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Research article

No causal relationship between ankylosing spondylitis and Parkinson's disease: Insights from Mendelian randomization studies

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ABSTRACT

Background: Retrospective cohort and cross-sectional studies have indicated an association between ankylosing spondylitis (AS) and Parkinson's disease (PD). However, owing the multitude of limitations, a consistent conclusion has not been determined. Furthermore, whether a causal relationship exists between these two diseases remains unclear.
Methods: We conducted a two-way Mendelian randomization (MR) analysis using genome-wide association study data. For patients with PD, we utilised data from the ieu-b-7 database, whereas for patients with AS, we employed the three databases with the largest sample sizes for a combined analysis. These databases included ebi-a-GCST005529, finn-b-M13 ANKYLOSPON, and finn-b-M13 ANKYLOSPON STRICT. Our primary method of analysis was inverse variance weighting (IVW), supplemented by four other effective methods, to comprehensively infer a potential causal relationship between AS and PD. Additionally, we conduct various sensitivity analyses to assess the robustness of our estimates.
Results: Based on our IVW MR analysis, no significant causal relationship between AS and PD was observed (odds ratio [OR] = 1.01, 95 % confidence interval [CI] = 0.99–1.03, P = 0.26). Additionally, our reverse MR analysis found no evidence supporting a significant causal relationship between PD and AS (OR = 0.93, 95 % CI = 0.85–1.01, P = 0.068). These results were substantiated by comprehensive sensitivity analyses that indicated minimal bias in the causal estimates.
Conclusion: In contrast to numerous existing clinical studies, this study failed to provide evidence supporting a significant impact of AS on PD risk, or vice versa. Further investigations regarding the potential causal mechanisms linking AS and PD are warranted.

1. Introduction

Ankylosing spondylitis (AS) is an autoimmune chronic inflammatory rheumatic disease that primarily affects the axial skeleton,

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peripheral joints, and entheses, and leads to severe chronic pain [1]. Its onset and progression are closely associated with heightened production of tumour necrosis factor-α (TNF-α), interleukin(IL)-6, and IL-17 [2,3]. Recent studies have suggested that the gut immune axis (local immunometabolic environment) is involved in AS pathogenesis [4]. The clinical manifestations of AS, driven by chronic inflammation, extend beyond affected joints and include inflammatory bowel disease, glomerulonephritis, osteoporosis, uveitis, and cardiopulmonary complications [5]. Recent reports have indicated an increased risk of ischaemic heart disease, depression, dementia, and stroke in patients with AS [6–9]. AS is characterised by chronic proinflammatory immune activity, which is now recognised as a fundamental element in neurodegenerative diseases [10]. However, the precise mechanism through which AS affects the central nervous system remains unclear.

Parkinson's disease (PD) is the second most common neurodegenerative disorder of the central nervous system and is characterized by symptoms such as bradykinesia, resting tremor, tonic postural instability, and muscle stiffness [11]. Non-motor symptoms include sleep disturbance, constipation, hyposmia, cognitive impairment, cognitive decline, depression, and anxiety [12]. The pathophysiology of PD involves a massive loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to reduced dopamine levels in the brain along with the deposition of synuclein aggregates known as Lewy bodies [13]. The aetiology of PD is multifactorial, with mounting evidence supporting the role of neuroinflammation in the neurodegenerative processes. Immune system dysfunctions, including autoimmune responses, may contribute to the disease pathogenesis [14]. Previous studies investigating pro-inflammatory cytokines in the serum and cerebrospinal fluid of patients with PD have shown significant elevations in TNF-α and IL-6 levels [15, 16]. Furthermore, serum IL-6 and IL-17 are positively correlated with the severity of PD symptoms [17]. However, an association between AS and PD occurrence remains unclear.

Numerous observational clinical studies have investigated the association between autoimmune diseases and PD. Epidemiological investigations exploring the link between AS and PD have reported that patients with AS have an increased risk of developing PD. For instance, a retrospective cohort study in Taiwan involving 6440 patients with AS and 25,760 matched healthy controls revealed a significantly higher PD prevalence in the AS cohort than in the healthy controls [18]. Similarly, a nationwide cohort study conducted in the Republic of Korea identified AS as a risk factor for PD [19]. However, a nationwide epidemiological study in Sweden that tracked patients with autoimmune diseases did not find an increased risk for PD in patients with AS [20]. Currently, studies specifically addressing the association between AS and PD rely primarily on retrospective methodologies that are susceptible to selection bias and often lack comprehensive clinical data, thereby limiting the availability of high-quality evidence. Moreover, case-control and cohort studies have inherent limitations such as inadequate representation of diverse ethnicities, small sample sizes, and the presence of potential confounding factors and biases. These limitations underscore the challenge of drawing definitive causal conclusions solely from observational designs [21]. Consequently, uncertainty persists regarding the existence of a causal relationship between AS and PD and the directionality of this relationship remains unclear. Given the conflicting results from prior observational studies, rigorous analytical scrutiny of a causal link between AS and PD is imperative to bolster the robustness of the existing evidence.

