative pathways.

## Discussion

Air pollution is the most significant environmental health risk, as air pollutants are geographically dispersed and not confined to national boundaries [15]. Among air pollutants, particulate matter (PM2.5) is one of the most dangerous substances causing human disease. Strong evidence exists for a clear association between long-term exposure to particulate matter and public health risks [16], particularly pulmonary and cardiovascular disease [17]. In our study, we selected Alzheimer's disease and delirium as representative neurologic disorders commonly occurring in the elderly population. Alzheimer's disease is a typical example of organic lesions, while delirium exemplifies a functional abnormality. By focusing on these two distinct manifestations of neurologic impairment, we aimed to comprehensively investigate any impact of environmental factors on both structural and functional aspects of the aging brain.

The occurrence of air pollution has attracted much attention, and whether PM2.5 affects neurological disorders has gained attention. Therefore, we conducted a Mendelian randomization (MR) analysis to assess the causal effect of PM2.5 on Alzheimer's disease and delirium. The results showed that the presence of PM2.5 in the environment did not contribute to the development of Alzheimer's disease and delirium, alleviating concerns about air pollution causing these conditions in some older adults.

As individuals age, various bodily systems, including the nervous system, undergo physiological aging [18]. The aging of the nervous system can lead to degenerative changes in neurons, reduced synaptic connections, and decreased nerve conduction velocity, thereby

increasing the risk of developing neurologic disorders [19]. Among neurologic diseases, cognitive dysfunction and altered consciousness are the most common manifestations [20]. Alzheimer's disease is a prevalent condition causing these clinical presentations due to organic lesions, while delirium is a frequent manifestation of functional abnormalities. In clinical practice, Alzheimer's disease patients may exhibit symptoms of delirium, and cognitive decline in delirium patients may be misinterpreted as Alzheimer's disease [21]. Several risk factors, such as advanced age, chronic diseases, medication use, and infections, are associated with both conditions [22]. Consequently, some patients may simultaneously suffer from both diseases or develop one condition on top of the other. By focusing on common neurologic clinical manifestations encountered in clinical settings, we aim to investigate Alzheimer's disease as a representative of organic lesions [23] and delirium [24] as a representative of functional abnormalities.

A 10-year prospective cohort study from Taiwan demonstrated that PM2.5 exposure was associated with Alzheimer's disease development [25]. A retrospective survey by Mortamais M et al. showed a 20% increase in the risk of Alzheimer's disease and dementia for every 5 $\mu g/m^3$ increase in PM2.5 exposure [26]. Based on the current study, the proposed hypothesis may be that PM2.5 directly invades the circulation and crosses the blood-brain barrier (BBB), inducing neuroinflammation that ultimately contributes to Alzheimer's disease development [2]. However, there are some contradictory findings. Van Wijngaarden et al. studied New York State residents chronically exposed to PM2.5 and found that PM2.5 exposure was not significantly associated with hospitalization rates for Alzheimer's disease or dementia [27]. Our study verified that PM2.5 has no adverse effect on Alzheimer's disease from the perspective of single nucleotide polymorphisms.

Typically characterized by an acute deterioration in cognitive function and attention, delirium is a common mental disorder among elderly patients, with up to 42% of hospitalized patients affected by this condition [28]. Delirium is often associated with prognosis in elderly patients, primarily in terms of prolonged hospitalization, increased mortality, and increased need for follow-up care [29]. Delirium is a non-specific acute brain failure due to exogenous or endogenous factors, thus having an impact on psychopathology and behavior as it has many pathophysiologic mechanisms, including neurotransmitters, inflammation, electrolyte disorders, metabolic disorders, physiologic stressors, and genetic factors [30]. Because of the co-morbid characteristics of the senior population, the expected end pathways leading to delirium are often inconclusive. A widely accepted concept is the "threshold theory": it is hypothesized that the relationship between low thresholds and harmful factors plays a central role in the development of delirium. If the threshold is low, a mildly toxic substance is enough to trigger delirium, and vice versa [31]. Air is essential for people's survival, and air pollution cannot be avoided. Whether long-term exposure to PM2.5 is a central factor in causing delirium raises our concern. No research team has explored the effect of PM2.5 on delirium symptoms, and our study fills a particular gap.

Our study utilizes MR analysis for the first time, exploring the causal relationship between PM2.5 and Alzheimer's disease and delirium at the single nucleotide polymorphisms (SNPs) level. Previous epidemiologic studies have shown a controversial relationship between PM2.5 and Alzheimer's disease, which may be influenced by confounders and reverse causality. Based on MR analysis, Mendel's law of independent assortment selects genetic variation as an exposure factor, making the findings more reliable. Second, the genes appeared before the emergence of the disease, which ruled out an effect of reverse causation. In addition, MR analyses were performed with data from published GWAS combined studies, and the large sample size improves the validity of the test. The findings refine our understanding of the role of PM2.5 in neurologic disorders.

Our study has limitations. First, the GWAS data included in the MR analysis were mainly from European populations and lacked validation from other ethnic groups. There was some heterogeneity in the MR analysis of Alzheimer's disease with PM2.5 that may have affected our results. Our results may also be limited by the inherent flaws of MR analysis, such as selection bias, to the extent that they need to be fully considered.

## Disclosure of conflict of interest

None.

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