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No Bidirectional Causal Relationship Between Traumatic Brain Injury and Parkinson's Disease: A Two-Sample Mendelian Randomization Study

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Keywords: causal inference | Mendelian randomization | Parkinson's disease | traumatic brain injury

ABSTRACT

Background: The incidence of Parkinson's disease (PD) is significantly increased in older people who have experienced traumatic brain injury (TBI), suggesting that TBI may be a potential risk factor for PD. However, the causal relationship remains ambiguous.

Objective: To investigate the association between TBI and PD using Mendelian randomization (MR) analyses.

Methods: Four genome-wide association databases were reviewed in detail, including GWAS Catalog, FinnGen, IEU Open-GWAS, and UK Biobank. Genetic data for TBI were obtained from the FinnGen data set, including 7430 clinically diagnosed cases and 404,751 controls, and PD was obtained from a meta-analysis in the GWAS Catalog, including 42,792 cases and 568,693 controls. The bidirectional two-sample MR analyses were used to investigate the causal association between TBI and PD.

Results: There was no evidence of a causal relationship between TBI and an increased risk of PD (IVW; OR = 1.11; 95% CI, 0.91–1.36; $p = 0.308$). Similarly, genetically predisposed PD was not associated with a high risk of TBI (IVW; OR = 0.96; 95% CI, 0.91–1.02; $p = 0.209$). Results from MR-Egger regression, weighted mode, and weighted median analyses were consistent with those from the IVW analysis. Additional sensitivity analyses further supported the robustness of our conclusions.

Conclusions: No causal relationship was found between TBI and PD.

1 | Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disease second only to Alzheimer's disease in prevalence. According to a recent estimate, there are at least 1 million people with PD in the United States [1] and nearly 3.62 million [2] in China, which is expected to rise to 13 million by 2040 [3]. Despite considerable progress in understanding the pathogenesis of PD, there is still an urgent need for effective drugs to inhibit neurodegeneration and disease progression. The identification of modifiable risk factors and the development of intervention strategies to reduce PD

Huan Wang and Yibin Huang contributed equally to this study.

incidence and delay disease progression are, therefore, of great importance.

Traumatic brain injury (TBI) is brain damage caused by a penetrating injury or blow that disrupts normal brain function. Moderate to severe TBI often leads to disability or death in older patients [4]. Epidemiological studies have shown that the risk of developing PD is significantly increased in US veterans with a history of TBI [5]. There is also evidence to suggest that TBI is a likely environmental factor contributing to the development of PD [6]. In terms of pathogenesis, researchers have tried to find some links between TBI and PD in animal models, which have shown decreased levels of substantia nigra dopamine transporters, decreased BDNF and increased inflammatory factors in TBI patients [7]. However, the probable link between TBI and neurodegeneration has attracted attention. The authors found that TBI may be a potential risk factor for frontotemporal dementia other than PD. And those with mild TBI that did not affect consciousness were also unlikely to develop PD [8]. So, the causal relation between TBI and PD remains controversial.

On the other hand, most people with PD, especially those with late-stage disease, have postural instability and gait problems. This would greatly increase the incidence of falls [9]. Studies have shown that 45%–68% of people with PD fall each year, and 50%–86% of people with PD fall repeatedly [10]. Because of these special motor symptoms, people with PD are more likely to experience TBI than the general population [11]. However, the causality relationship between PD and TBI is still poorly understood.

By treating genetic variants (typically single-nucleotide polymorphisms, SNPs) as instrumental variables (IVs), Mendelian randomization (MR) is used to assess the causality of exposures to diseases outcomes. MR could eliminate the confounding bias, reverse causality, and measurement error despite the effect of genetic instruments [12]. MR analysis has more advantages than clinical trials, which require financial resources, material, and time resources [13]. We now used a two-sample MR study to investigate the possible association between these two diseases.

2 | Materials and Methods

2.1 | Study Design

This retrospective observational study used bidirectional two-sample MR analysis to evaluate causality between TBI and PD. In forward MR analysis, TBI was considered as an exposure and PD as an outcome. Conversely, PD was regarded as an exposure and TBI as an outcome. The aggregate GWAS summary statistics used in this study were publicly available, and all contributing primary studies had obtained specific ethical approvals and informed consent. As this is an observational study using only publicly available summary-level data, our Institutional Review Board granted a waiver for ethical approval and informed consent. The MR design was based on three core principles: (1) relevance assumption, where genetic variants used as IVs are strongly associate with the exposure (TBI or PD); (2) independence assumption, which ensures SNPs are not associated with confounding factors; and (3) exclusion restriction assumption, where SNPs only influence the outcome (PD or TBI) through the exposure (TBI or PD) and not through other pathways (Figure 1). The present study followed the STROBE-MR guidelines [14].

