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Original Research

Causal Relationship between Sex Hormones and Risk of Developing Common Neurodegenerative Diseases: A Mendelian Randomization Study

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Abstract

Background: Neurodegenerative diseases are a group of unexplained disorders of the central nervous system, and studies have shown that a large number of genetic and environmental factors are associated with these diseases. Since these diseases show significant gender differences in epidemiology, sex hormones are thought to be strongly associated with these diseases. In this study, we used Mendelian randomization to explore the causal relationship between sex hormones and the risk of developing neurodegenerative diseases. **Methods**: We obtained genetic instrumental variables for sex hormones (sex hormone-binding globulin [SHBG], estradiol levels [EL], and bioavailable testosterone [BT]) separately through the Integrative Epidemiology Unit (IEU) database (https://gwas.mrcieu.ac.uk/). We analyzed the causal relationship of each with the risk of developing neurodegenerative diseases (Amyotrophic Lateral Sclerosis [ALS], Parkinson's disease [PD], and Alzheimer's disease [AD]) using inverse variance weighted (IVW) in Mendelian randomization. Data were then analyzed for sensitivity. **Results**: BT was negatively associated with the risk of developing ALS (odds ratio [OR] = 0.794; 95% confidence interval [95% CI] = 0.672–0.938; p = 0.006). EL and SHBG were not associated with a risk for developing neurodegenerative diseases (ALS, PD, AD). **Conclusions**: Elevated BT is associated with a reduced risk of developing ALS. Further research is needed to investigate the underlying mechanisms of action for this correlation and how it can be used as a potential target of action to reduce the risk of developing ALS.

Keywords: sex hormones; neurodegenerative diseases (NDs); mendelian randomization (MR); causal effect

1. Introduction

Neurodegenerative diseases (NDs) are a group of chronic, multivariate, progressive diseases characterized by neuronal degeneration and necrosis. Common NDs include Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS), which have been regarded as persistent and difficult to treat because of their unknown etiology, and poor prognosis. Therefore, early detection and prevention of these diseases have become a hot research topic in recent years. Epidemiologic studies suggest that there is a significant gender difference in the incidence of NDs. For example, studies have shown that two-thirds of patients with AD in the United States are women and that the prevalence of AD is twice as high in women as men [1]. Among patients with ALS, the prevalence is twice as high in men as in women [2]. For patients with PD, the prevalence is 1.5 times higher in men than in women [3]. These gender differences in disease prevalence suggest that the disease development may be related to sex hormone levels.

Sex hormones have been shown to correlate with NDs, however, the underlying biological mechanisms of these correlations are not clear [4]. Studies have shown that estrogen can reduce beta amyloid (Aβ) aggregation [5], which is at odds with estimates suggesting that AD is twice as prevalent in women as men. As men age, androgen levels decrease [6] and testosterone levels are lower in patients with AD than in normal individuals [7,8]. This seems to imply the protective effect of androgens against AD. It has also been shown that estrogen reduces dopamine (DA) depletion in female rats [9,10].

To date, the role of androgens in patients with PD is not clear [4]. Similarly, little research has been done on the role of sex hormones in ALS. Studies have shown that estrogen can counteract neuroinflammation [11] and that estradiol increases motor neuron survival in male ALS mice [12]. Sex hormone-binding globulin (SHBG) plays a crucial role in the biological action of sex hormones. SHBG is a protein synthesized and secreted by the liver, which, when it reaches the bloodstream, binds directly to sex hormones and regulates their biological activity. A biologically active sex hormone is defined as a sex hormone that is not bound to SHBG.

Although studies have shown a close association between sex hormones and NDs, these studies are not systematic and comprehensive, and due to the limitations of the

