Mendelian Randomization Study of the Causal Relationship between PM2.5 and Neurodegenerative Diseases

Xiaohong Liu[1], Meiyu He[2], Guibin Wang[3*]

[1] The Second Affiliated Hospital of Hunan Normal University, Changsha 410003, Hunan, China.

[2] Hunan Longshan County People's Hospital, Longshan 416800, Hunan, China.

[3] The Second Affiliated Hospital of Hunan Normal University, Changsha 410003, Hunan, China.

DOI: 10.32629/jcmr.v5i3.2773

Abstract: Background: In recent years, a large number of studies have evaluated the relationship between particulate matter 2.5 (PM2.5) and the incidence rate and mortality of neurodegenerative diseases (NDDs), but the conclusion is controversial. Methods: The publicly available statistical data from genome-wide association studies were used for two sample MR. Inverse variance weighted is used as the main analysis, MR Egger regression, maximum likelihood, simple median, and weighted median are used for supplementary validation. Results: MR analysis results indicate that for every standard deviation increase in PM2.5 exposure, the risk of Alzheimer's disease (AD) increases by 41% (95% CI: 1.10 ~ 1.82, P=0.008). However, there is no causal association between PM2.5 and NDDs such as Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and Dementia with Lewy bodies. Sensitivity analysis did not detect heterogeneity and pleiotropy, indicating that the analysis results are robust. Conclusion: There is a causal relationship between PM2.5 and the risk of AD, and reducing PM2.5 exposure may be of great significance for the prevention of AD.

***Keywords*:** particulate matter; neurodegenerative diseases; mendelian randomization

1. Introduction

Neurodegenerative diseases (NDDs) are a group of heterogeneous neurological diseases characterized by the progressive loss of neurons in the central nervous system or peripheral nervous system. NDDs mainly include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (amyotrophic lateral sclerosis), ALS), multiple sclerosis (MS), Dementia with Lewy bodies (DLB)[1]. NDDs tends to occur in middle-aged and elderly people. With the increasing aging of the population, the incidence of NDDs continues to rise, bringing heavy economic burden to society and families. It is of great significance to prevent and control the occurrence and development of NDDs.

Air pollution has become a major global public health problem. Studies have shown that PM2.5 exposure may lead to the occurrence and development of NDDs, and long-term PM2.5 exposure is associated with the risk of neurodegenerative diseases such as AD and PD. However, observational studies are susceptible to confounding factors and reverse causation, and whether PM2.5 exposure is associated with NDDs is still controversial, and the causal relationship between the two needs further research.

Mendelian randomization (MR) uses genetic variants strongly associated with exposure factors as instrumental variables (IVs) to assess the causal relationship between exposure factors and disease[2]. This study intends to use the two-sample MR Method, and use the genome-wide association studies (GWAS) on PM2.5 and NDDs (AD, PD, ALS, MS, DLB) to summarize statistical data. To explore the causal association between PM2.5 exposure and NDDs incidence.

2. Objects and methods

2.1 Study object

The GWAS data in this study come from IEU Open GWAS database. The exposure factor is PM2.5, and the outcome variables are NDDs, including AD, PD, ALS, MS, and DLB (Table 1).

Table 1. GWAS information of PM2.5 and NDDs

data	Dataset	Sample size	Population	Website
PM2.5	ukb-b-11312	423796	European	https://gwas.mrcieu.ac.uk/datasets/ukb-b-11312/
AD	ebi-a-GCST90012877	472868	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90012877/
PD	ieu-b-7	482730	European	https://gwas.mrcieu.ac.uk/datasets/ieu-b-7/
ALS	ebi-a-GCST90027163	138086	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90027163/
MS	ebi-a-GCST003566	15,283	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST003566/
DLB	ebi-a-GCST90001390	6,618	European	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90001390/

2.2 Study methods

2.2.1 Study design

In order to reveal the causal association between PM2.5 and NDDs, this study conducted a two-sample MR Analysis using the aggregated data from the IEU Open GWAS database. The study design fulfills three fundamental assumptions: (1) There exists a strong association between genetic variation and PM2.5; (2) Genetic variation remains unaffected by confounding factors; (3) The impact of genetic variation on NDDs solely occurs through PM2.5.