2.2 | Data Sources

Genetic data for TBI were obtained from the FinnGen data set, including 7430 clinically diagnosed cases and 404,751 controls (https://r10.finngen.fi/pheno/TRAUMBRAIN_NONCONCUS). And the genetic data for PD were obtained from a meta-analysis in the GWAS Catalog, including 42,792 cases and 568,693 controls [15] (https://www.ebi.ac.uk/gwas/studies/GCST90275127).

2.3 | Selection of Instrumental Variables

In order to filter suitable IVs, we carried out a number of quality control procedures. First, we identified independent SNPs strongly associated with PD using a significance threshold of $p < 5 \times 10^{-8}$. As there were no SNPs meeting this criterion for TBI, we relaxed the threshold to $p < 5 \times 10^{-7}$ to ensure sufficient IV selection. We then applied a clumping procedure with an $R^2 < 0.001$ and a distance of 10,000 kb from the independent SNP [16] to exclude SNPs in strong Linkage Disequilibrium. Finally, to ensure the consistency of allele effects, we harmonized the exposure and outcome datasets, eliminating SNPs with ambiguous alleles and those with intermediate frequencies.

In addition, we calculated *F*-statistics to assess the strength of the IVs and reduce the impact of potential bias [17]. In general, only IVs with *F*-statistics > 10 were retained for subsequent MR analysis, as *F*-statistics < 10 are considered weak and were deleted. In this study, R^2 was calculated as $2 \times \mathrm{EAF} \times (1 - \mathrm{EAF}) \times \beta^2$, and F was calculated using the formula $[(N - k - 1)/k] \times [R^2/(1 - R^2)]$, where N is the GWAS sample size, K is the number of SNPs, EAF is the effect allele frequency, β is the effect sizes, and SE is the standard error.

2.4 | Statistical Analysis

The present study used bidirectional two-sample MR analysis to estimate the relationship between TBI and PD. The IVW approach was the primary method for evaluating effect estimates, combining Wald ratio estimates of causal effects of different SNPs through a meta-analysis method. This approach increases the statistical power of MR analysis by including multiple variants. In addition, three supplementary MR methods were used: MR-Egger regression, the weighted median [18–20], and the weighted mode [21]. For each binary exposure, the risk of each outcome was expressed as an odds ratio (OR) with a 95% CI per log-OR increase.

Heterogeneity among the IVs was assessed using Cochran's *Q* test and a funnel plot. If significant heterogeneity was observed at $p < 0.05$, the random-effects IVW method was used. Conversely, if no heterogeneity was detected, the fixed-effects IVW method was used. The MR-Egger regression intercept test was used to assess the potential impact of pleiotropic effects of genetic variants on the estimation of causal relationships. A

