



Parkinson's Disease and Major Depressive Disorder: A Bidirectional Mendelian Randomization Study

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Abstract:

Background: A substantial gap in knowledge exists regarding the causal relationship between Parkinson's disease and major depressive disorder.

Objective: A bidirectional Mendelian randomization analysis was conducted to investigate the causal relationship between major depression and Parkinson's disease.

Methods: Pooled data from the Genome-Wide Association Study (GWAS) was used to obtain information on major depressive disorder (MDD) and Parkinson's disease (PD). single nucleotide polymorphisms (SNPs) were used as instrumental variables. Two-sample bidirectional Mendelian randomization analysis was used to examine causal associations between major depressive disorder (MDD) and Parkinson's disease (PD). The primary method used for this Mendelian randomization (MR) analysis was the inverse variance weighting (IVW) method. Sensitivity analyses, including Cochran's Q test, the MR Egger intercept, and the leave-one-out method, were also performed.

Results: The results did not support a causal relationship in any direction between MDD and PD. When MDD was used as an exposure factor, IVW analysis indicated that MDD did not lead to a modified risk of developing PD (OR=1.02, 95%CI: 0.78-1.34, P=0.89>0.05). Likewise, when PD was used as an exposure factor, IVW showed that PD was not associated with an altered risk of developing major depressive disorder (OR=0.99, 95%CI: 0.97~1.01, P=0.27>0.05).

Conclusion: This study's findings do not provide evidence for a causal relationship between Parkinson's disease and major depressive disorder.

Key words: Parkinson's disease; Mendelian randomization study; major depressive disorder; genetic association; causality

Introduction

Parkinson's disease and major depressive disorder are both public health issues that are in need of urgent attention. Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease, and affects more than 1% of the elderly population worldwide.[1,2] PD is associated with high rates of disability that severely impact the quality of life of patients, and current treatments only partially relieve symptoms and fail to slow disease progression, leading to a great global burden.[3] Major depressive disorder (MDD) is a prevalent mental illness, affecting approximately 4.7% of the global population. [4,5] This burden remains consistent throughout life for both sexes. [6] symptoms such as bradykinesia

and limb tremor, Parkinson's patients often present with non-motor symptoms including depression, anxiety, and cognitive dysfunction.[1] Somatization symptoms, such as reduced activity and limb rigidity, may also occur in patients with major depressive disorder.[7] Epidemiologic studies have also shown an association between PD and major depressive disorder. Depression is a common nonmotor symptom that can occur at any stage of PD. Approximately 50% of PD patients have reported depressive-like symptoms, 35% have had clinically significant depression, and 19% have comorbid depression. [8,9] Major depressive disorder is often comorbid with other disorders. PD patients are more likely to have comorbid depression than the general population and patients with other chronic diseases. [7,10]

There is a significant lack of knowledge regarding the causal relationship between Parkinson's disease and major depressive disorder. Understanding the relationship between Parkinson's disease and major depressive disorder may have a positive impact on the prevention, diagnosis, and treatment of both diseases. However, it is important to note that most of the previous studies were observational studies with limited sample sizes, combined with the influence of different settings, sampling methods, and diagnostic criteria, and their results contain unavoidable confounding factors and are subject to potential reverse causality. Mendelian randomization (MR) analysis, which uses genetic variants closely associated with exposure to assess the causal relationship between exposure and outcome, can overcome the effects of confounding and reverse causation.[11] Genome-wide association studies (GWAS) provide a wealth of pooled data on the association between exposure or disease and genetic variation.[12] We conducted a two-sample, bidirectional Mendelian randomization analysis using publicly available large-sample data to explore the possible causal relationship between Parkinson's disease and major depressive disorder.

Methods

Study Overview

A brief description of the study design is displayed in Fig 1. We conducted a bidirectional two-sample MR study to assess the causal relationship between MDD and PD. The MR utilizes genetic variations as proxies for risk factors, the instrument variables (IVs). Effective IVs must satisfy three key assumptions: (1) the IVs are strongly and directly associated with the exposure; (2) the IVs are independent of any confounders of the exposure-outcome association; (3) the IVs do not affect the outcome through pathways other than the exposure.