A Mendelian randomization (MR) analysis is a robust methodology that harnesses aggregated data from a genome-wide association study(GWAS) to dissect causal relationships between exposures and outcomes [22]. Consistent with Mendel's principle of independent assortment, this approach posits that each heritable trait passes from one generation to the next autonomously and is devoid of influence from other traits. The stochastic assortment of genetic variants during meiosis, coupled with post-fertilisation fixation, effectively mitigates residual confounding factors and clarifies the issues of reverse causation.

In this study, we employed naturally occurring genetic instrumental variables (IVs) in our MR analyses, drawing on individual- or population-level data from various studies to emulate randomised controlled trials [23,24]. We adopted the widely accepted two-sample MR analysis method to circumvent the need for individual-level data. We conducted a comprehensive two-way two--sample MR analysis using publicly available summary statistics from GWAS datasets. This approach enabled us to scrutinise the causal relationships and delineate the directionality between AS and PD.

2. Methods

2.1. Study design

This study examined the bidirectional causality between AS and PD using MR, and adhered to the guidelines outlined in Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization [25]. The MR methodology must satisfy three fundamental premises: (1) genetic variation is directly associated with exposure factors; (2) genetic variation is independent of potential confounders; and (3) genetic variation influences the outcomes solely through exposure factors [26].

2.2. Data sources

Genetic data for AS were sourced from the FinnGen database (https://r9.finngen.fi/) (accessed on 10 April 2024) and the International Genetics of Ankylosing Spondylitis (IGAS) consortium [27]. The AS datasets from FinnGen (finn-b-M13_ANKYLOSPON and finn-b-M13_ANKYLOSPON_STRICT) comprised 2860 patients and 270,964 controls and 1193 patients and 374,621 controls, respectively. The AS dataset from the IGAS (ebi-a-GCST005529) included 9069 patients and 13,578 controls. The UK Biobank ankylosing spondylitis datasets, UKB-a-88 and UKB-b-18194 (self-reported), comprised 968 patients with 336,191 controls and 1296 patients with 461,637 controls, respectively. PD summary data were obtained from the 2019 International Parkinson's Disease Genomics Consortium [28], which provided publicly available pooled data comprising 33,647 patients with PD and 449,056 controls. Since all databases are publicly available, no additional ethical approval was required.

2.3. Instrumental variables assessment

The instrumental variables were rigorously selected to ensure the validity and robustness of the causality analysis of between AS and PD. Single-nucleotide polymorphisms (SNPs) significantly associated with the exposure factors (P < 5E-08) were initially identified as IVs. To avoid the effect of linkage disequilibrium (LD), the thresholds were set to r2 < 0.001and window size >10,000 kb [29]; all palindromic SNPs were further excluded. In addition, to eliminate weak instrumental variables, we only included F-statistics >10 for the IVs. We also used Steiger filtering to reduce reverse causality effects and exclude variables with a greater explanatory effect on outcome compared to exposure [30].

Ten SNPs associated with AS were identified in the finn-b-M13_ANKYLOSPON dataset, and 5 SNPs associated with AS were identified in the finn-b-M13_ANKYLOSPON_STRICT dataset from FinnGen. We extracted 5 SNPs related to AS from the IGAS dataset. Seven AS-associated SNPs were identified in the UKB-a-88 dataset, whereas 5 AS-associated SNPs were identified in the UKB-b-18194 dataset. For PD as the exposure in the reverse MR analysis, we selected 65 SNPs.

2.4. Mendelian randomization and meta-analysis

To incorporate SNPs that strictly adhered to the basic premise, we initially employed IVW [31] for our analyses. Complementary methods such as MR-Egger, weighted median, simple mode, and weighted mode were also utilised. The results are presented as odd ratios (ORs) with corresponding 95 % confidence intervals (95 % CIs).