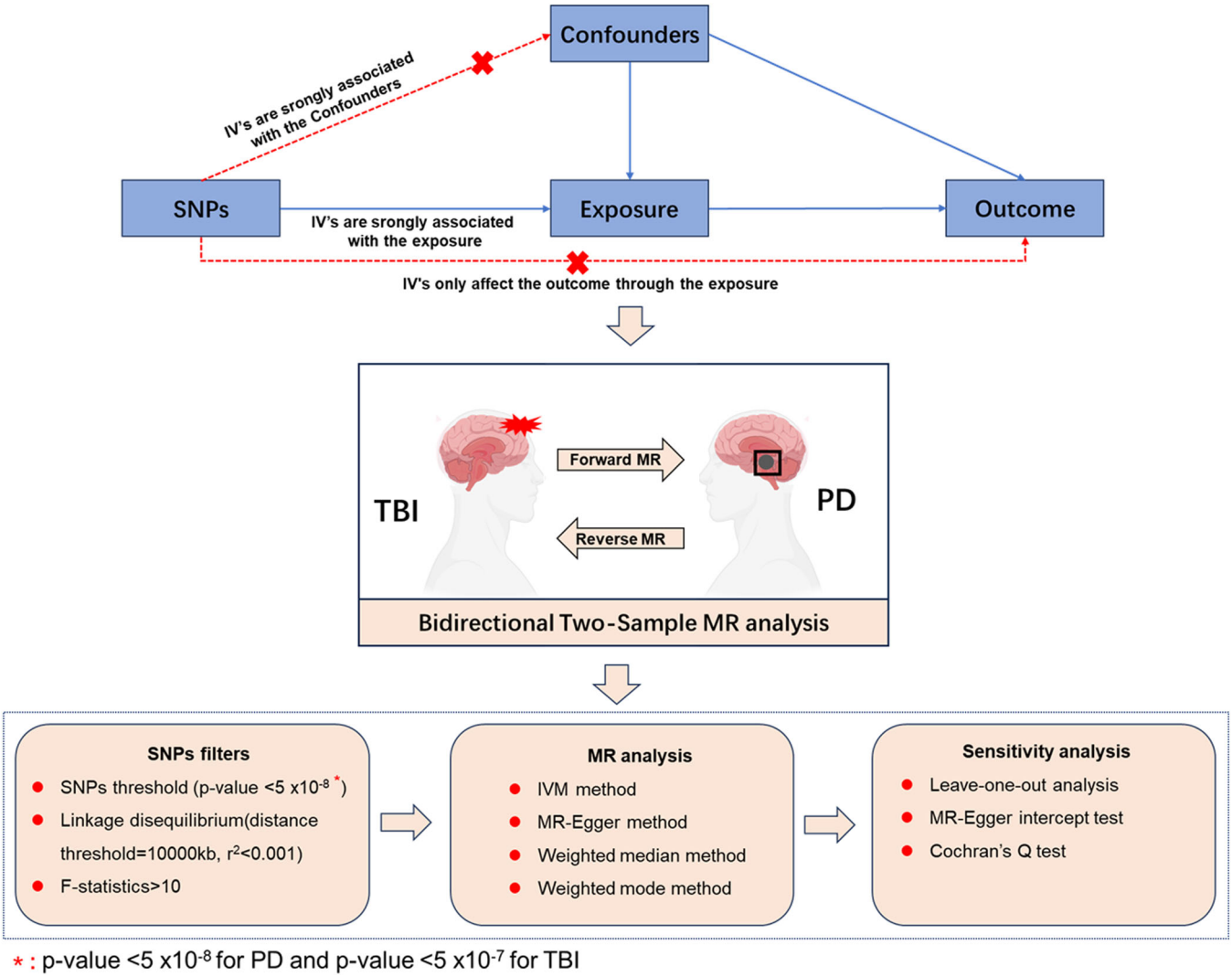

FIGURE 1 | Study design of the present study. IVW, inverse variance weighted; MR, Mendelian randomization; TBI, traumatic brain injury; PD, Parkinson's disease; SNPs, single-nucleotide polymorphisms.

$p < 0.05$ in the intercept test indicated the presence of pleiotropy. A leave-one-out analysis was performed to test the causal association was predominantly influenced by a single SNP. In this analysis, each IV was systematically removed to validate the robustness of the MR results. Statistical significance was determined using a two-tailed $p < 0.05$. All MR analyses were performed using the Two Sample MR (Version 0.5.10) and MRPRESSO (Version 1.0) packages in R version 4.3.3.

3 | Results

3.1 | Causality Between TBI and PD

We identified four independent SNPs associated with TBI and used them as IVs. Each SNP had an *F*-statistics > 10, indicating a strong association with exposure compared with outcome (Supporting Information S4: Table S1). MR estimates from different methods were presented in Figure 2. Overall, there was no observed causality were seen between TBI and PD. The primary IVW results showed that an increased risk of TBI was not statistically associated with an increased risk of PD (OR = 1.11, 95% CI: 0.91–1.36, $p = 0.308$). Similarly, consistent results were obtained using the MR-Egger, the weighted median, and the weighted mode methods. The scatterplot showing the effect sizes of the SNPs for TBI is shown in Figure 3A. Heterogeneity testing of individual SNPs showed no significant heterogeneity ($Q = 0.826$, $p = 0.843$) (Table 1). Furthermore, horizontal pleiotropy did not appear to bias the causality assessment of PD with TBI, as demonstrated by the result of the MR-Egger regression and MR-PRESSO global test (intercept = 0.037, SE = 0.584, $p = 0.586$) (Table 1). The leave-one-out analysis showed that the causal estimates of PD and its subtypes were not significantly influenced by the SNP. Supporting Information S1–S3: Figures 1–3 show the forest plots, and funnel plots, leave-one-out analysis plots.