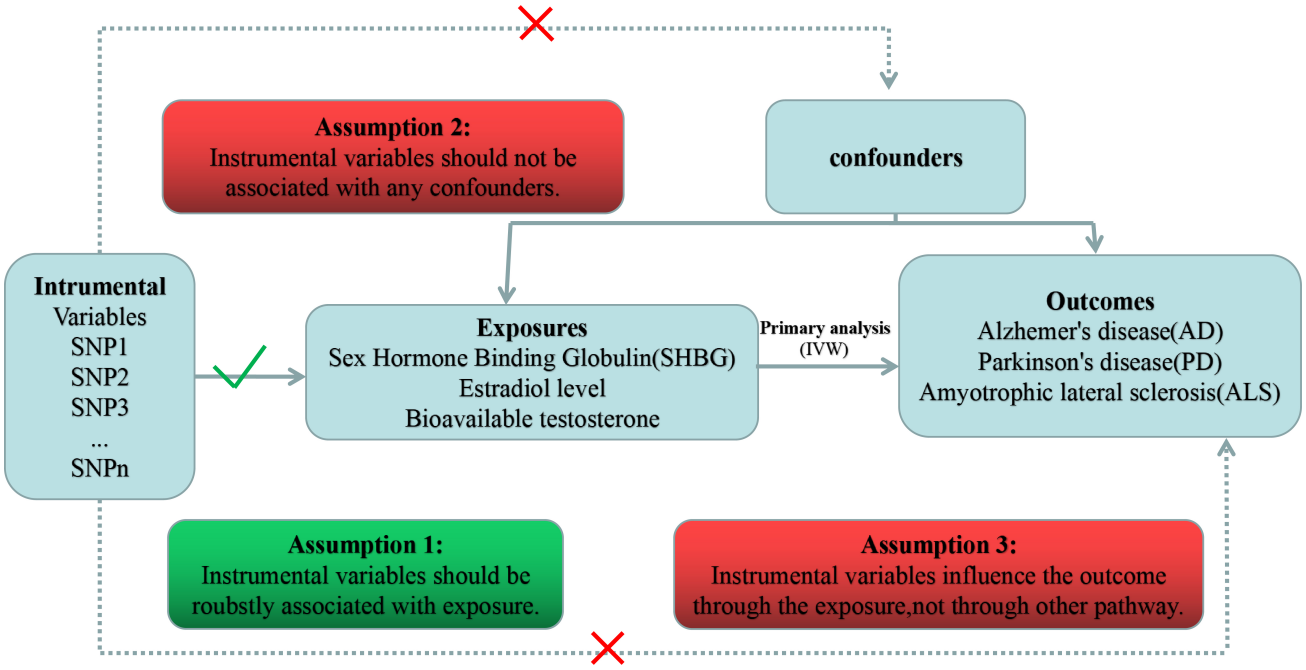

Fig. 1. Design flow chart of the present study. IVW, inverse-variance-weighted; SNP, single-nucleotide polymorphism; SHBG, sex hormone-binding globulin; AD, Alzheimer's disease; PD, Parkinson's disease; ALS, Amyotrophic Lateral Sclerosis.

experimental conditions, they often produce biased results or contradictory conclusions. This may lead to biased conclusions due to the inability of the study design to exclude reverse causality and confounding factors. In addition, traditional randomized controlled trial (RCT) experiments require a large amount of human, material, and financial resources, making it impractical to conduct RCT experiments on this issue.

Mendelian randomization (MR) has been increasingly used to infer risk factors and disease causality. Based on the stochastic nature of genetic variation during meiosis, MR uses environmentally relevant genetic variants as instrumental variables (single nucleotide polymorphisms: SNPs) to assess causality between exposure and outcome. As these genetic variants were randomly assigned at conception before disease onset, MR analyses can effectively exclude confounding factors and identify determinants of a given outcome. In the present study, we systematically evaluated the causal relationship between sex hormones and NDs by using the MR method.

2. Methods

2.1 Research Design

In the present study, we used a two-sample MR study approach to assess the causal relationship between genetic instrumental variables for sex hormones and NDs. Due to the need for two-sample randomized data analysis, exposures and outcomes were derived from non-overlapping data sources (see **Supplementary Table 1**). Both samples (exposure and outcome) were from European populations. The MR design had to fulfill three assumptions: (1) the instrumental variables were strongly correlated with exposure ($p < 5 \times 10^{-8}$); (2) the instrumental variables were not influenced by underlying factors; (3) the instrumental variables influenced the outcome only through the exposure factors (see Fig. 1).

SHBG, estradiol level (EL), and bioavailable testosterone (BT) were provided by the Integrative Epidemiology Unit (IEU) database (https://gwas.mrcieu.ac.uk/). SHBG data were obtained from a European population of 214,989 participants; EL data were obtained from 13,367 European descents; and those related to BT were obtained from 382,988 European descents. Data related to NDs was also obtained from the IEU database [13]. Briefly, the PD data were derived from the European population of 2162 cases and 216,630 controls; those related to AD were derived from 39,106 cases and 46,828 controls; those related to ALS were derived from 20,806 cases and 59,804 controls. All data for this study were obtained from public databases and no additional ethical approval was required.