2.2.2 Selection of instrumental variables

The threshold for selecting a single nucleotide polymorphism (SNP) strongly associated with PM2.5 was set at $P<5\times10-6$. To account for linkage imbalance between SNPs, the threshold of r2 was adjusted to 0.001 and kilobase pair kb to 10,000. The F statistic ($F=\beta2/se2$) was calculated to identify weak instrumental variables. Heterogeneity test was conducted to exclude SNPs with significant heterogeneity, while only SNPs showing significant correlation with PM2.5 were chosen as instrumental variables.

2.2.3 Statistical methods

In this study, inverse variance weighted (IVW), MR-Egger regression, maximum likelihood estimation, simple median method and weighted median method were used to estimate the causal association between PM2.5 and NDDs[3]. IVW is the main analysis method, and compared with other methods, IVW has higher efficiency. Using MR-Egger to detect horizontal pleiotropy, if the P-value is greater than 0.05, it indicates that there is no horizontal pleiotropy. Cochran's Q test was used to detect whether there was heterogeneity. If $P > 0.05$, there was no heterogeneity. Horizontal pleiotropy was detected using MR-PROSSO, and outliers were detected, and if there were outliers, they were removed. In addition, a leave-one analysis was performed to determine whether the causal association effect was influenced by a single SNP. All statistical analyses were performed using TwoSampleMR and MR-PRESSO packages in R 4.2.3 software. The threshold of statistical significance was $P < 0.05$.

3. Results

According to the screening conditions of instrumental variables in this study, SNPS strongly correlated with PM2.5 were selected as instrumental variables to evaluate the causal association between PM2.5 and AD, PD, ALS, MS, and DLB (Figure 1). The F statistic for all SNPs is greater than 10, indicating that no weak instrumental variable exists.

IVW results showed that genetically predicted PM2.5 was associated with an increased risk of AD (OR = 1.41, 95% CI: 1.10 ~ 1.82, P=0.008), with statistical significance. The direction of causal effect obtained by MR-Egger regression, maximum likelihood estimation, simple median method, weighted median method and other methods is consistent (Figure 1 and Figure 2). No causal association was found between PM2.5 and other NDDs (AD, PD, ALS, MS, DLB) (Figure 1). Cochran's Q was used to test the heterogeneity among IVs, and P in Cochran's Q test of IVW and MR-Egger regression were both greater than 0.05, indicating that there was no heterogeneity among IVs, and the possibility of causal association being affected by differences among IVs was not high (Table 2). The global test results of MR-Egger intercept and MR-PRESSO showed that MR Analysis was not affected by pleiotropy ($P > 0.05$, Table 2). The leave-one-out analysis showed little effect on the results after sequentially removing each SNP, suggesting that individual SNPS do not have a significant effect on the overall causal effect estimate (Figure 3).