3.2 | Causal Effects of PD on TBI

For the reverse MR, we selected 26 SNPs as IVs. The *F*-statistics were > 10 for each SNP and all 26 IVs, indicating stronger associations with the exposure than with outcome (Supporting Information S4: Table S2). The MR estimates did not indicate

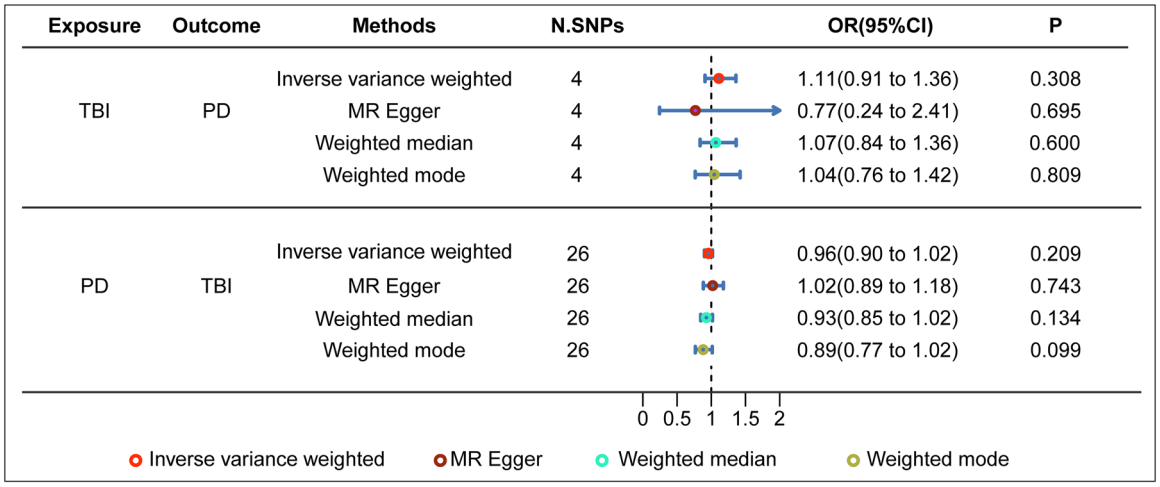

FIGURE 2 | The forest plot of the bidirectional MR results. MR, Mendelian randomization; OR, odds ratio; PD, Parkinson's disease; SNPs, single-nucleotide polymorphisms; TBI, traumatic brain injury.

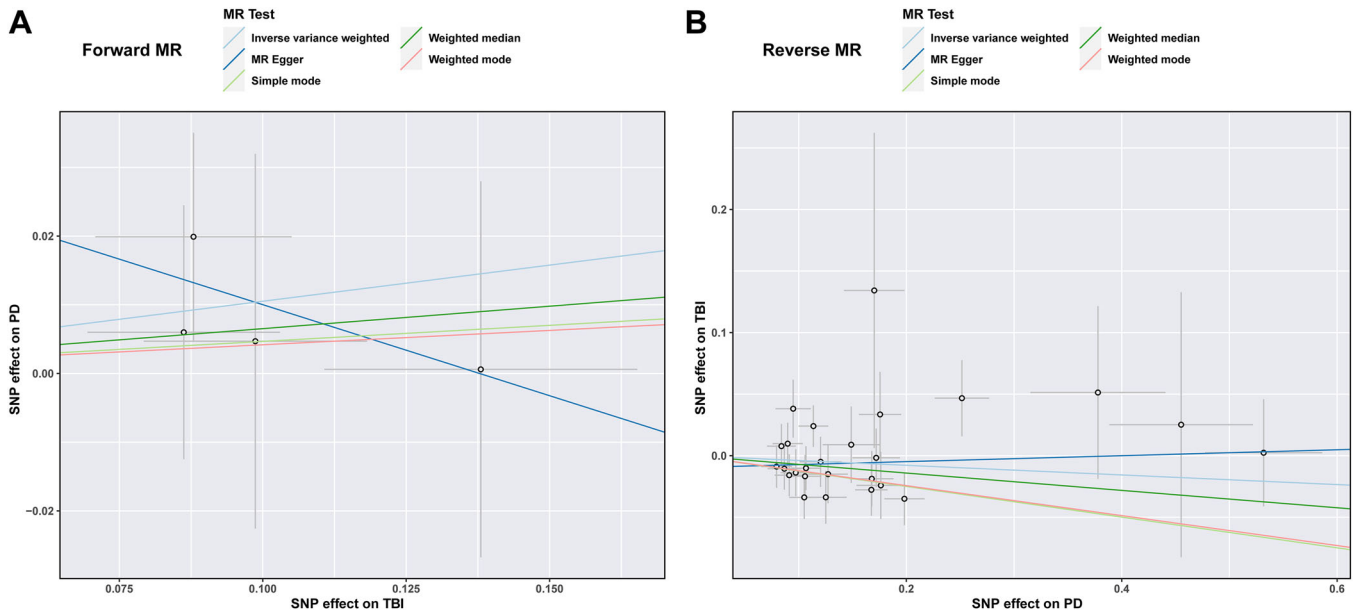

FIGURE 3 | Scatterplot of the causality between TBI and PD using different MR methods. (A) Causal estimates for TBI on PD. (B) Causal estimates for PD on TBI. The individual SNP effect on the outcome (dot and vertical line) versus its effect on the exposure (point and horizontal line) has been delineated in the background. Each line represents a different MR method. The slope of each line corresponds to the causal estimates for each method.