Sensitivity analyses were conducted to evaluate the heterogeneity and horizontal pleiotropy. In cases where significant heterogeneity was detected using Cochran's Q-test ($P < 0.05$), we supplemented the analysis with the random effects IVW approach. To address horizontal pleiotropy, we conducted the MR-Egger [32] intercept test and employed the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) [33]. Additionally, we employed the leave-one-out method to assess the impact of removing individual SNPs on the overall results.

For the MR analysis results, we performed a meta-analysis to combine the effect estimates. A fixed-effects model was chosen when $I2 \leq 50$ % and $P \geq 0.05$. Conversely, a random-effects model was used when I2 was> 50 % and $P < 0.05$.

All analyses were conducted using the R language (R version 4.2.0) and relevant R packages, including TwoSampleMR, MRPRESSO, and meta (see Fig. 1).

3. Results

3.1. Causal impact of ankylosing spondylitis on Parkinson's disease

In this study, we analysed three AS-related GWAS datasets that comprised 20 SNPs, each with IVF statistics exceeding 10. These findings indicated the adequacy of SNP information for MR investigations; detailed SNP-specific information is provided in Table S1. The MR analysis results are displayed in Fig. 2. Utilising the IVW method, our conclusion revealed no significant causal relationship between AS and PD risk across the analysed datasets (finn-b-M13 ANKYLOSPON database: OR = 1.02, 95 % CI = 0.99–1.05, P = 0.158; finn-bM13_ANKYLOSPON_STRICT database: OR = 1.00, 95 % CI = 0.97–1.02, P = 0.78; ebi-a-GCST005529 database: OR = 0.91, 95 % CI = 0.75–1.09, P = 0.292).

Additionally, the meta-analysis that combined the three AS databases also demonstrated the absence of a significant causal link between AS and PD risk (I = 27 %, OR = 1.01, 95 % CI = 0.99–1.03, P = 0.26)(Fig. 3). Notably, no substantial heterogeneity or horizontal pleiotropy was detected in the MR analysis (Supplementary Table 2). A scatterplot detailing the causal effects of AS and PD is shown in Supplementary Fig. 1. Furthermore, the leave-one-out analysis revealed no SNP outliers, which indicated the stability of our results (Supplementary Fig. 2).

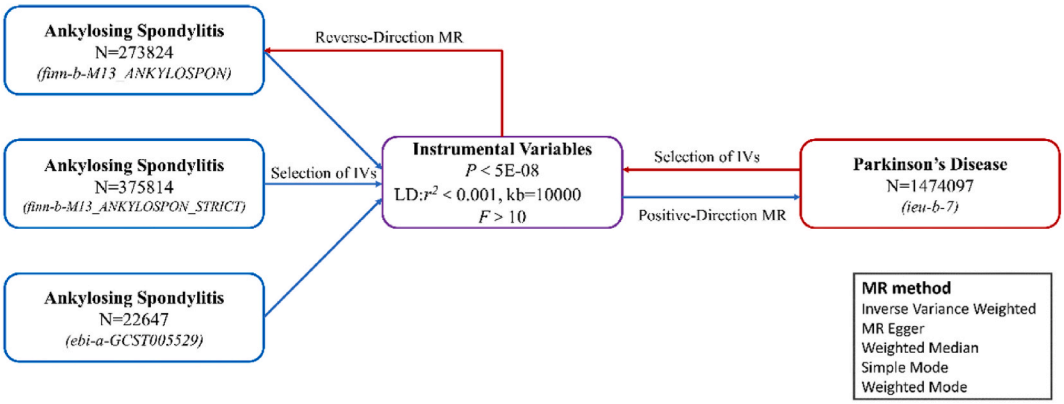

Fig. 1. Study design of the bidirectional MR analysis between as and PD.