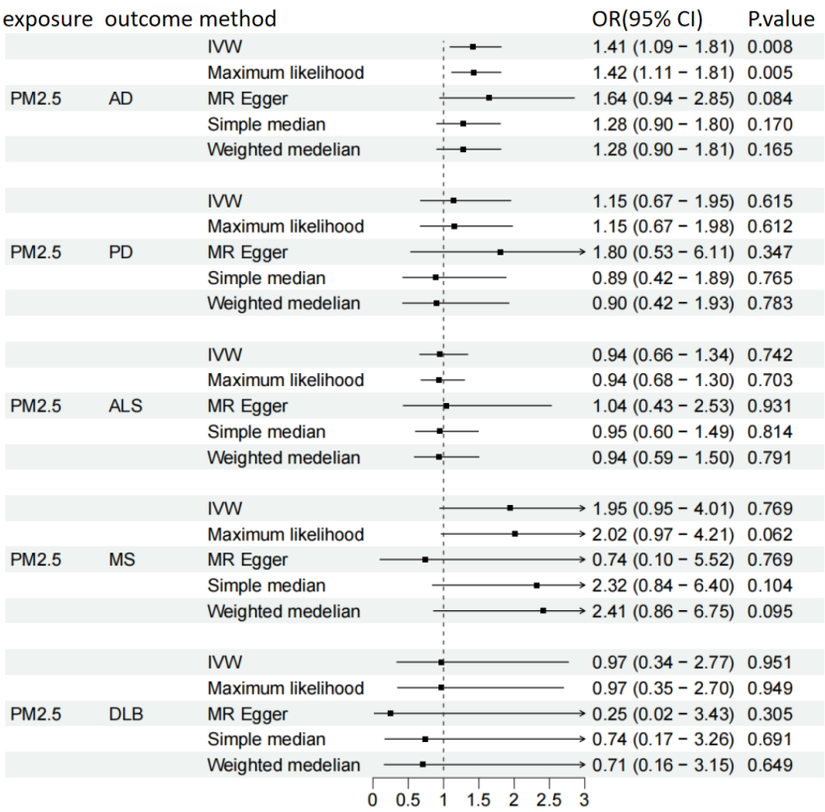

Figure 1. Forest plot of MR analysis

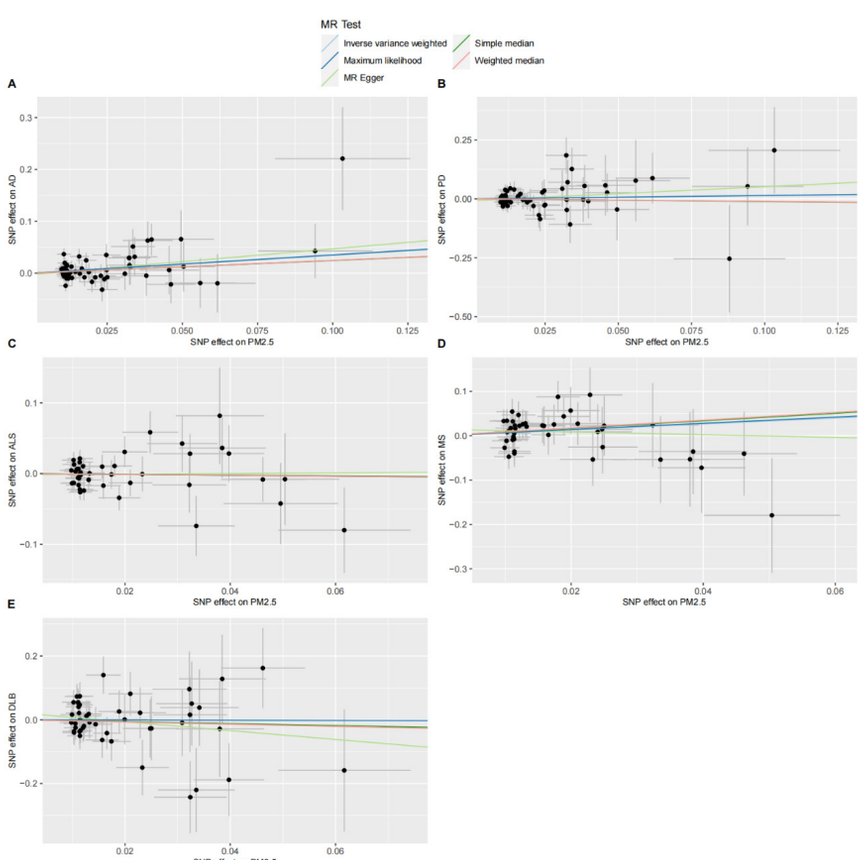

Figure 2. Scatter plot of MR analysis

Table 2. Heterogeneity and Pleiotropy Tests

outcome	IVW	MR-egger	MR-egger intercept	MR-PRESSO
AD	0.224	0.207	0.544	0.243
PD	0.919	0.914	0.448	0.918
ALS	0.121	0.102	0.812	0.111
MS	0.714	0.718	0.317	0.704
DLB	0.3	0.31	0.275	0.293