causality between these two diseases (Figure 2). The primary IVW suggested an increased risk of PD was not statistically associated with an increased risk of TBI (OR = 0.96, 95% CI: 0.90–1.02, $p = 0.209$). The MR-Egger, weighted median, and weighted mode methods consistently yielded similar results. The scatterplot illustrating the effect sizes of SNPs for PD is shown in Figure 3B. Heterogeneity testing between individual SNPs revealed no significant heterogeneity ($Q = 24.469$, $p = 0.492$) (Table 1). Furthermore, horizontal pleiotropy did not appear to affect the causal assessment of TBI with PD, as indicated by the result of the MR-Egger regression and the MR-PRESSO global test (intercept = −0.01, SE = 0.073, $p = 0.345$) (Table 1). The leave-one-out analysis showed that the causal estimates of TBI and its subtypes were not driven by any SNP. Supporting Information S1–S3: Figures 1–3 show the forest plots, funnel plots, and leave-one-out analysis plots.

4 | Discussion

TBI, particularly in its more severe forms, has been widely considered a risk factor for PD [22]. However, the causal direction remains unclear due to the conflicting evidence from existing observational studies [23]. Using GWAS summary statistics, this two-sample MR analysis aimed to explore the causal relationship between these two conditions. Our findings indicate no causal relationship between TBI and PD.

Epidemiological studies have consistently reported an increased risk of PD among individuals with a history of TBI [24]. Two large population-based cohort studies have demonstrated a higher incidence of PD in individuals with a history of moderate to severe TBI [8, 25]. Additionally, several meta-analyses have found that TBI, irrespective of severity, is associated with a higher risk of PD

TABLE 1 | Causal effects of TBI and PD evaluated by various MR methods.

Method	N. SNPs	OR	SE	*p*	Heterogeneity test Cochran's *Q*	*p*	Pleiotropy test MR-Egger intercept	*p*
Forward MR (TBI–PD)								
IVW	4	1.111	0.103	0.308	0.826	0.843	0.037	0.586
MR Egger	4	0.767	0.584	0.695	0.411	0.814		
Weighted median	4	1.067	0.125	0.6				
Weighted mode	4	1.043	0.158	0.809				
Reverse MR (PD–TBI)								
IVW	26	0.962	0.031	0.209	24.469	0.492	−0.01	0.345
MR Egger	26	1.024	0.073	0.743	23.541	0.488		
Weighted median	26	0.932	0.047	0.134				
Weighted mode	26	0.885	0.071	0.099				

compared to individuals without TBI [6, 26]. More recently, a study analyzing multiple prospective cohorts also identified an increased risk of incident PD in patients with a remote history of TBI. This finding is further supported by postmortem neuropathological examinations conducted during follow-up [27].

The underlying mechanisms linking TBI to PD remain unclear, but several pathological processes have been proposed, including inflammation, metabolic dysregulation, and abnormal protein aggregation. In particular, axonal injury and transport dysfunction following TBI, especially in more severe injuries, may contribute to the accumulation of pathological protein such as α-synuclein [28, 29]. Additionally, the acute neuroinflammatory response following TBI involves glial cells activation, the release of proinflammatory cytokines and chemokines, and the recruitment of peripheral immune cells [30]. Prolonged neuroinflammation may exacerbate neurodegeneration, thereby increasing PD susceptibility [31].

Despite these observational findings, postmortem studies provide only cross-sectional data, limiting their ability to establish causality. To address this, we employed MR analysis, which minimizes confounding and reverse causation. Our results suggest that severe TBI alone is not a causal determinant of PD. This aligns with contemporary research efforts identifying PD risk factors, including sleep disturbances [32], plasma α-synuclein [33], inflammatory bowel disease [34], and so on.

Several factors may explain the discrepancy between our MR results and previous observational findings. First, the environmental exposures measured in the existing studies may be associated with confounders that may lead to biased estimates, which may partially explain the inconsistency between observational findings and our MR results. Second, TBI, especially of higher severity, has been considered a risk factor for all-cause PD. Therefore, the present study used GWAS data from severe TBI populations were used for MR analysis. Although MR is based on genetic data rather than self-reported exposure, genetic differences between different TBI severities should not be a concern. However, the higher mortality rate and shorter life expectancy of these patients may influence the results of the MR analysis, as many PD patients were diagnosed years after the onset of clinical symptoms [35]. In addition, several studies suggest that the risk of developing PD is increased soon after TBI but gradually decreases over time [36, 37]. TBI may temporarily disrupt dopamine signaling via acute neuroinflammation. However, the long-term risk of PD may depend on sustained α-synuclein accumulation or interactions with other risk factors such as chronic neuroinflammation, which may partly explain the reason why we obtained a negative result [38]. It is well known that the major drawback of MR is horizontal pleiotropy [39]. Further large-scale studies are still needed to verify the findings of the present study.