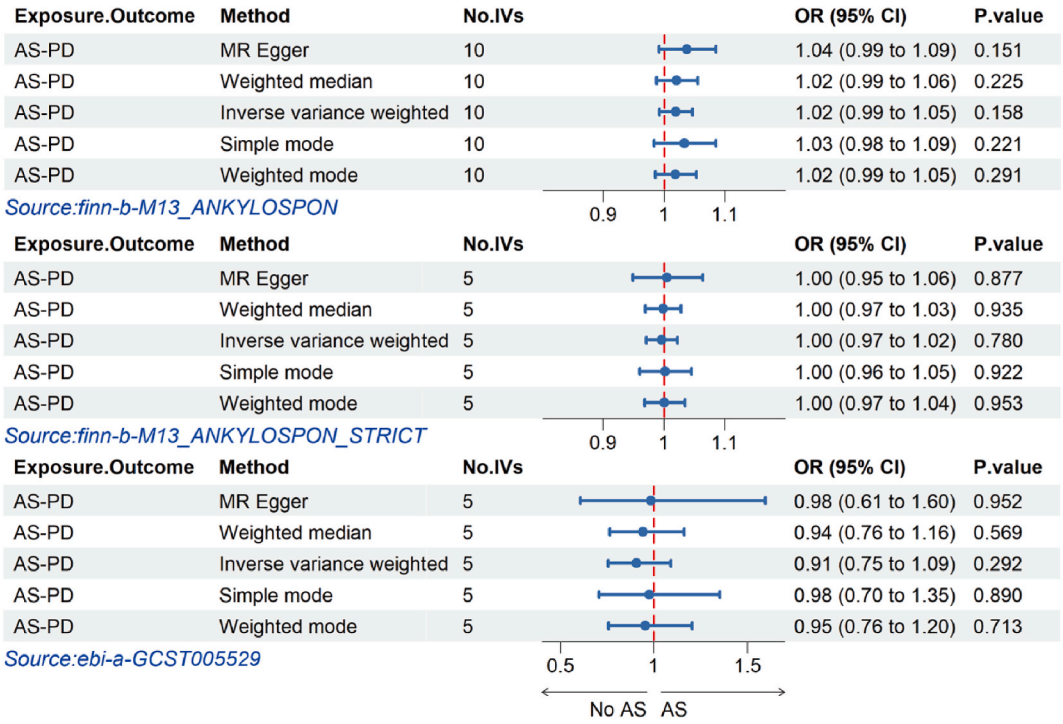

Fig. 2. Full results of MR estimates for the association between ankylosing spondylitis and Parkinson's disease.

To further validate our findings, we performed additional analyses using the UK Biobank dataset (self-reported non-cancer disease code: ankylosing spondylitis), although the number of AS cases in these datasets was relatively small. The 5 AS-related datasets that we analysed encompassed nearly all publicly available GWAS data for this condition. Consistent with our prior analyses, using the IVW method, we found no significant causal relationship between AS and PD risk in these datasets (UKB-a-88 dataset: OR = 24.94, 95 % CI = 0.11–5531.33, P = 0.236; UKB-b-18194 dataset: OR = 1,815,527.21, 95 % CI = 0.00–24,460,900,000,000,000, P = 0.765). No evidence of significant heterogeneity or horizontal pleiotropy was detected in the MR analysis (Supplementary Table 2). Scatter plots illustrating the causal relationship between AS and PD are presented in Supplementary Fig. 3. Furthermore, the leave-one-out analysis revealed no SNP outliers, which confirmed the robustness of our results (Supplementary Fig. 4).

3.2. The causal impact of Parkinson's disease on ankylosing spondylitis

In this study, we conducted reverse MR analysis to examine the possibility of reverse causality between PD and AS. A comprehensive analysis was performed using 65 IVs, each with F-statistics exceeding 10 SNPs. The high F-value ensured the adequacy of the SNP information for MR studies, with detailed IV information provided in Table S3. Employing the IVW method, our analysis revealed no significant causal association between PD and AS, with the results indicating an OR of 0.93 (95 % CI = 0.85–1.01, P = 0.068), as depicted in Fig. 4. Moreover, our MR analysis did not detect significant heterogeneity or horizontal pleiotropy (Supplementary Table 5). A scatterplot illustrating the causal effects of PD and AS is shown in Supplementary Fig. 5. Additionally, the knockout analysis revealed no SNP outliers, further confirming the robustness of our findings (Supplementary Fig. 6).

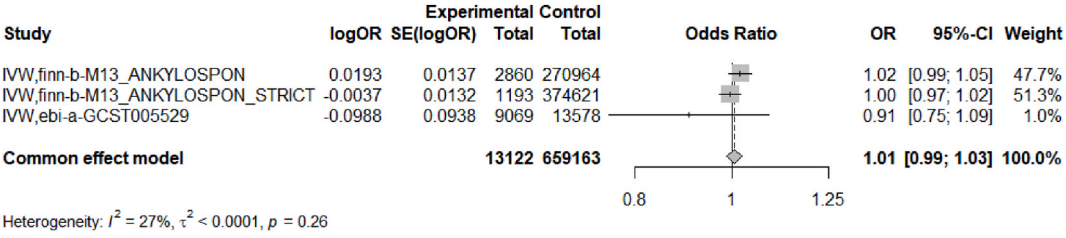

Fig. 3. M Calculation of the association between the ankylosing spondylitis dataset and Parkinson's disease after combined analysis.