2.2 Selection of Genetic Instrumental Variables

Genetic instrumental variables for BT, EL, and SHBG were provided by the IEU database (https://gwas.mrcieu.ac.uk/). In total, 124 independent SNPs associated with BT were extracted ($p < 5 \times 10^{-8}$), with linkage disequilibrium (LD) ($r^2 < 0.001$) [14]. Instrumental variables (IVs) of exposure had to be screened according to the following criteria: (1) p-value level of SNPs ($p < 5 \times 10^{-8}$); (2) SNPs aggregation using the PLINK algorithm ($r^2 < 0.001$): (3) Removal of SNPs showing potential pleiotropy. In addi-

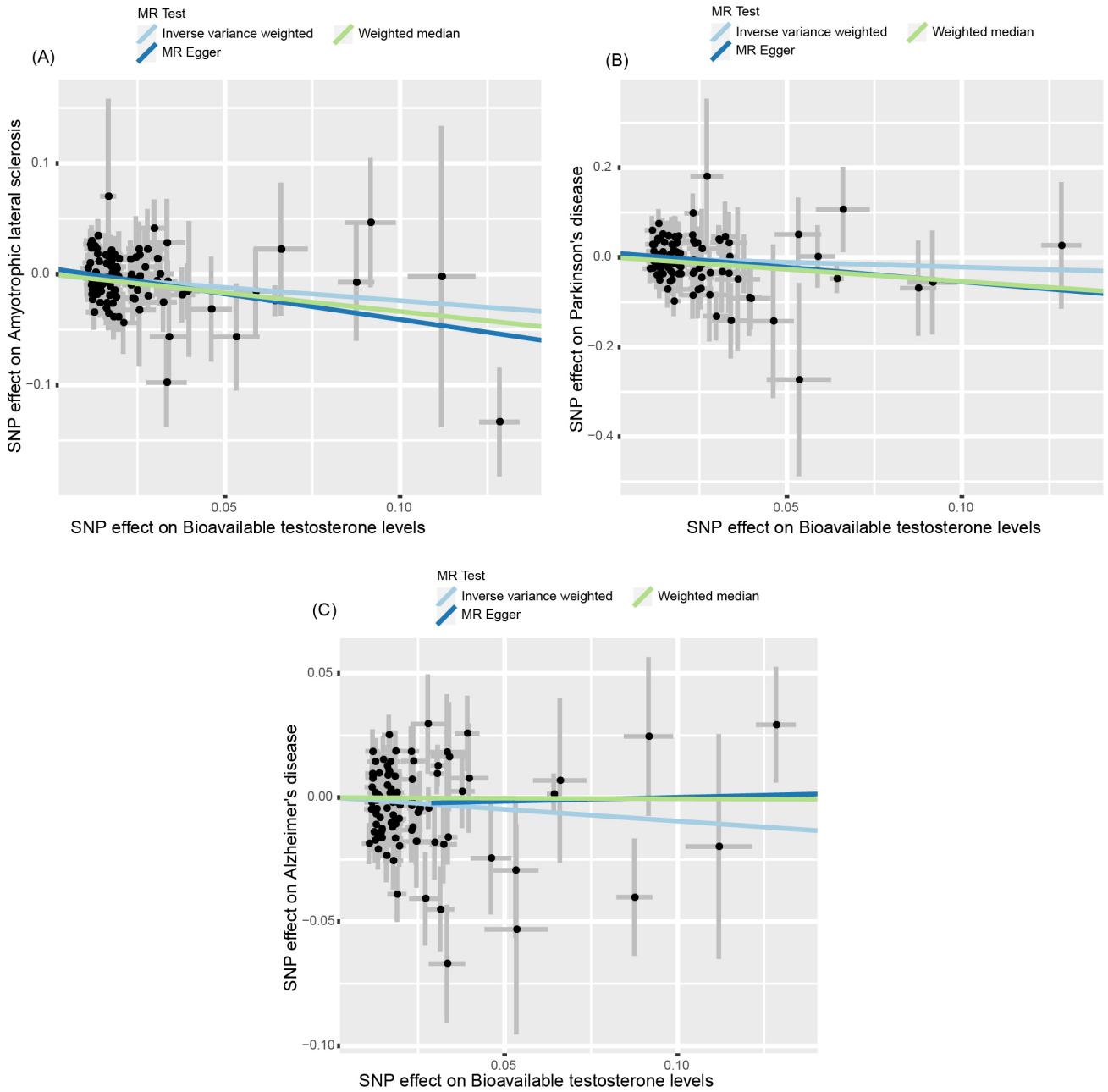

Fig. 2. Scatter plot of the causal effects of BT on the risk of ALS (A), PD (B), and AD (C). BT, Bioavailable testosterone; ALS, Amyotrophic Lateral Sclerosis; PD, Parkinson's disease; AD, Alzheimer's disease; MR, Mendelian randomization.

tion, a total of 13 independent SNPs associated with EL were extracted ($p < 5 \times 10^{-8}$), and a total of 197 independent SNPs associated with SHBG were extracted ($p < 5 \times 10^{-8}$). Detailed information for SNPs included was presented in **Supplementary Tables 2–4**.