Patients with PD, particularly those in the later stages (Hoehn–Yahr 3–5), often experience falls due to gait instability and postural imbalance, which can lead to recurrent TBI [40]. Consequently, PD-related fall injuries have been considered a potential risk factor for TBI. However, our reverse MR analysis showed that PD is not a causal factor for TBI. TBI encompasses a range of pathological and functional impairments resulting from external brain injury, including both primary and secondary brain damage [41]. It is commonly associated with road traffic accidents, blunt force trauma, fall, and birth-related injuries, all of which contribute to an increased risk of TBI. Given that patients with a higher risk of falls are more prone to TBI, including PD [42], it is plausible that falls themselves, rather than an underlying condition, are the primary contributors to the occurrence of TBI. In terms of pathogenesis, although brain dysfunction caused by α-synuclein aggregation and neuroinflammation increases the risk of falling in PD patients [43], it does not mean that there is a direct relationship between PD and TBI. Further studies are needed to confirm the causality between these risk factors and TBI.

There are some limitations to this study. As with other MR analyses, our results may be influenced by horizontal pleiotropy, where IVs affect the outcome through pathways outside the exposure of interest [44]. It is impossible to completely rule out this possibility, whereas the results of MR Egger showed no evidence of pleiotropy. Furthermore, we set the p at 1×10^{-7} to include more SNPs, which means that it will be comparatively small when it comes to explaining the percentage of variance between IVs and exposures. The presence of other unavoidable

undetected confounders may affect the causal inference. Nevertheless, our study provides a novel perspective on the relationship between TBI and PD. Future research using more sophisticated causal inference approaches, such as nonlinear MR methods or studies incorporating detailed individual-level data, may be necessary to further explore potential threshold effects or interactions with other risk factors.

5 | Conclusion

Our study found no evidence of a causal relationship between TBI and PD. Further GWAS and advanced causal inference studies are needed to validate these findings and explore potential underlying mechanisms.

Author Contributions

Huan Wang: software, conceptualization, writing – original draft. **Yibin Huang:** conceptualization, writing – original draft. **Ziwen Zhu:** writing – review and editing. **Yanzi Peng:** writing – review and editing. **Guolian Wei:** writing – review and editing. **Xijin Wang:** writing – review and editing. **Qiang Guan:** writing – review and editing. **Lingjing Jin:** writing – review and editing. **Ya Feng:** writing – review and editing, funding acquisition, supervision. **Jingxing Zhang:** funding acquisition, supervision, writing – review and editing. All authors contribute to the writing and revision of the paper, and approved this version to be submitted.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Summary data from the FinnGen study on TBI are available at https://r10.finngen.fi/pheno/TRAUMBRAIN_NONCONCUS. Summary data from the GWAS Catalog of PD are available at https://www.ebi.ac.uk/gwas/studies/GCST90275127.

Transparency Statement

The lead authors, Ya Feng and Jingxing Zhang, affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. W. Yang, J. L. Hamilton, C. Kopil, et al., "Current and Projected Future Economic Burden of Parkinson's Disease in the U.S," *NPJ Parkinson's Disease* 6 (2020): 15.

2. S. Qi, P. Yin, L. Wang, et al., "Prevalence of Parkinson's Disease: A Community-Based Study in China," *Movement Disorders* 36 (2021): 2940–2944.

3. V. Božok, L. Yu, J. Palgi, and U. Arumäe, "Antioxidative CXXC Peptide Motif From Mesencephalic Astrocyte-Derived Neurotrophic Factor Antagonizes Programmed Cell Death," *Frontiers in Cell and Developmental Biology* 6 (2018): 106.

4. A. Capizzi, J. Woo, and M. Verduzco-Gutierrez, "Traumatic Brain Injury," *Medical Clinics of North America* 104 (2020): 213–238.

5. V. Delic, J. H. Karp, M. Guzman, et al., "Repetitive Mild TBI Causes pTau Aggregation in Nigra Without Altering Preexisting Fibril Induced Parkinson's-Like Pathology Burden," *Acta Neuropathologica Communications* 10 (2022): 170.

6. S. Jafari, M. Etminan, F. Aminzadeh, and A. Samii, "Head Injury and Risk of Parkinson Disease: A Systematic Review and Meta-Analysis," *Movement Disorders* 28, no. 9 (2013): 1222–1229.