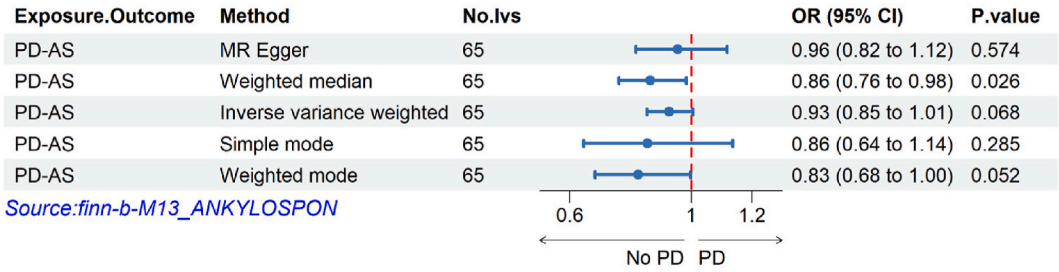

Fig. 4. Full results of MR estimates for the association between Parkinson's disease and ankylosing spondylitis.

4. Discussion

To our knowledge, no prior investigation has undertaken using a bidirectional MR analysis to elucidate the interplay between AS and PD. By leveraging the three most expansive AS-related GWAS databases, along with a substantial cohort of patients with PD GWAS datasets, we endeavoured to delve deeper into the potential genetic underpinnings of the relationship between AS and PD, building upon previous clinical enquiries. Our findings were substantiated by pertinent sensitivity analyses, which confirmed the robustness of our outcomes. Recently, there has been heightened interest in exploring the relationship between autoimmune disorders and PD. A multitude of researchers have explored the plausible association between AS and PD, which have yielded conflicting conclusions. However, our results failed to provide evidence supporting a reciprocal genetic linkage between AS and PD. Nonetheless, the paucity of GWASs pertaining to AS and PD underscores the necessity of circumspection when interpreting these findings.

Our MR findings align with those of a previous nationwide observational study conducted in Sweden by Li et al., who tracked 310,522 patients diagnosed with 33 autoimmune diseases. Their follow-up of patients with AS did not reveal an elevated risk for developing PD [20]. However, it is noteworthy that several prior observational investigations reported an association between AS and PD, which contrasts with our results. For instance, a cohort study conducted in Taiwan from 2000 to 2010 involving 6440 patients with AS and 25,760 healthy controls indicated a significantly increased incidence of PD among patients with AS (adjusted hazard ratio[HR] = 1.75, $P < 0.001$) [18]. Another study by Yoon et al. [19], a nationwide longitudinal, population-based matched cohort study in the Republic of Korea, showed that patients with AS exhibited a significantly heightened risk for PD (HR = 1.82, 95 % CI 1.38–2.39, $P < 0.001$). Similarly, a nationwide retrospective cross-sectional study in Israel suggested an increased risk of PD among patients with AS (OR = 2.75, 95 % CI 2.04–3.72, $P < 0.0001$) [34]. A recent meta-analysis also reported an elevated risk of PD for patients with AS (RR = 1.55, 95 % CI 1.31–1.83, $P < 0.001$), while acknowledging the heterogeneity of study outcomes (I = 32.1 %) [35]. Although, these findings indicate an association between AS and PD, observational studies cannot establish causality, and observed associations in real-world settings may be influenced by population disparities and residual confounding factors.

The aforementioned observational studies that reported an elevated risk of PD for patients with AS were predominantly conducted in Asia and potentially introduce geographical and ethnic biases. Thus, the generalisability of this association to other ethnic groups and geographical regions remains unclear. The observational nature of these studies further complicates the determination of a relationship between AS and PD due to factors such as sample size limitations, racial homogeneity, and insufficient information. Caution is warranted when interpreting evidence from observational studies because they do not establish causal relationships and may inadequately account for confounding factors. More robust analyses are necessary to ascertain whether AS increases the risk of PD and to provide substantial evidence and clinical recommendations. Our study utilised the largest publicly available GWAS databases of patients with PD and AS (both from European populations), which is consistent with previous observational studies conducted in Sweden. Contrary to the previous hypotheses, our findings revealed no direct causal relationship between AS and PD.