2.3 Statistical Analysis

In our study, five methods were used for MR analysis: inverse variance weighted (IVW), MR-Egger, weighted median, simple mode, and weighted mode. The IVW method was used as the primary method to analyze the causal relationship between sex hormones and NDs. The MR-Egger method includes an intercept, which could explain the average pleiotropy effect of all genetic variations [15]. In addition, to further assess whether the presence of pleiotropic IVs influences the causal estimation, we detected horizontal pleiotropy [16]. Multiple validities of genes occur when IVs affect outcomes through multiple pathways other than exposure, so we further performed Cochran statistics funnel filling, leave-one-out analysis, and MR-egger intercept tests to detect the presence of multiple validities.

Heterogeneity was detected if the p-value of the Cochran Q-test was less than 0.05. Logistic regressions

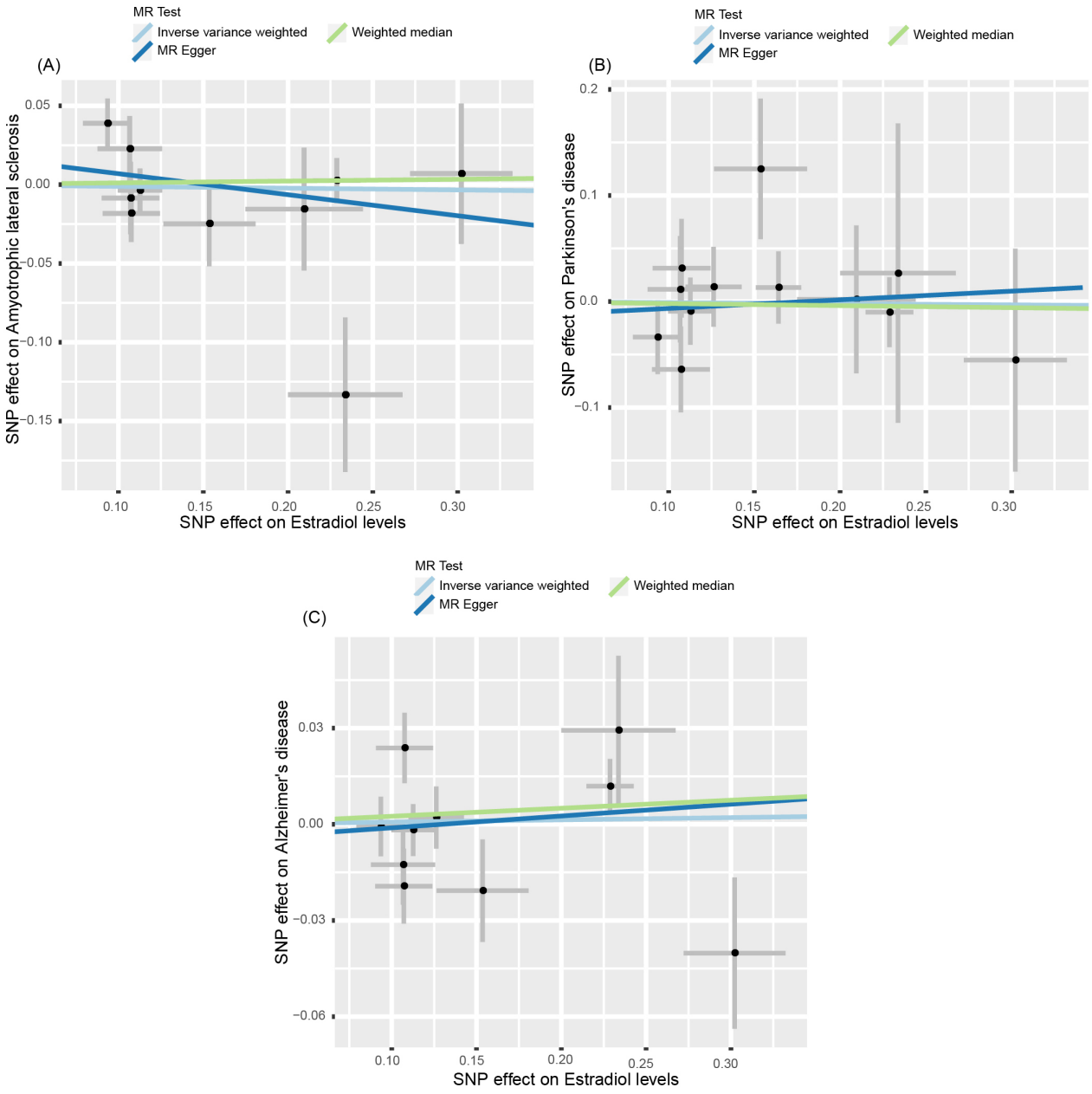

Fig. 3. Scatter plot of the causal effects of EL on the risk of ALS (A), PD (B), and AD (C). EL, Estradiol levels.

based on the assessment of horizontal multinomials were also performed. To determine whether causal estimates were driven by any single SNP, leave-one-out analyses were performed, by which each exposure-related SNP was discarded in turn to repeat the IVW analysis. Due to multiple tests in this study, Bonferroni corrections were performed and the main results possessed statistical significance at p-values < 0.017 (0.050/3). As such, p-values from 0.017 to 0.050 were considered to have potential statistical significance [17]. All analyses were performed using the R program (version 4.3.1; website: https://www.r-project.org/) and the "TwoSampleMR" package (version 0.5.6; website: https://mrcieu.github.io/TwoSampleMR/index.html) [18].

3. Results

3.1 Instrumental Variables in this Study