7. D. Gustafsson, A. Klang, S. Thams, and E. Rostami, "The Role of BDNF in Experimental and Clinical Traumatic Brain Injury," *International Journal of Molecular Sciences* 22 (2021): 3582.

8. R. Raj, J. Kaprio, M. Korja, E. D. Mikkonen, P. Jousilahti, and J. Siironen, "Risk of Hospitalization With Neurodegenerative Disease After Moderate-to-Severe Traumatic Brain Injury in the Working-Age Population: A Retrospective Cohort Study Using the Finnish National Health Registries," *PLoS Medicine* 14 (2017): e1002316.

9. J. Wilczyński, M. Ścipniak, K. Ścipniak, et al., "Assessment of Risk Factors for Falls Among Patients With Parkinson's Disease," *BioMed Research International* 2021 (2021): 5531331.

10. P. H. S. Pelicioni, J. C. Menant, M. D. Latt, and S. R. Lord, "Falls in Parkinson's Disease Subtypes: Risk Factors, Locations and Circumstances," *International Journal of Environmental Research and Public Health* 16 (2019): 2216.

11. T. T. Eric Nyam, C. H. Ho, Y. L. Wang, et al., "The Risk of Traumatic Brain Injury Occurring Among Patients With Parkinson Disease: A 14-Year Population-Based Study," *World Neurosurgery* 113 (2018): e328–e335.

12. E. Birney, "Mendelian Randomization," *Cold Spring Harbor Perspectives in Medicine* 12 (2022): a041302.

13. J. Bowden and M. V. Holmes, "Meta-Analysis and Mendelian Randomization: A Review," *Research Synthesis Methods* 10 (2019): 486–496.

14. V. W. Skrivankova, R. C. Richmond, B. A. R. Woolf, et al., "Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement," *Journal of the American Medical Association* 326 (2021): 1614–1621.

15. J. J. Kim, D. Vitale, D. V. Otani, et al., "Multi-Ancestry Genome-Wide Association Meta-Analysis of Parkinson's Disease," *Nature Genetics* 56 (2024): 27–36.

16. G. R. Abecasis, D. Altshuler, A. Auton, et al., "A Map of Human Genome Variation From Population-Scale Sequencing," *Nature* 467 (2010): 1061–1073.

17. S. Burgess and S. G. Thompson, "Avoiding Bias From Weak Instruments in Mendelian Randomization Studies," *International Journal of Epidemiology* 40 (2011): 755–764.

18. F. P. Hartwig, N. M. Davies, G. Hemani, and G. Davey Smith, "Two-Sample Mendelian Randomization: Avoiding the Downsides of a Powerful, Widely Applicable but Potentially Fallible Technique," *International Journal of Epidemiology* 45 (2016): 1717–1726.

19. X. Huang, X. Guo, W. Gao, et al., "Causal Association Between Years of Schooling and the Risk of Traumatic Brain Injury: A Two-Sample Mendelian Randomization Analysis," *Journal of Affective Disorders* 354 (2024): 483–490.

20. K. J. Yin, J. X. Huang, P. Wang, et al., "No Genetic Causal Association Between Periodontitis and Arthritis: A Bidirectional Two-Sample Mendelian Randomization Analysis," *Frontiers in Immunology* 13 (2022): 808832.

21. F. P. Hartwig, G. Davey Smith, and J. Bowden, "Robust Inference in Summary Data Mendelian Randomization via the Zero Modal Pleiotropy Assumption," *International Journal of Epidemiology* 46 (2017): 1985–1998.

22. B. L. Brett, R. C. Gardner, J. Godbout, K. Dams-O'Connor, and C. D. Keene, "Traumatic Brain Injury and Risk of Neurodegenerative Disorder," *Biological Psychiatry* 91 (2022): 498–507.

23. M. Balabandian, M. Noori, B. Lak, Z. Karimizadeh, and F. Nabizadeh, "Traumatic Brain Injury and Risk of Parkinson's Disease: A Meta-Analysis," *Acta Neurologica Belgica* 123 (2023): 1225–1239.

24. G. Meyfroidt, P. Bouzat, M. P. Casaer, et al., "Management of Moderate to Severe Traumatic Brain Injury: An Update for the Intensivist," *Intensive Care Medicine* 48 (2022): 649–666.

25. R. C. Gardner, A. L. Byers, D. E. Barnes, Y. Li, J. Boscardin, and K. Yaffe, "Mild TBI and Risk of Parkinson Disease: A Chronic Effects of Neurotrauma Consortium Study," *Neurology* 90 (2018): e1771–e1779.