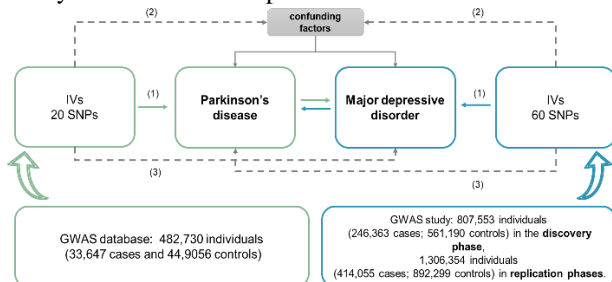
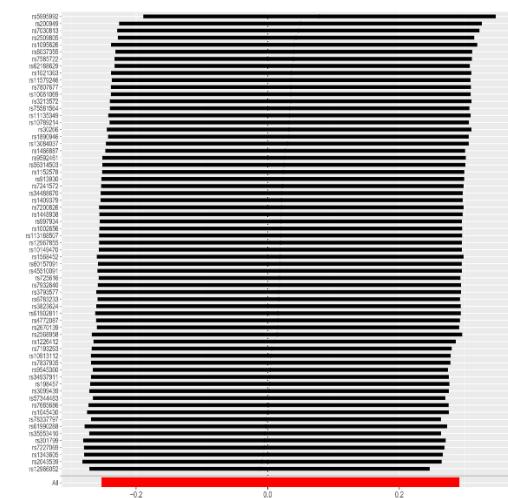


Figure 1
Conceptual framework diagram for Mendelian randomization analysis. IVs, instrument variants; SNP, single-nucleotide polymorphisms;



Supplementary figure 1
MR leave-one-out sensitivity analysis for PD on MDD



Supplementary figure 2
MR leave-one-out sensitivity analysis for MDD on PD

Data Source

GWAS data for PD were derived from the International Parkinson's Disease Genomics Consortium (IPDGC). This GWAS is the most comprehensive and recent for PD, which comprised 482,730 individuals (33,647 cases and 44,9056 controls).

We obtained MDD GWAS data from the study of Howard et al [13]. Their work is the largest published GWAS for MDD to date, enrolling 807,553 individuals (246,363 cases; 561,190 controls) in the discovery phase, and 1,306,354 individuals (414,055 cases; 892,299 controls) in replication phases. As lack of agreement from 23andMe, we used the summary statistics for all assessed genetic variants in UK Biobank and PGC_139k in the reverse-direction MR. This summary statistics included 500,199 individuals(170,756 cases; 329,443 controls).

Criteria of Instrumental Variables

To ensure accuracy and effectiveness, we identified SNPs as IVs with the following criteria: (i) genome-wide significance and strong correlation with exposure factors ($P < 5e-8$); (ii) independence to minimize the violation of the linkage disequilibrium ($r^2 < 0.01$ within a window of 10000 kb using

European samples from 1000 Genomes Project); (iii) sufficient strength ($F\text{-statistic} > 10$). The F-statistic was calculated using the formula $F = R^2/(1 - R^2) * (N - K - 1)/K$. N represents the sample size of the exposure GWAS, and K is the number of SNPs. R^2 is the proportion of variance explained by the SNPs in the exposure database.

Statistical Analysis

Mendelian Randomisation (MR) is an analytic approach that uses genetic variants as ‘instruments’ to study the causal relationship between modifiable exposures and outcomes. We employed five different MR methods for analyses. The main analytical method was the Inverse Variance Weighted (IVW) method. IVW is an effective causal effect estimation method for genetic variants as IVs[14]. Despite IVW, we conducted the Egger regression (MR-Egger) method, weighted median method, simple median method, and maximum likelihood method as complementary methods. By employing the above five MR methods, we aimed to minimize bias and obtain reliable estimates of the causal relationship between the exposure of interest and the outcome. Since the outcome variables were dichotomous, the statistics of the above five methods include p-values and OR values. When the p-value of the MR result is less than 0.05, it indicates a causal association between the exposure and the outcome. When the OR value is greater than 1, it suggests a positive association between the exposure and the outcome. When the OR value is less than 1, it suggests a negative association between the exposure and the outcome.

For sensitivity analyses, we conducted the Cochran Q method to measure the heterogeneity ($p < 0.05$ suggests a significant heterogeneity). [15] the Egger-intercept test and MR-PRESSO test were used to identify SNP pleiotropy. [16] Leave-one-out analysis was performed to assess the degree of dependence of the result on a specific variant.

All statistical analyses in this study were conducted using the R software package (v4.3.2) in the R language application. MR analyses were completed using the R package “TwoSampleMR”(v 0.5.10).