After data harmonization, 187 SNPs for AD, 189 SNPs for PD, and 187 SNPs for ALS were selected as genetic instruments to conduct MR analyses for SHBG and NDs. To conduct MR analyses for EL and NDs, 10 SNPs for AD, 12 SNPs for PD, and 10 SNPs for ALS were selected as genetic instruments. To conduct MR analyses for BT and NDs, 105 SNPs for AD, 110 SNPs for PD, and 108 SNPs for ALS were selected as genetic instruments.

Table 1. Mendelian randomization analysis results for the causal associations of sex hormone (SHBG, Bioavailable testosterone) with AD, PD, and ALS.

Method	SHBG				Bioavailable testosterone			
	SNPs(N)	OR	95% CI	*p*-value	SNPs(N)	OR	95% CI	*p*-value
AD								
IVW	197	1.002	0.946∼1.061	0.932	124	0.909	0.806∼1.025	0.121
Weighted median	197	0.969	0.897∼1.047	0.429	124	0.994	0.835∼1.184	0.954
MR Egger	197	0.983	0.886∼1.090	0.746	124	1.032	0.809∼1.318	0.795
Simple mode	197	1.061	0.920∼1.224	0.411	124	0.871	0.580∼1.308	0.508
Weighted mode	197	0.973	0.896∼1.055	0.512	124	1.042	0.851∼1.276	0.687
PD								
IVW	197	0.972	0.830∼1.138	0.726	124	0.804	0.561∼1.151	0.234
Weighted median	197	1.202	0.901∼1.602	0.209	124	0.585	0.332∼1.103	0.064
MR Egger	197	1.256	0.954∼1.655	0.105	124	0.523	0.240∼1.135	0.104
Simple mode	197	1.055	0.581∼1.917	0.859	124	0.565	0.153∼2.088	0.394
Weighted mode	197	1.159	0.852∼1.576	0.347	124	0.546	0.242∼1.231	0.148
ALS								
IVW	197	1.043	0.965∼1.127	0.286	124	0.794	0.672∼0.938	0.006
Weighted median	197	1.093	0.975∼1.225	0.124	124	0.714	0.538∼0.947	0.019
MR Egger	197	1.117	0.971∼1.286	0.122	124	0.627	0.439∼0.896	0.011
Simple mode	197	0.904	0.696∼1.172	0.448	124	0.728	0.401∼1.321	0.299
Weighted mode	197	1.111	0.970∼1.272	0.127	124	0.728	0.504∼1.052	0.094

IVW, inverse variance weighted; MR, mendelian randomization; ALS, amyotrophic lateral sclerosis; SNPs, single nucleotide polymorphisms; OR, odds ratio; 95% CI, 95% confidence interval; SHBG, Sex hormone-binding globulin.