26. D. C. Perry, V. E. Sturm, M. J. Peterson, et al., "Association of Traumatic Brain Injury With Subsequent Neurological and Psychiatric Disease: A Meta-Analysis," *Journal of Neurosurgery* 124 (2016): 511–526.

27. P. K. Crane, L. E. Gibbons, K. Dams-O'Connor, et al., "Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings," *JAMA Neurology* 73, no. 9 (2016): 1062.

28. C. S. Hill, M. P. Coleman, and D. K. Menon, "Traumatic Axonal Injury: Mechanisms and Translational Opportunities," *Trends in Neurosciences* 39 (2016): 311–324.

29. G. F. Bruggeman, I. K. Haitsma, C. M. F. Dirven, and V. Volovici, "Traumatic Axonal Injury (TAI): Definitions, Pathophysiology and Imaging-A Narrative Review," *Acta Neurochirurgica* 163 (2021): 31–44.

30. R. Kölliker-Frers, L. Udovin, M. Otero-Losada, et al., "Neuroinflammation: An Integrating Overview of Reactive-Neuroimmune Cell Interactions in Health and Disease," *Mediators of Inflammation* 2021 (2021): 9999146.

31. S. C. Woodburn, J. L. Bollinger, and E. S. Wohleb, "The Semantics of Microglia Activation: Neuroinflammation, Homeostasis, and Stress," *Journal of Neuroinflammation* 18 (2021): 258.

32. Y. Ling, J. Zhu, F. Yan, L. A. Tse, S. Kinra, and M. Jiang, "Sleep Behaviors and Parkinson's Disease: A Bidirectional Mendelian Randomization Analysis," *Behavioural Brain Research* 441 (2023): 114281.

33. Q. Zhang, Z. Lin, Y. He, J. Jiang, and D. Hu, "Mendelian Randomization Analysis Reveals No Causal Relationship Between Plasma α-Synuclein and Parkinson's Disease," *Molecular Neurobiology* 60 (2023): 2268–2276.

34. D. Freuer and C. Meisinger, "Association Between Inflammatory Bowel Disease and Parkinson's Disease: A Mendelian Randomization Study," *NPJ Parkinson's Disease* 8 (2022): 55.

35. M. C. Gonzalez, I. Dalen, J. Maple-Grødem, O. B. Tysnes, and G. Alves, "Parkinson's Disease Clinical Milestones and Mortality," *NPJ Parkinson's Disease* 8 (2022): 58.

36. A. Ascherio and M. A. Schwarzschild, "The Epidemiology of Parkinson's Disease: Risk Factors and Prevention," *Lancet Neurology* 15 (2016): 1257–1272.

37. F. Fang, H. Chen, A. L. Feldman, F. Kamel, W. Ye, and K. Wirdefeldt, "Head Injury and Parkinson's Disease: A Population-Based Study," *Movement Disorders* 27 (2012): 1632–1635.

38. Y. H. Chen, E. Y. K. Huang, T. T. Kuo, J. Miller, Y. H. Chiang, and B. J. Hoffer, "Impact of Traumatic Brain Injury on Dopaminergic Transmission," *Cell Transplantation* 26 (2017): 1156–1168.

39. M. Verbanck, C. Y. Chen, B. Neale, and R. Do, "Detection of Widespread Horizontal Pleiotropy in Causal Relationships Inferred From Mendelian Randomization Between Complex Traits and Diseases," *Nature Genetics* 50 (2018): 693–698.

40. H. Kataoka and K. Sugie, "Health-Related Quality of Life May Predict Disease Staging in 10 Years in Parkinson Disease With Hoehn-Yahr Stage III," *Neurology: Clinical Practice* 11 (2021): e261–e266.

41. S. H. Rauchman, A. Zubair, B. Jacob, et al., "Traumatic Brain Injury: Mechanisms, Manifestations, and Visual Sequelae," *Frontiers in Neuroscience* 17 (2023): 1090672.

42. J. Dunne, G. A. Quiñones-Ossa, E. G. Still, et al., "The Epidemiology of Traumatic Brain Injury Due to Traffic Accidents in Latin America: A Narrative Review," *Journal of Neurosciences in Rural Practice* 11 (2020): 287–290.

43. D. Rokad, S. Ghaisas, D. S. Harischandra, et al., "Role of Neurotoxicants and Traumatic Brain Injury in α-Synuclein Protein Misfolding and Aggregation," *Brain Research Bulletin* 133 (2017): 60–70.

44. W. Spiller, D. Slichter, J. Bowden, and G. Davey Smith, "Detecting and Correcting for Bias in Mendelian Randomization Analyses Using Gene-by-Environment Interactions," *International Journal of Epidemiology* 48 (2019): 702–712.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.