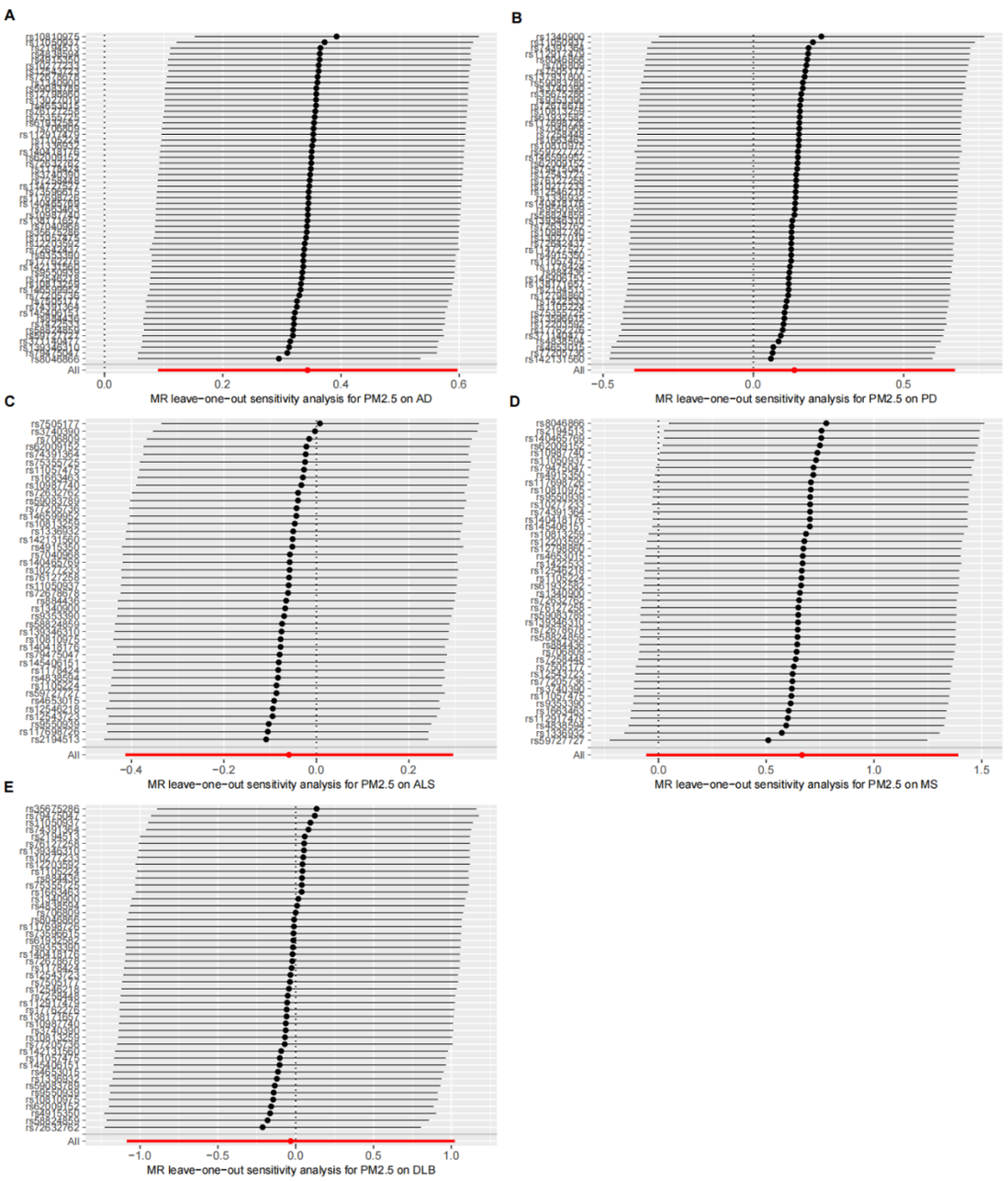

Figure 3. Plots of Leave-one-out analysis

4. Discussion

In this study, five MR methods were utilized to examine the causal relationship between PM2.5 and NDDs from a genetic perspective using publicly available GWAS datasets. The results indicate that exposure to PM2.5 is linked with an

elevated risk of developing AD; however, no causal association was found between PM2.5 and PD, ALS, MS, or DLB.

There is compelling evidence suggesting that the aging brain may exhibit increased susceptibility to neurotoxicity induced by air pollution, thereby resulting in cognitive impairment[1]. Given the profound global population aging, the proportion of individuals aged over 60 years will surge from 12% to 22% (2.1 billion) between 2015 and 2050. Hence, it is imperative to identify potential risk factors and develop efficacious prevention and control strategies. Although numerous observational studies have reported a plausible association between PM2.5 and NDDs, there exists a dearth of genetic evidence, while traditional observational studies suffer from limitations such as small sample sizes, reverse causation, and confounding factors. In this study, the MR Method was employed to assess the causal relationship between exposure factors and outcome variables by utilizing genetic variation effectively; thereby excluding interference from confounding factors and reverse causation while unveiling potential genetic associations between PM2.5 and NDDs.

Both epidemiological studies and animal experiments have consistently demonstrated an association between PM2.5 exposure and AD. The findings of a large-scale longitudinal cohort study involving 63 million participants revealed that an increase in PM2.5 exposure by every 5μg·m-3 was associated with a corresponding 13% rise in the risk of initial hospital admission for Alzheimer's disease (AD) and related dementia. The cause of AD is complex, driven by many factors such as environment and heredity. Activation of microglia and deposition of amyloid β are considered to be key pathogenesis of AD. Animal experiments have confirmed