3.2 MR for BT and NDs

As shown in Table 1 and Fig. 2A, a negative causal effect of BT on ALS was identified using the IVW method (odds ratio (OR) = 0.794; 95% confidence interval (95% CI): 0.672–0.938; p = 0.006) and the weighted median method (OR = 0.714; 95% CI: 0.538–0.947; p = 0.019). However, the simple mode analysis and weighted mode analysis did not detect a causal relationship between BT on ALS risk (Table 1). The MR-Egger method detected no directional pleiotropy for IVs (intercept = 0.006, p = 0.15). However, there are no causal relationships between BT on PD and AD risk (Table 1, Fig. 2B,C).

3.3 Estradiol and NDs

In Table 2 and Fig. 3, the IVW analysis results showed no genetically causal relationship between EL and ALS (p = 0.674), PD (p = 0.899), and AD (p = 0.828). The findings of other MR-analysis methods also showed no causal association between EL and NDs (ALS, PD, AD) (Table 2).

3.4 SHBG and NDs

In Table 1 and Fig. 4, the IVW analysis results showed no genetically causal relationship between SHBG and ALS (p = 0.286), PD (p = 0.726), and AD (p = 0.932). The findings of other MR-analysis methods also showed no causal association between SHBG and NDs (Table 1).

4. Discussion

Our study systematically assessed the causal relationship between sex hormones and the risk of developing common NDs, which greatly enriches the existing research findings. Our study suggests that the level of BT is negatively associated with the risk of developing ALS, whereas EL and SHBG are not associated with the risk of developing NDs. Previous studies have shown that in patients with ALS, those with higher testosterone levels have the condition progress at a faster rate and involve the respiratory muscles [19]. At the same time, it has been shown that castration in an ALS mouse model prolongs survival, while androgen supplementation exacerbates motor neuron loss and decreases survival rates [20–22]. In contrast, blocking the androgen receptor instead leads to accelerated disease onset [23]. Our study suggests that androgens reduce the risk of ALS. The beneficial impact of BT on ALS might be attributed to its neuroprotective properties. Testosterone crosses the blood-brain barrier and exerts its direct impact on the central nervous system by activating androgen receptors or by being converted into other steroid hormones involved in improving human neurons and astrocyte survival [24,25]. Studies also reported that testosterone could act directly on mitochondrial membranes to inhibit the generation of reactive oxygen species and increase the sirtuin-1 expression [26].

The vast majority of studies suggest that estrogen has neuroprotective effects on ALS, for example, estrogen can directly target neurons and act as an anti-apoptotic agent

Table 2. Mendelian randomization analysis results for the causal associations of sex hormone (SHBG, estradiol) with, AD, PD, and ALS.

Method	SHBG				Estradiol			
	SNPs(N)	OR	95% CI	*p*-value	SNPs(N)	OR	95% CI	*p*-value
AD								
IVW	197	1.002	0.946∼1.061	0.932	13	1.006	0.945∼1.072	0.828
Weighted median	197	0.969	0.897∼1.047	0.429	13	1.025	0.964∼1.090	0.424
MR Egger	197	0.983	0.886∼1.090	0.746	13	1.037	0.864∼1.245	0.703
Simple mode	197	1.061	0.920∼1.224	0.411	13	0.964	0.846∼1.099	0.602
Weighted mode	197	0.973	0.896∼1.055	0.512	13	1.033	0.968∼1.103	0.348
PD								
IVW	197	0.972	0.830∼1.138	0.726	13	0.989	0.840∼1.164	0.899
Weighted median	197	1.202	0.901∼1.602	0.209	13	0.980	0.787∼1.220	0.861
MR Egger	197	1.256	0.954∼1.655	0.105	13	1.085	0.662∼1.777	0.752
Simple mode	197	1.055	0.581∼1.917	0.859	13	1.070	0.790∼1.450	0.667
Weighted mode	197	1.159	0.852∼1.576	0.347	13	0.988	0.781∼1.251	0.926
ALS								
IVW	197	1.043	0.965∼1.127	0.286	13	0.988	0.938∼1.041	0.674
Weighted median	197	1.093	0.975∼1.225	0.124	13	1.011	0.953∼1.072	0.704
MR Egger	197	1.117	0.971∼1.286	0.122	13	0.875	0.764∼1.001	0.060
Simple mode	197	0.904	0.696∼1.172	0.448	13	0.958	0.875∼1.050	0.374
Weighted mode	197	1.111	0.970∼1.272	0.127	13	1.002	0.946∼1.061	0.932

IVW, inverse variance weighted; MR, mendelian randomization; ALS, amyotrophic lateral sclerosis; SNPs, single nucleotide polymorphisms; OR, odds ratio; 95% CI, 95% confidence interval; SHBG, Sex hormone-binding globulin.