However, in observational studies, the increased prevalence of PD among patients with AS compared to that in the general population may be attributed to various mechanisms. Firstly, an increasing number of autopsy analyses of human samples and animal and cell model studies have suggested the involvement of neuroinflammation in PD onset and progression [36,37]. Activation of cellular mediators, including microglia and astrocytes, enhances inflammation via direct α-synuclein stimulation and indirect inflammatory signalling [38,39], resulting in reactive oxygen species and upregulated expression of cytokines and chemokines such as TNF, IL-1, IL-2, and IL-6 in central and peripheral organs [40]. Inflammation is a key contributor to the degeneration of dopaminergic neurones in the substantia nigra. Moreover, a recent GWAS discovered a genetic overlap between PD and certain autoimmune diseases, identifying 17 new loci that overlap with PD, which indicates that these loci may mediate PD through immune mechanisms [41,42]. This suggests that immune dysfunction is not merely a consequence but rather an interactive component of PD neurodegeneration. Some studies have suggested that the inflammatory pathway involving TNF-α plays a role in PD pathogenesis and may serve as a therapeutic target [43,44]. Interestingly, TNF-α is implicated in AS and is present at elevated levels in the blood of patients with AS [45].

Notably, the medications used to treat AS may affect the likelihood of patients with AS developing PD. Immunosuppressants commonly used to treat AS exhibit uncertain neural mechanisms of action. A clinical study indicated that patients with AS receiving immunosuppressive treatment had a higher risk of developing PD than those not receiving immunosuppressive treatment [18]. Additionally, several clinical trials have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs) have protective effects against PD [18,19,46].

Our discussion regarding the relationship between AS and PD is primarily confined to a genetic causation perspective. However, it is essential to acknowledge that the association between AS and PD involves numerous complex underlying mechanisms, including interactions between environmental and genetic factors crucial for disease pathogenesis, which warrant further comprehensive investigation. Subsequent studies should explore the effects of neuroinflammation, immunosuppressants, and NSAIDs to elucidate the association between AS and PD. Integrating these aspects may offer a more holistic understanding of the AS-PD relationship.

Our MR study has certain limitations. The absence of detailed participant demographic and clinical data restricted our ability to conduct subgroup analyses. Moreover, the study focused on the impact of lifetime genetic exposure, which could have led to an overestimation of the practical effects of targeted interventions. Furthermore, our analysis was based primarily on data from populations of European ancestry, which may limit the generalisability of our findings to other populations. Given the presence of population-specific genetic variation, future studies involving more ethnically diverse cohorts are essential to validate these results in different contexts. Although we employed rigorous sensitivity analyses, including MR-Egger, weighted median, and MR-PRESSO, to account for horizontal pleiotropy and other biases, residual confounding may still have persisted. Horizontal pleiotropy, in which genetic variants influence multiple traits through distinct biological pathways, may have introduced bias, despite efforts to mitigate it. Additionally, the inherent limitations of MR analyses, such as the reliance on validated genetic instruments, may have led to potential bias due to weaker instrument effects.

5. Conclusion

In summary, our MR findings suggested that AS and PD are not causally related in either direction. Future MR studies should validate our findings and utilise improved methods to generate less biased MR estimates while incorporating newer and more comprehensive GWAS summary data. Further research is needed to fully validate our results, including large-sample and long-term follow-up studies, and to explore multiple comprehensive mechanisms. It must be acknowledged that our MR analysis focused solely on genetic relationships and did not elucidate other potential causal relationships.

Financial disclosure/conflict of interest

The authors declare no competing interests.

CRediT authorship contribution statement

Jinhua Chen: Writing – original draft, Project administration, Funding acquisition, Conceptualization. **Qiuhan Xu:** Writing – original draft, Supervision, Software, Methodology, Investigation, Data curation, Conceptualization. **Yiling Wang:** Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Sisi Jiang:** Validation, Supervision, Resources. **Baorong Zhang:** Writing – review & editing, Supervision, Funding acquisition. **Jun Tian:** Writing – review & editing, Supervision, Project administration, Funding acquisition.

Data availability statement

All pertinent data are accessible within the manuscript and accompanying Supporting Information files.

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Declaration of competing interest

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.

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Appendix A. Supplementary data

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