that exposure to diesel exhaust particles (an important source of PM2.5) can increase the number of hippocampal inflammatory cytokines and activated microglia in mice, impairs the neurobehavior and cognition of mice. Consistent with previous studies, our results further support a genetic association between PM2.5 and AD, reinforcing the causal nature of this relationship.

At present, a large number of studies have explored the relationship between PM2.5 and PD, ALS, MS and DLB, but the research results are inconsistent. Our study did not observe a genetic association between them, suggesting that we need to further consider the relationship between PM2.5 and the above NDDs and verify our results in a larger database containing different ethnic groups. In addition, the specific mechanisms of how PM2.5 affects the nervous system and leads to NDDs are not fully understood. Therefore, future research should aim to elucidate the biological effects of PM2.5 and how it may affect neurological health through potential molecular pathways.

5. Conclusions

In summary, this study confirms a genetic association between PM2.5 exposure and AD. This finding not only enhances public awareness of the potential neurotoxicity of PM2.5, but also provides scientific evidence for the early prevention and intervention of AD, which has important guiding significance for public health policy and disease management.

References

[1] Erkkinen M G, Kim M O, Geschwind M D. Clinical Neurology and Epidemiology of the Major Neurodegenerative Diseases [J]. Cold Spring Harbor perspectives in biology, 2018, 10(4).

[2] Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies [J]. Human molecular genetics, 2014, 23(R1): R89-98.

[3] Deng Z, Wang H, Huang K, et al. Association between vascular risk factors and idiopathic normal pressure hydrocephalus: a Mendelian randomization study [J]. Journal of neurology, 2023, 270(5): 2724-33.

[4] Kilian J, Kitazawa M. The emerging risk of exposure to air pollution on cognitive decline and Alzheimer's disease - Evidence from epidemiological and animal studies [J]. Biomedical journal, 2018, 41(3): 141-62.