[27,28]. This anti-apoptotic effect also applies to motor neurons [29]. However, in our study, estrogen was not associated with the risk of developing ALS. High estrogen levels are negatively associated with the severity of PD symptoms in women, and menopausal women are at a higher risk of developing PD [30–32]. Previous studies have reported that estrogen replacement therapy during the early postmenopausal period could mitigate the risk of PD and improve prognosis [33,34]. Estrogen is therefore thought to have neuroprotective effects by slowing down the onset and progression of the disease [35]. However, the current study did not detect the effect of estrogen on PD.

Exactly what role androgens play in the pathogenesis of PD is not well understood so far. Some studies suggest that testosterone deficiency may be associated with PD and that testosterone therapy may improve specific symptoms in patients with PD, including improving motor function and increasing general well-being [36–38]. However, some studies also provide evidence that total testosterone levels correlate with biomarkers of PD severity, suggesting that testosterone might play a role in male vulnerability to PD [39]. Therefore, the role of testosterone in PD remains equivocal. Our study suggests that testosterone is not associated with the risk of developing PD.

AD, the most common ND, has a high prevalence and mortality rate, and there is a lack of effective clinical treatments. Previous studies have shown that both BT and estrogen are effective in reducing Aβ production and aggregation [5,40]. Additionally, estrogen therapy has been shown to have a beneficial effect on slowing the development of AD [41,42]. However, these studies are not reproducible [43,44]. In contrast, our study aptly demonstrates that estrogen is not associated with the risk of developing AD. In men, circulating testosterone levels decrease progressively with age. In patients with AD, testosterone levels have been reported to be lower than in controls [7,8]. In addition, androgens are naturally neuroprotective and support neuronal growth [45,46]. However, it has also been shown that testosterone has no beneficial effects on cognitive function in men [47]. Our study also demonstrates that testosterone does not correlate with the risk of developing AD. Some studies have shown that SHBG is associated with the risk of developing AD [48], however, there are also studies showing that SHBG is associated with the risk of developing ALS, but not AD [49]. Therefore, it is currently difficult to reach a consensus on the causal relationship between SHBG and the risk of developing NDs, and our data suggest that there is no causal relationship between SHBG and the risk of developing NDs. Taken together, the current study failed to detect the effect of SHBG or estradiol on NDs or the effect of BT on NDs except for ALS, which was inconsistent with a majority of previous studies.

Some key points should be noted. Previous epidemiological studies are based on traditional observational design, which is susceptible to confounds or reverse causality, and thus the observed associations might be biased. Another point to note is that the current study used genome-wide association studies (GWAS) summary statistics and