Results

Causal effects of PD on MDD

With the criteria presented above, we identified 22 PD-associated SNPs. Among the 22, 20 were available in the dataset of MDD. We used the 20 SNPs as IVs in the analysis of PD on MDD.

According to the IVW method results, PD was not significantly associated with an altered incidence of MDD (OR=0.99, 95% CI: 0.97-1.01, $P=0.27 > 0.05$). The results of other complementary methods were aligned in direction and carried similar meaning with IVW.

In the sensitivity analyses, the MR-Egger test showed no evidence of directional pleiotropy ($P=0.854$), further confirming the validity of the results. The Cochran Q statistic for heterogeneity was significant for the IVW method and MR-Egger method. However, the leave-one-out analysis showed no extreme outliers, suggesting

that the result was not changed after removing any single variant.

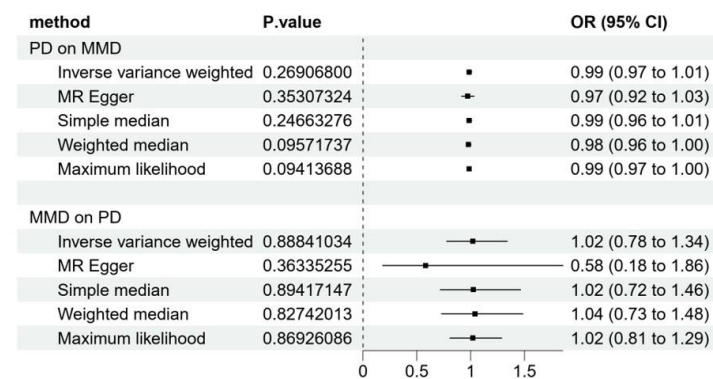


Figure 2
MR estimates of assessing the causal effect between PD and MDD

Causal effects of MDD on PD

Regarding the criteria, we selected 76 MDD-associated SNPs. 70 in 76 were available in the dataset of PD. In the harmonizing process, 5 SNPs (rs12052908, rs1933802, rs2029865, rs2247523, rs2876520) were removed for being palindromic with intermediate allele frequencies. Eventually, we got 65 SNPs as IVs in the analysis of MDD on PD.

We found no evidence of causality in the reverse direction between MDD and PD. The results of the five MR methods we performed all suggest that MDD was not significantly associated with an altered incidence of PD.

In the sensitivity analyses, we observed no directional pleiotropy regarding the tests and statistics shown in the table. The Cochran Q statistic showed significant between-SNP-heterogeneity. However, the leave-one-out analysis indicated any single SNPs did not drive the result.

Discussion

Our analyses do not support a causal association between PD and MDD in any direction. This finding suggests that there is currently no evidence to support a causal relationship, rather than contradicting previous evidence of an association between PD and MDD. The nature of PD depression has been controversial, with researchers suggesting that it is a combination of PD and depression, and others suggesting that it is a result of neurodegeneration and is part of the PD process.[8,9] Our study suggests that there is no causal relationship between Parkinson's disease and depression in either direction and that depression in Parkinson's disease is a non-motor symptom of Parkinson's disease rather than a comorbid condition of depression. Numerous research studies support this view. Depression in Parkinson's disease may be associated with dopaminergic striatal defects and decreased availability of dopamine transporters in the left lateral geniculate nucleus; Parkinson's patients with depression tend to have more severe clinical symptoms and pathophysiological manifestations;[17] Dopamine agonists may alleviate depression in Parkinson's disease.[18] Further research is urgently needed to improve our understanding of the relationship between depression

in PD and major depressive disorder, which will have a positive impact on the clinical practice of both conditions.

It is important to note that our study has limitations. The study's data was obtained from a public sample database and only included European populations, making it difficult to generalize the results. Second, the SNPs included in this study had significant heterogeneity. However, the results of this study remain reliable because of the absence of horizontal pleiotropy and because the leave-one-out method did not identify any SNPs that had a significant effect on the results of the study. Finally, MDD is a phenotype that is strongly influenced by the environment, and studies that use genetic factors to explain the onset of depression have limited strength.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

Y.X-Z: Writing—original draft. Y.Q.-G: Writing—review and editing.

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Data availability statement

Data sharing not applicable. No new data were created or analyzed in this study.

Statement of Ethics

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the (patients/ participants OR patients/participants legal guardian/next of kin) was not required to participate in this study in accordance with the national legislation and the institutional requirements.

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