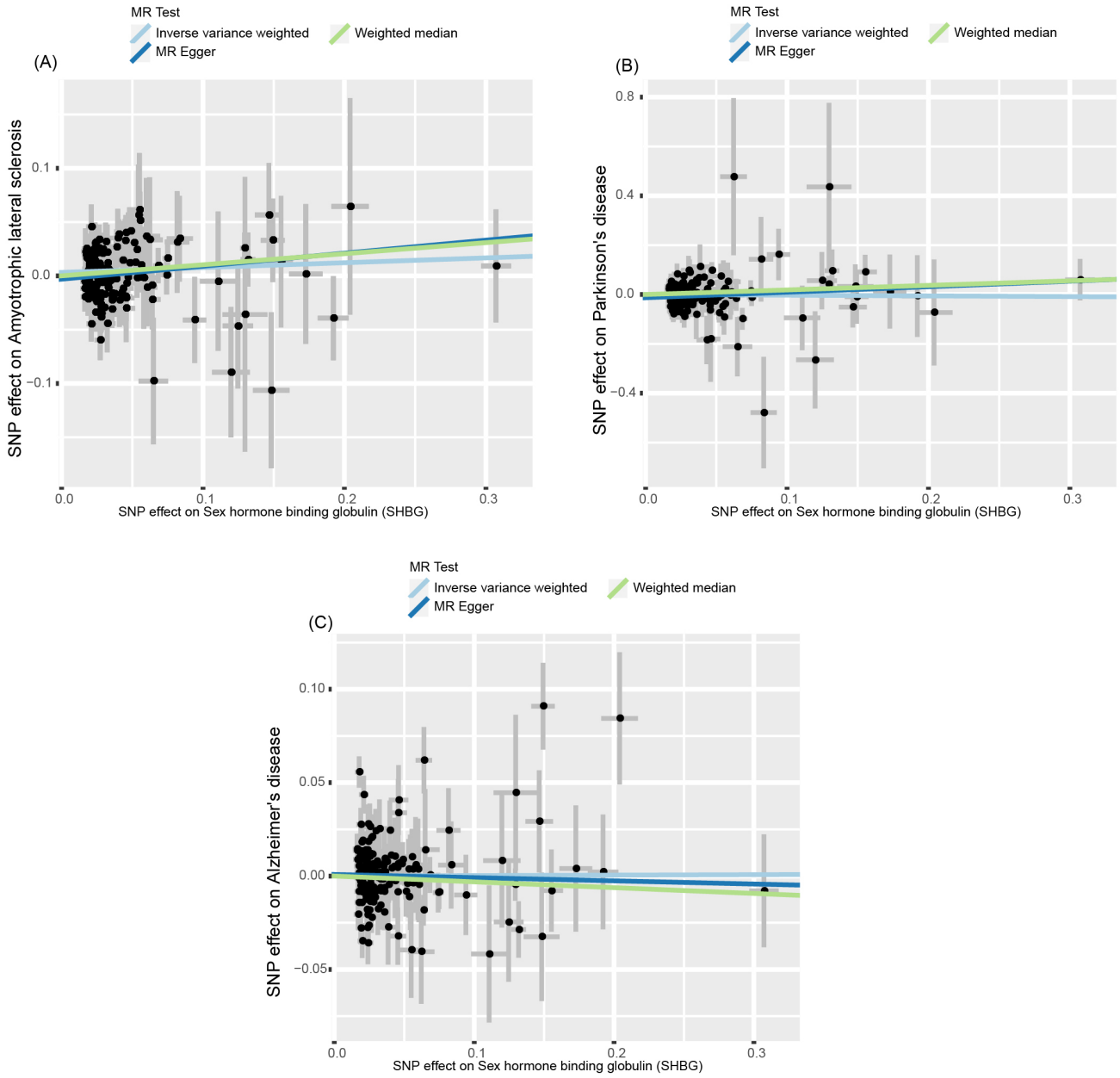

Fig. 4. Scatter plot of the causal effects of SHBG on the risk of ALS (A), PD (B), and AD (C). SHBG, Sex hormone-binding globulin.

thus was unable to conduct sex stratification analysis, which could impact the MR results. Considering the controversial results, more studies are warranted to aid more relevant evidence.

To the best of our knowledge, this is the first systematic MR study conducted to study the relationship between sex hormones and the risk of NDs. MR studies have more advantages than traditional observational studies. For example, it can overcome the effects of confounding and reverse causation [50]. Thus, we were able to provide new insights that may contribute to a better understanding of the causal relationship between sex hormones and NDs. In addition, we used various MR analysis methods to obtain more accurate results. We used recently published GWAS data and performed multiple sensitivity analyses to assess the robustness of our findings.

Although we used MR analyses, the present study has some limitations: (1) as mentioned above, we are unsure of the proportion of false questionnaire reports in the GWAS data; (2) the population included in the present study was predominantly European. Since the results of causal association analysis may also be influenced by ethnicity, further MR studies in other ethnicities should be conducted to validate the present findings; (3) there may be population sharing between the two European sample sets, leading to overuse of genetic information; (4) only publicly available GWAS data were used in our study, thus making sex stratification analysis unavailable. Indeed, the beneficial effects of

estradiol in women with PD have been extensively demonstrated in previous studies [51]. The E3N study has reported that postmenopausal hormone therapy might decrease PD incidence [52]. A recent MR study also reported that a later age at menopause was associated with a decreased risk of PD in women, using the Parkinson's Environment and Gene (PEG) and the Parkinson's Disease in Denmark (PASIDA) datasets stratified by sex [53]. These studies highlighted the important role of sex in PD. Thereby, further investigation is warranted when future GWAS data stratified by sex is publicly available.

5. Conclusions

Our study first confirmed a causal relationship between BT and the risk of ALS. However, there no causal relationship between SHBG, EL, and NDs was detected. Therefore, the detection of BT levels may be beneficial for early prevention of ALS. Further studies on the biological mechanism of this causal relationship are needed.

Availability of Data and Materials

All the data used in this work are publicly available in the IEU database (https://gwas.mrcieu.ac.uk/). The data generated in this work are provided in the main text or supplementary materials.

Author Contributions

JHG and QH designed the research. QH and QL were responsible for the completeness of the data analysis and the accuracy of the data analysis, wrote the manuscript, and performed the data analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Only publicly available summary-level GWAS data were used in this work, and thus ethics approval or consent to participate was not required.

Acknowledgment

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.jin2304078.

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